



REVIEW

Efficacy and Safety of Medication for Attention-Deficit Hyperactivity Disorder in Children and Adolescents with Common Comorbidities: A Systematic Review

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ABSTRACT

Introduction: Comorbid psychiatric conditions in children and adolescents with attention-deficit hyperactivity disorder (ADHD) occur frequently, complicate management, and are associated with substantial burden on patients and caregivers. Very few systematic reviews have assessed the efficacy and safety of

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medications for ADHD in children and adolescents with comorbidities. Of those that were conducted, most focused on a particular comorbidity or medication. In this systematic literature review, we summarize the efficacy and safety of treatments for children and adolescents with ADHD and comorbid autism spectrum disorders, oppositional defiant disorder, Tourette's disorder and other tic disorders, generalized anxiety disorder, and major depressive disorder.

Methods: We searched MEDLINE, Embase, and ClinicalTrials.gov (to October 2019) for studies of patients (aged < 18 years) with an ADHD diagnosis and the specified comorbidities treated with amphetamines, methylphenidate and derivatives, atomoxetine (ATX), and guanfacine extended-release (GXR). For efficacy, placebo-controlled randomized controlled trials (RCTs) or meta-analyses of RCTs were eligible for inclusion; for safety, all study types were eligible. The primary efficacy outcome measure was ADHD Rating Scale IV (ADHD-RS-IV) total score.

Results: Of 2177 publications/trials retrieved, 69 were included in this systematic literature review (5 meta-analyses, 37 placebo-controlled RCTs, 16 cohort studies, 11 case reports). A systematic narrative synthesis is provided because insufficient data were retrieved to combine ADHD-RS-IV total scores or effect sizes. Effect sizes for ADHD-RS-IV total scores were available for ten RCTs and ranged from 0.46 to

1.0 for ATX and from 0.92 to 2.0 for GXR across comorbidities. The numbers and types of adverse events in children with comorbidities were consistent with those in children without comorbidities, but treatment should be individualized to ensure children can tolerate the lowest effective dose.

Conclusion: Limited information is available from placebo-controlled RCTs on the efficacy (by ADHD-RS-IV) or safety of medication in children with ADHD and psychiatric comorbidities. Further studies are required to support evidence-based drug selection for these populations.

Keywords: Adolescent; Attention deficit hyperactivity disorder; Child; Comorbidity; Pharmacotherapies

Key Summary Points

Why carry out this study?

Comorbid psychiatric conditions in children and adolescents with attention-deficit hyperactivity disorder (ADHD) occur frequently, complicate management, and are associated with substantial burden on patients and caregivers.

This systematic literature review summarizes the efficacy and safety of amphetamines, methylphenidate and derivatives, atomoxetine (ATX), and guanfacine extended-release (GXR) for children and adolescents with ADHD and comorbid autism spectrum disorders, oppositional defiant disorder, Tourette's disorder and other tic disorders, generalized anxiety disorder, and major depressive disorder.

What was learned from the study?

Effect sizes for ADHD Rating Scale IV total scores were available for ten randomized placebo-controlled trials and ranged from 0.46 to 1.0 for ATX and 0.92 to 2.0 for GXR across comorbidities.

Although the numbers and types of adverse events in children with comorbidities were consistent with those in children without comorbidities, treatment should be individualized to ensure that children can tolerate the lowest effective dose.

Further studies are required to support evidence-based drug selection for children with ADHD and psychiatric comorbidities.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.14387378>.

INTRODUCTION

Comorbid psychiatric conditions in children and adolescents with attention-deficit hyperactivity disorder (ADHD) are highly prevalent, complicate management and treatment [1, 2] and contribute to substantial burden on patients and caregivers [3, 4]. More than half of all children and adolescents diagnosed with ADHD have one or more psychiatric comorbidity, and more than one-quarter have two or more comorbidities [1]. Common comorbidities in children with ADHD include, but are not limited to, conduct disorders, particularly oppositional defiant disorder (ODD), Tourette's disorder and other tic disorders, generalized anxiety disorders, and major depressive disorder (MDD) [5]. Less is known about the prevalence of comorbid autism spectrum disorder, partly because of the evolution of the definition and diagnostic criteria for this condition [5].

In general, first-line treatment of children and adolescents with ADHD should include parent-based behavior management training and classroom-based behavioral training in combination with or before the administration

of pharmacological treatment [6]. Pharmacological treatments decrease ADHD symptom (i.e., inattention, hyperactivity, and impulsivity) severity and, combined with behavior training, contribute to improvements in functional outcomes, such as self-esteem, independence, social relationships, and educational status [7]. The pharmacological treatments currently recommended for use in adolescents and children include fast-acting psychostimulants (i.e., amphetamines, methylphenidate) and non-stimulants (i.e., atomoxetine [ATX], alpha-2 agonists) [6]. In contrast to the 2014 Japanese clinical guidelines, which recommend both stimulants and non-stimulants as first-line pharmacological treatment for children and adolescents (≥ 6 years) with ADHD [8], European and North American guidelines recommend stimulants as first-line pharmacological treatment, followed by non-stimulants, such as ATX or guanfacine extended-release (GXR), for those who do not respond to or cannot tolerate stimulants [7, 9–11]. In all settings, however, the presence of comorbidities adds complexity to the management of children and adolescents with ADHD [7, 8], and certain medications may be preferred or contraindicated depending on the comorbidities that are present.

Multiple systematic reviews and meta-analyses have assessed the efficacy and safety of medications for ADHD in children and adolescents [12–15]. Of the few systematic reviews and meta-analyses conducted in children and adolescents with comorbidities, most have focused on a particular comorbidity or medication [16–23]. The objectives of this systematic literature review are to summarize the efficacy and safety of medications, including amphetamine and its derivatives (AMPs), methylphenidate and its derivatives (MPHs), ATX, and GXR for treatment of children and adolescents with ADHD and the following common psychiatric comorbidities: autism spectrum disorders, ODD, Tourette's disorder and other tic disorders, generalized anxiety disorder, and MDD.

METHODS

A literature search protocol was developed for this study in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Sources and Search Terms

In accordance with the protocol, we searched MEDLINE (1946 to October 2, 2019) and Embase (1974 to October 2, 2019) via Ovid. Searches were adapted for each database and included keywords (Medical Subject Heading or Emtree) and free-text terms for ADHD, comorbidities (autism spectrum disorders, ODD, Tourette's disorder and other tic disorders, generalized anxiety disorder, MDD), and medications (AMPs, MPHs, ATX, GXR). Clonidine was not included because at that time it was not a universally approved medication for ADHD in children and adolescents. ClinicalTrials.gov was searched on October 29, 2019 (completed studies with results that included patients aged ≥ 6 years and < 18 years with ADHD). Searches were limited to studies in humans, with no restrictions on publication dates or language. The complete search strategies used for MEDLINE and Embase are available in the Electronic Supplementary Material (ESM): Electronic search strategies.

Eligibility Criteria

The inclusion criteria were as follows: studies of patients (aged ≥ 6 years and < 18 years) with a diagnosis of ADHD and any one or more of the specified comorbidities (autism spectrum disorders, ODD, Tourette's disorder and other tic disorders, generalized anxiety disorder, and MDD); single-arm or comparative studies including oral administration (any dose) of AMPs, MPHs, ATX, or GXR in ≥ 1 treatment arm and a treatment duration ≥ 7 days (to avoid single-dose studies or studies with limited

treatment durations); and studies reporting the clinical efficacy and/or safety of medications for ADHD symptoms.

For efficacy outcomes, only placebo-controlled randomized controlled trials (RCTs) or meta-analyses of RCTs of patients on active treatment were eligible. For safety outcomes, patients on active or maintenance treatment were included; all study types were eligible.

The main exclusion criteria were as follows: studies of adult (aged ≥ 18 years) patients with ADHD or patients diagnosed with ADHD using the Diagnostic and Statistical Manual of Mental Disorders (DSM), 2nd Edition; studies that included child and adolescent patients with ADHD only, did not state whether patients with comorbidities were included or excluded, and did not report results separately for patients with ADHD and comorbidities; studies of other drugs, such as anticonvulsants or atypical antipsychotics, other routes of administration, or single oral administration of treatments; or studies of patients with epilepsy or congenital risk factors (e.g., heart disease) or who were pregnant. Duplicate publications or publications reporting duplicate data, conference proceedings or abstracts, review articles, commentaries, and guidelines and consensus statements were not eligible.

Reference lists from relevant systematic reviews and meta-analyses were screened manually to identify any additional eligible studies.

Screening and Data Extraction

Searches were collated using bibliographic management software. An initial screen of the title and abstract of each publication was conducted by one individual (non-author) to remove duplicate publications and identify potential publications for inclusion. Inclusion was confirmed after a review of the full text of all potential publications by a second individual (non-author). For instances where inclusion was uncertain, the decision to include or exclude was resolved by consensus between the two individuals, and the authors reviewed and approved the articles identified for inclusion in the review. One individual extracted all data

into prespecified data tables and a second individual checked all extracted data; disagreements were resolved by consensus. Data were extracted into prespecified tables and included the study design, ADHD diagnosis criteria, percentage of patients with each comorbidity (as described in each publication), the primary efficacy outcome for each study, ADHD treatments administered (type, dose, duration), discontinuation rates, the number, age, and sex of patients enrolled in each treatment arm, and the efficacy and safety outcomes as described below.

Outcomes

Comorbidities are reported as described in each publication. The primary efficacy outcome measure was the ADHD Rating Scale IV (ADHD-RS-IV) total score (investigator and/or parent-rated), which is a validated measure of changes in ADHD symptom severity in response to treatment [24] and for which a minimal clinically important difference has been defined [25]. Secondary efficacy outcomes were ADHD-RS-IV subscale scores and the Clinical Global Impression-Improvement (CGI-I) scale and the Clinical Global Impression-Severity (CGI-S) scale for ADHD (score or response rate). Other clinical or behavioral outcomes for assessing the efficacy of treatments for reducing ADHD symptoms were retrieved but are not reported here. Safety outcomes related to treatment of ADHD were collected as reported and included the frequency and nature of treatment-related adverse events, changes in body weight, blood pressure, and heart rate or pulse rate, and data on exacerbation of ADHD or comorbidity symptoms.

Assessment of Study Quality

An assessment of the risk of bias for each placebo-controlled RCT reporting effect sizes or for which effect sizes could be calculated for the primary outcome was conducted using the Cochrane Collaboration Risk of Bias tool [26]. The Cochrane Collaboration tool involves an evaluation of the risk of bias in the following domains: generation of allocation sequence,

allocation concealment, masking of study personnel and participants, masking of outcome assessor, attrition, and selective outcome reporting. A study was defined as having a low risk of bias if zero domains were rated as high risk and ≤ 3 domains were rated as unclear, or as having a moderate risk of bias if zero or one domain was rated as high risk but ≥ 4 domains were rated as unclear; all other cases were assumed to have a high risk of bias [27].

Statistical Analyses and Data Synthesis

Quantitative data synthesis was not conducted because there were insufficient data to combine ADHD-RS-IV total scores or effect sizes. A systematic narrative synthesis is provided, with information presented in text and tables to summarize and explain the characteristics and findings of the included studies. Because quantitative data synthesis was not conducted, quantitative assessments of publication bias or assessments of outcome reporting bias were not conducted.

RESULTS

Literature Search Output

A total of 2177 publications/trials were retrieved (Fig. 1). The main reason for exclusion was duplicate publication, followed by publications/trials not conducted in patients with the comorbidities of interest. 72 publications/trials met all the eligibility criteria; of these, 69 reported on the primary and/or secondary efficacy outcomes [17, 18, 20, 28–46] and/or safety outcomes [16, 18, 19, 28–34, 36, 38–41, 43–91] and were included in the systematic review. Of the five meta-analyses and 37 placebo-controlled RCT publications/trials retrieved, 13 assessed patients with comorbid autism spectrum disorder, 14 with comorbid ODD, nine with comorbid Tourette’s disorder and other tic disorders, and six with comorbid generalized anxiety disorder and/or MDD (Table 1). The mean age of patients enrolled in most meta-analyses and placebo-controlled RCTs ranged from 7.3 to 14.6 years, and 62.1–100% were male (Table 1).

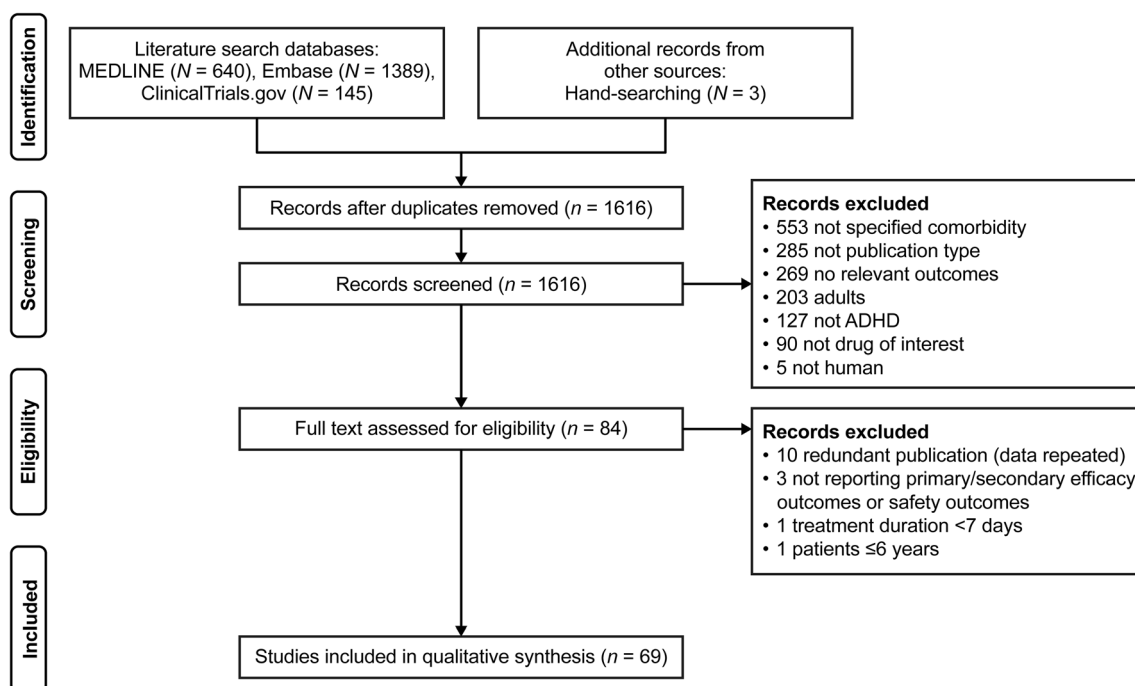


Fig. 1 Flow chart of publication selection process. *ADHD* Attention-deficit hyperactivity disorder

Table 1 Characteristics of included meta-analyses or randomized controlled trials categorized by type of comorbidity and treatment

Citation	Study design	ADHD diagnosis criteria	Key comorbidities	Primary efficacy measure	Treatment arms	Patients enrolled or included in analysis	Mean age, years (SD)	Male (%)	Treatment duration	Relevant outcome measure(s)
Autism spectrum disorder: MPHs										
Reichow, 2013 [19]	MA—3 trials reporting safety data	[66, 84, 92]	NR	PDD—NR%	CPRS, CTRS, SNAP-IV, DSM-IV, ADHD general scales	MPHs	NR	NR	NR	≥ 1 week
Safety										
Handen, 2000 [66]	RCT—crossover	ADHD symptoms	Autistic disorder: 69.2% PDD-NOS: 30.8% ODD: 53.8% ^a	NR	MPHs 0.3, 0.6 mg/kg, PBO	n = 13	7.4 (1.7)	76.9	1 week each	Safety
Kim, 2017 [70]	RCT—parallel	K-SADS-PL	Autistic disorder: 100% ODD: 37%	ADHD-RS-IV	MPHs 0.3 mg/kg MPHs 0.5 mg/kg	n = 9 n = 18	9.3 (2.9) 9.1 (3.1)	89 95	6 weeks	Safety
Pearson, 2013 [43]	RCT—crossover	DSM-IV-TR + ADHD symptoms	Autistic disorder: 79.2% PDD-NOS: 8.3%	NR	MPHs 0.21, 0.35, 0.48 mg/kg, PBO	n = 24	8.8 (1.7)	79.2	1 week each	CGI-I, CGI-S Safety
NCT00178503										
RUPP, 2005 [84]	RCT—crossover	ADHD symptoms	Autistic disorder: 71.2% PDD-NOS: 21.2% Asperger: 7.6%	ABC—hyperactivity	MPHs 2.5–5, 2.5–10, 5–20 mg/kg, PBO	n = 66 (RCT) n = 34 responders (OLE)	7.5 (2.2)	89.4	1 week each RCT + 8 weeks OLE	Safety
Autism spectrum disorder: ATX										
Patra, 2019 [18]	MA—3 trials	[36, 38, 50]	ADHD symptoms	NR	Parent-rated ADHD symptoms, social behavior, serious adverse events	ATX, PBO	n = 241		9.3–10.0	75–80
6–10 weeks	CGI-I Safety									
Arnold, 2006 [50]	RCT—crossover	DSM-IV	Autistic disorder: 43.8% PDD-NOS: 50% Asperger: 6.3%	ABC hyperactivity	ATX, PBO	n = 16	9.3 (2.9)	75.0	6 weeks each	Safety

Table 1 continued

Citation	Study design	ADHD diagnosis criteria	Key comorbidities	Primary efficacy measure	Treatment arms	Patients enrolled or included in analysis	Mean age, years (SD)	Male (%)	Treatment duration	Relevant outcome measure(s)
Handen, 2015 [36]	RCT—parallel	ADHD symptoms	Autistic disorder: 44.5% PDD-NOS: 39.1% Asperger: 16.4%	SNAP-IV and Home Situations Questionnaire	ATX + PT ATX PBO + PT PBO	<i>n</i> = 32 for each group	8.0 (1.9) 8.6 (2.3) 7.7 (1.5) 8.2 (2.4)	96.9 81.3 84.4 78.1	10 weeks	CGI-ADHD-I Safety
Harferkamp, 2012 [38]	RCT—parallel	DSM-IV-TR	Autistic disorder: 59.8% PDD-NOS: 33.0% Asperger: 5.2%	ADHD-RS-IV	ATX PBO	<i>n</i> = 48 <i>n</i> = 49 (RCT)	9.9 (2.7) 10.0 (2.9)	87.5 83.7	8 weeks RCT	ADHD-RS-IV (INV) CGI-ADHD-I Safety
NCT00380692					OLE	<i>n</i> = 88 (OLE)	10.0 (2.9)	86.3	+ 20 weeks OLE	Safety
NCT00498173 [41]	RCT—parallel	ADHD symptoms	Autistic disorder: 38.3% PDD-NOS: 38.3% Asperger: 23.3%	ADHD-RS-IV	ATX PBO	<i>n</i> = 29 <i>n</i> = 31	9.3 (2.6) 8.4 (2.1)	89.7 90.3	8 weeks	ADHD-RS-IV (parent:INV) Safety
Autism spectrum disorder: GXR										
Handen, 2008 [37]	RCT—crossover	ADHD symptoms	Intellectual disability or autism	NR	GXR, PBO	<i>n</i> = 11	7.3 (1.4)	90.9	6 weeks	CGI, CGI-S Safety
Seahill, 2015 [45]	RCT—parallel	ADHD symptoms	Autistic disorder: 82.3% PDD-NOS: 14.5% Asperger: 3.2%	ABC hyperactivity subscale—parent-rated	GXR PBO	<i>n</i> = 30 <i>n</i> = 32	8.5 (2.25)	86.7 84.4	8 weeks	ADHD-RS-IV (INV) CGI-I Safety
Oppositional defiant disorder: amphetamine										
Spencer, 2006 [46]	RCT—parallel	NR	ODD: 79.2%	SNAP-IV ODD subscale	AMPs PBO	<i>n</i> = 248 <i>n</i> = 60	10.6 (2.8) 10.5 (3.0)	68.5 71.7	4 weeks	CGI-ADHD-I Safety

Table 1 continued

Citation	Study design	ADHD diagnosis criteria	Key comorbidities	Primary efficacy measure	Treatment arms	Patients enrolled or included in analysis	Mean age, years (SD)	Male (%)	Treatment duration	Relevant outcome measure(s)
Oppositional defiant disorder: MPHs										
Connor, 2000 [55]	RCT—parallel	DSM-III-R	ODD/CD: 100%	NR	MPHs CLON	<i>n</i> = 8 for each group	8.9 (2.6) 9.3 (1.7)	100	12 weeks	Safety
Jahangard, 2017 [68]	RCT—parallel	DSM-IV	ODD: 100%	NR	MPHs + CLON MPHs MPHs + risperidone	<i>n</i> = 42 for each group	10.1 (2.4) 8.7 (1.3)	76.2 71.4	8 weeks	Safety
Klorman, 1990 [71]	RCT—crossover	DSM-III	ODD: 50% ODD + CD: 25% Adjustment disorder with depressive mood: 35.4%	NR	MPHs, PBO	<i>n</i> = 48	14.1 (1.7)	87.5	3 weeks each	Safety
Kolko, 1999 [72]	RCT—crossover	DSM-III-R	ODD: 56% CD: 44%	NR	MPHs 0.3, 0.6 mg/kg PBO	<i>n</i> = 22	NR	100	6 weeks	Safety
Oppositional defiant disorder: ATX										
Cheng, 2007 [17]	MA—2 trials [39, 42]	NR	ODD: NR%	ADHD-RS-IV	ATX PBO	<i>n</i> = 137 <i>n</i> = 76	NR	NR	NR	ADHD-RS-IV (parent:INNV) CGI-S
Schwartz, 2014 [20]	MA—9 trials	NR	ODD: various%	ADHD-RS-IV parent-rated	ATX PBO	<i>n</i> = 2158 <i>n</i> = 1539	NR	NR	4–18 weeks	ADHD-RS-IV (parent:INNV) CGI-S
Bangs, 2008 [30]	RCT—parallel	DSM-IV	ODD: 100%	SNAP-IV ODD subscale	ATX PBO	<i>n</i> = 156 <i>n</i> = 70	9.5 (1.9) 9.7 (1.9)	91.7 97.1	8 weeks	CGI-I, CGI-S Safety
Dell'Agnello, 2009 [32]	RCT—parallel	DSM-IV	ODD: 100%	SNAP-IV ADHD subscale	ATX PBO	<i>n</i> = 105 <i>n</i> = 32	9.7 (2.2) 10.0 (2.4)	93.3 90.6	8 weeks	CGI-ADHD-S Safety
Dittman, 2011 [33]	RCT—parallel	DSM-IV-TR	ODD: 100%	SNAP-IV ODD subscale	ATX PBO	<i>n</i> = 121 <i>n</i> = 59	10.9 (3.1) 11.1 (2.8)	86.0 81.4	9 weeks	CGI-S Safety
NCT00192023										
Garg, 2015 [63]	RCT—parallel	DSM-IV-TR	ODD: 100%	Vanderbilt ADHD Diagnostic Parent Rating Scale	MPHs ATX	<i>n</i> = 15 <i>n</i> = 22	8.7 (2.4) 9.1 (2.6)	80.0 77.3	8 weeks	Safety

Table 1 continued

Citation	Study design	ADHD diagnosis criteria	Key comorbidities	Primary efficacy measure	Treatment arms	Patients enrolled or included in analysis	Mean age, years (SD)	Male (%)	Treatment duration	Relevant outcome measure(s)
Kaplan, 2004 [39]	RCT—pooled	DSM-IV	ODD: 100%	ADHD-RS-IV	ATX PBO	n = 53 n = 45	9.8 (1.5) 10.2 (1.5)	79.2 80.0	9 weeks	ADHD-RS-IV (parent:INV) CGI-ADHD-I Safety
Newcorn, 2005 [42]	RCT—parallel	DSM-IV	ODD: 100%	ADHD-RS-IV	ATX 0.5 mg/kg ATX 1.2 mg/kg ATX 1.8 mg/kg PBO	n = 21 n = 27 n = 34 n = 34	11 (2.1)	76.5	8 weeks	ADHD-RS-IV (parent: INV) CGI-ADHD-S Safety
Oppositional defiant disorder: GXR										
Connor, 2010 [31] NCT00367835	RCT—parallel	DSM-IV-TR	ODD: 100%	CPRS-R:L oppositional subscale	GXR PBO	n = 138 n = 79	9.4 (1.7) 9.3 (2.0)	64.0 76.9	9 weeks	ADHD-RS-IV (INV) Safety
Tourette's disorder and other tic disorders: AMPs and MPHs										
Bloch, 2009 [16]	MA—4 trials [40, 52, 61]	NR	Tic disorders: NR	Change in rating scales for tic and ADHD severity	MPHs: NR PBO: NR	n = 191	NR	NR	NR	Safety
Castellanos, 1997 [52]	RCT—crossover	DSM-III-R	Tourette: 95% Motor tic: 5% ODD: 30% ^a Enuresis: 20% ^a	Tic severity (TSURS) and CTRS hyperactivity	MPHs, AMPs, PBO	n = 20	9.4 (2.0)	100	9 weeks	Safety
Gadow, 1999 [62]; Gadow, 2007 [61]; Gadow, 2011 [60]	RCT—crossover + OLE	DSM-III-R/ DSM-IV	Tourette: 96% Motor tic: 4%	YGTSS	MPHs 0.1, 0.3, 0.5 mg/kg PBO	n = 71 (RCT) n = 34 (OLE)	8.9 (1.9) 8.9 (1.9)	80.3 91.2	6 weeks 2 years	Safety
Law, 1999 [76]	RCT—parallel	DSM-III-R	Tics: 29.7%	Exacerbation or worsening of tic severity	MPHs PBO	n = 46 n = 45	8.4 (1.6) 8.3 (1.5)	80.4 82.2	52 weeks	Safety

Table 1 continued

Citation	Study design	ADHD diagnosis criteria	Key comorbidities	Primary efficacy measure	Treatment arms	Patients enrolled or included in analysis	Mean age, years (SD)	Male (%)	Treatment duration	Relevant outcome measure(s)
Tourette's Syndrome Study Group, 2002 [40]	RCT—parallel	DSM-IV	Tourette: 94% Motor tic: 5% Vocal tic: 0.8% ODD: 38% ^a	CASQ-T	MPHs	<i>n</i> = 37	10.7 (2.0)	92	8 weeks	CGI-ADHD-I
					CLON	<i>n</i> = 34	9.7 (1.8)	85		Safety
Tourette's disorder and other tic disorders: ATX Allen, 2005 [28]	RCT—parallel	DSM-IV	Tourette: 79.1% Motor tic: 29.7% Vocal tic: 17.6% ODD: 21.6% ^a	YGTSS total score	MPHs + CLON	<i>n</i> = 33	10.6 (1.9)	73		
					PBO	<i>n</i> = 32	9.7 (1.8)	91		
Tourette's disorder and other tic disorders: GXR Scahill, 2001 [44]	RCT—parallel	DSM-IV	Tourette: 59.0% Motor tic: 35.3%	NR	ATX	<i>n</i> = 76	10.9 (2.5)	92.1	18 weeks	ADHD-RS-IV (parent: INV)
					PBO	<i>n</i> = 72	11.5 (2.4)	84.7		CGI-S Safety
Generalized anxiety disorder and/or major depressive disorder: MPHs Abikoff, 2005 [48]	RCT—parallel	DSM-IV	Generalized anxiety: 78–100% Separation anxiety: 50–80% Social phobia: 28–30% ODD: 25–29% Anxiety: 41.8%	SNAP-IV ADHD subscale PARS	GXR	<i>n</i> = 17 for each group	10.4 (2.0)	91.2	8 weeks	ADHD-RS-IV (teacher: INV)
					PBO					CGI-I Safety
Diamond, 1999 [56]	RCT—parallel	DSM-III-R		NR	MPHs	<i>n</i> = 8	10.8 (2.6)	NR	8 weeks	Safety
					MPHs + fluvoxamine	<i>n</i> = 12	10.4 (2.7)			
Generalized anxiety disorder and/or major depressive disorder: ATX Bangs, 2007 [29]	RCT—parallel	DSM-IV	MDD: 100%	ADHD-RS-IV CDRS-R	+ Anxiety	<i>n</i> = 72	14.6 (1.8)	72.2	9 weeks	ADHD-RS-IV (parent: INV)
					MPHs	<i>n</i> = 70	14.2 (1.5)	74.3		CGI-S, CGI-I Safety

Table 1 continued

Citation	Study design	ADHD diagnosis criteria	Key comorbidities	Primary efficacy measure	Treatment arms	Patients enrolled or included in analysis	Mean age, years (SD)	Male (%)	Treatment duration	Relevant outcome measure(s)
Geller, 2007 [34]	RCT—parallel	DSM-IV	Anxiety: 100%	ADHD-RS-IV PARS	ATX PBO	n = 55 n = 58	12.2 (2.8) 11.8 (2.5)	62.1 67.4	12 weeks	ADHD-RS-IV (INV) CGI-S Safety
Griffiths, 2018 [35]	RCT—crossover	DSM-IV	Anxiety: 100% ODD: 55.3% ^a	Response inhibition, sustained attention, fearful facial emotion	ATX, PBO	n = 38	11.2 (2.7)	73.7	6 weeks each	ADHD-RS-IV (parent:INV) Safety
Kratochvil, 2005 [73]	RCT—parallel	DSM-IV	MDD: 45.7% Other mood: 15.6% Generalized anxiety: 33.5%	Safety and tolerability	ATX ATX + fluoxetine	n = 46 n = 127	11.6 (2.4) 11.2 (2.7)	65.2 74.8	5 weeks	Safety

ABC Aberrant Behavior Checklist, *ADHD* attention-deficit hyperactivity disorder, *ADHD-RS-IV* ADHD Rating Scale IV, *AMPs* amphetamine or a derivative, *ATX* atomoxetine, *CASQ-T* Conners' Abbreviated Symptom Questionnaire-Teacher, *CD* conduct disorder, *CDRS-R* Children's Depression Rating Scale-Revised, *CGI-I* Clinical Global Impression-Improvement, *CGI-S* Clinical Global Impression-Severity, *CLON* clonidine, *CPRS-R:L* Conners' Parent Rating Scale-Revised-Long Form, *CPRS* Conners' Parent Rating Scale, *CTRS* Conners' Teacher Rating Scale, *DSM-III-R* Diagnostic and Statistical Manual of Mental Disorders-3rd Edition Revised, *DSM-IV-TR* Diagnostic and Statistical Manual of Mental Disorders-4th Edition Text Revision, *ER* extended release, *GXR* guanfacine extended-release, *INV* investigator, *K-SADS-PL* Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime, *MA* meta-analysis, *MDD* major depressive disorder, *MPHs* methylphenidate or a derivative, *NR* not reported, *ODD* oppositional defiant disorder, *OLE* open-label extension, *PARS* Pediatric Anxiety Rating Scale, *PBO* placebo, *PDD-NOS* pervasive developmental disorder-not otherwise specified, *PT* parent training, *RCT* randomized controlled trial, *SD* standard deviation, *SNAP-IV* Swanson, Nolan, and Pelham Rating Scale-Revised, *TSURS* Tourette Syndrome Unified Rating Scale, *YGTS* Yale Global Tic Severity Scale

^a In addition to the comorbidity of interest and reported in ≥ 20% of patients

Efficacy

For primary and secondary efficacy, there were four meta-analyses [17, 18, 20, 39] and 18 placebo-controlled RCTs and associated extension studies [28–38, 40–46] (Table 1). Two meta-analyses/pooled analyses [17, 20] and 11 RCTs [28, 30, 31, 34, 35, 38, 39, 41, 42, 44, 45] reported ADHD-RS-IV total scores (investigator-rated, parent-investigator-rated, teacher-investigator-rated). Effect sizes were available for ten RCTs [28, 29, 31, 34, 35, 38, 39, 42, 44, 45] (Table 2), and the overall risk of bias was rated as low for six RCTs, moderate for three RCTs, and high for one RCT for which the risk of bias was unclear for all domains (Table 2; ESM Table S1).

Autism Spectrum Disorders

Among the eligible studies, most patients were diagnosed with autism spectrum disorder (38.3–100%), followed by pervasive developmental disorders-not otherwise specified (PDD-NOS) (8.3–50%), then Asperger's disorder (3.2–23.3%) (Table 1). When reported, approximately one-third to half of patients also had comorbid ODD (Table 1).

There were no studies on AMPs that assessed patients with comorbid autism spectrum disorders and no placebo-controlled RCTs on MPHs that assessed ADHD symptoms with ADHD-RS-IV (Table 1). There were two placebo-controlled RCTs on ATX [38, 41] and one placebo-controlled RCT on GXR [45] that assessed improvements in ADHD symptoms with ADHD-RS-IV. Of these, two studies [38, 45] showed significantly greater improvements in total scores and/or inattention and hyperactivity/impulsivity subscale scores with ATX and GXR compared with placebo (Table 2). Effect sizes for GXR and ATX were 2.03 and 0.87, respectively (Fig. 2).

There was one RCT on MPH [43], one meta-analysis [18] and two RCTs [36, 38] on ATX, and two RCTs on GXR [37, 45] that assessed secondary outcomes of CGI-I and/or CGI-S. CGI-I scores or response rates were consistently higher for MPHs, ATX, and GXR compared with placebo (ESM Table S2). There was one meta-

analysis [18] of 193 patients who participated in a placebo-controlled RCT [38] and crossover trial [36]. Although the quality of the included studies was assessed as low, significantly greater improvements in CGI-I scores were confirmed for ATX compared with placebo [18]. In one RCT [43] there was a significantly greater improvement in CGI-S with MPHs compared with placebo (ESM Table S2).

Oppositional Defiant Disorder

Almost all meta-analyses [17, 20] and RCTs [30, 32, 33, 39, 42] that assessed patients with ODD were focused on the efficacy of ATX (Table 1). There was one RCT on AMPs [46] that assessed a secondary efficacy outcome (CGI-ADHD-I), and no RCTs on MPHs that assessed the primary or secondary efficacy outcomes. Significantly greater improvements in ADHD-RS-IV total scores and/or inattention and hyperactivity/impulsivity subscale scores were reported in two RCTs [39, 42] assessing ATX and in the one RCT [31] assessing GXR. Findings for ATX were confirmed by one meta-analysis [17] of patients in two RCTs [39, 42] and one meta-analysis [20] of a subgroup of patients with ADHD and ODD in nine clinical trials. The effect sizes ranged from 0.47 to 0.72 for ATX and was 0.92 for GXR (Fig. 2). One subgroup meta-analysis directly assessed the effects of ATX using ADHD-RS-IV total scores among 3697 children with and without ODD [20]. No significant differences for ATX compared with placebo were found, irrespective of the proportion of children with ODD in each subgroup ($\leq 20\%$ ODD, 20 to $< 80\%$ ODD, and $\geq 80\%$ ODD) [20].

Findings from most eligible studies [17, 20, 30, 32, 33, 39, 42] reporting CGI-I and CGI-S with ATX were consistent with the findings for ADHD-RS-IV (ESM Table S2). In the one RCT [46] that assessed the efficacy of AMPs, significantly greater improvement in CGI-ADHD-I was reported for AMPs compared with placebo (ESM Table S2).

Tourette's Disorder and Other Tic Disorders

Of the one meta-analysis [16] and six RCTs [28, 40, 44, 52, 60–62, 76] (one with three

publications) retrieved, only three [28, 40, 44] reported efficacy outcomes (Table 1). Most patients were diagnosed with Tourette's disorder (59–96.3%) followed by motor or vocal tics (3.7–35.3%) (Table 1). When reported, over one-third of patients also had ODD (Table 1).

There were no RCTs on AMPs or MPHs that assessed the primary or secondary efficacy outcomes. Significantly greater improvements in ADHD-RS-IV total scores and/or inattention and hyperactivity/impulsivity subscale scores were reported for the two RCTs assessing ATX and GXR (Table 2). In these studies, the effect sizes for GXR and ATX were 1.23 and 0.6, respectively (Fig. 2). In all eligible studies, significantly greater improvements in CGI-I or CGI-S were reported for MPHs [40], ATX [28], and GXR [44] compared with placebo (ESM Table S2).

Generalized Anxiety Disorder and/or Major Depressive Disorder

There were no studies on AMPs or GXR that assessed patients with generalized anxiety disorder or MDD and no placebo-controlled RCTs on MPHs that assessed the primary or secondary efficacy outcomes (Table 1). Of the three placebo-controlled RCTs [29, 34, 35] that reported outcomes for patients with anxiety and MDD who were treated with ATX, significantly greater improvements in ADHD-RS-IV total scores and/or inattention and hyperactivity/impulsivity subscale scores compared with placebo were reported (Table 2). When reported, the effect sizes for ATX ranged from 0.46 to 1 (Fig. 2). Significantly greater improvements in CGI-S were reported for patients with comorbid anxiety and significantly greater CGI-I response rates were reported for patients with comorbid MDD (ESM Table S2).

Safety

For safety, there were four meta-analyses/pooled analyses [16, 18, 19, 39], 33 RCTs and associated extension studies [28–34, 36, 38, 40, 41, 43–46, 48, 50, 52, 55, 56, 60–63, 66–68, 70–73, 76, 84], 11 cohort studies [53, 54, 58, 69, 74, 79, 83, 86, 87, 90, 91], and 16 case reports or case series [47, 49, 51, 57, 59, 64, 65, 75, 77, 78,

80–82, 85, 88, 89]. Most of the meta-analyses and RCTs were conducted in patients with ADHD and autism spectrum disorders or ODD, and more information was available on treatment with MPHs and ATX in these patients, with very few studies on AMPs or GXR (Table 1). Most RCTs included fewer than 50 patients per treatment arm and most were placebo-controlled, with very few studies directly comparing pharmacological treatments (Table 1).

Adverse Events

When reported, the numbers and types of adverse events with AMPs, MPHs, ATX, and GXR from patients with comorbid autism spectrum disorders (RCTs [18, 19, 37, 41, 43, 45] and cohort studies [54, 58, 69, 83, 86, 90, 91]) and ODD (RCTs [30–33, 39, 46, 55, 63, 71, 72] and cohort studies [74, 79, 87]) were consistent with the numbers and types of adverse events observed with these treatments in patients without comorbidities (ESM Table S3). Two meta-analyses assessed the safety of MPHs in patients with comorbid PDD [19] and ATX in patients with comorbid autistic disorder [18]. The meta-analysis of MPHs [19] included three RCTs [66, 84, 92] and showed that, compared with placebo, decreased appetite, insomnia, depressive symptoms, irritability, and social withdrawal were significantly associated with MPHs. The meta-analysis of ATX [18] included three RCTs [36, 38, 50] and showed that, compared with placebo, nausea and vomiting, decreased sleep, and decreased appetite were significantly associated with ATX. Most adverse events reported with ATX during active treatment decreased in frequency during longer-term treatment [67].

Very few RCTs or cohort studies reported adverse events in patients with comorbid tic disorders [28, 52, 53] or with anxiety and/or MDD [29, 34, 73]. When reported, the adverse events associated with AMPs and MPHs [52], ATX [28, 29, 34, 73], and GXR [53] were consistent with the adverse events associated with these treatments in patients without comorbidities. One study found no differences in parent- or teacher-rated side effects between patients with and without comorbid anxiety after 4 months of treatment with MPHs following a titration phase [56]. There were no reports

Table 2 Summary of efficacy for ADHD Rating Scale IV outcomes

Study design Citation	Treatment comparison	Patients randomized (<i>n</i>)	Patients analyzed (<i>n</i>)	Main findings for ADHD-RS-IV	Risk of bias [27]	Effect size vs. PBO for ADHD-RS-IV total score
Autism spectrum disorder						
RCT Harfterkamp, 2012 [38]	ATX 1.2 mg/kg vs. PBO	97	ATX: 48 PBO: 49	Significantly greater improvements in total score, inattention, and hyperactivity/impulsivity subscale scores with ATX Mean difference from PBO: total score (– 6.7, $P < 0.001$), inattention subscore (– 2.7, $P = 0.003$), hyperactivity/impulsivity subscore (– 3.9, $P < 0.001$)	Low	0.87 ^a (INV)
RCT NCT00498173 [41]	ATX vs. PBO	60	ATX: 29 PBO: 31	Numerically greater improvements in total score, inattention, and hyperactivity/impulsivity subscale scores with ATX; statistical analyses NR	NR	NR
RCT Scahill, 2015 [45]	GXR < 3 mg/day vs. PBO	62	GXR: 30 PBO: 32	Significantly greater improvements from baseline in total score and hyperactivity/impulsivity subscale scores with GXR ($P < 0.0001$)	Low	2.03 (INV)
Oppositional defiant disorder						
MA Cheng, 2007 [17]	ATX vs. PBO (MA; dose NA)	213	ATX: 137 PBO: 76	Significantly greater improvements in total score (SMD – 0.70, $P < 0.05$), inattention (SMD – 0.69, $P < 0.05$), and hyperactivity/impulsivity (SMD – 0.60, $P < 0.05$) subscale scores with ATX	NR	NR
MA Schwartz, 2014 [20]	ATX vs. PBO (MA; dose NA)	3928	ODD ≤ 20% ATX: 521 PBO: 470 ODD > 20 to < 80% ATX: 1062 PBO: 677 ODD ≥ 80% ATX: 575 PBO: 392	Total score for ATX was superior to PBO (SMD: – 0.64, $P < 0.0001$) Total scores for ATX were similar irrespective of the presence of comorbid ODD (SMD ≤ 20% – 0.48 vs. SMD > 20 to < 80% – 0.63 vs. SMD ≥ 80% – 0.64, $P = 0.17$)	NR	NR
RCT Connor, 2010 [31]	GXR (< 4 mg/day) vs. PBO	217	GXR: 138 PBO: 79	Significantly greater improvements in total score with GXR (least squares mean difference from baseline = 23.8 vs. 11.5, $P < 0.001$)	Low	0.92 (INV)
RCT Kaplan, 2004 [39]	ATX (< 2 mg/kg) vs. PBO	98	ATX: 53 PBO: 45	Significant improvements in total score, inattention, and hyperactivity/impulsivity subscale scores compared with baseline with ATX but not PBO Significantly greater total score response rates (≥ 25% reduction) with ATX (65.4%) vs. PBO (36.4%), $P = 0.007$	Low	0.72 (parent:INV)
RCT Newcorn, 2005 [42]	ATX (0.5, 1.2, 1.8 mg/kg) vs. PBO	115	ATX0.5: 21 ATX1.2: 27 ATX1.8: 34 PBO: 31	Significantly greater improvements in total score (mean change from baseline – 13.4, $P = 0.03$) and inattention subscale scores (mean change from baseline – 6.9, $P = 0.02$) with ATX 1.8 mg/kg	High	ATX0.5: 0.47 ^a ATX1.2: 0.49 ATX1.8: 0.69 (parent:INV)

Table 2 continued

Study design Citation	Treatment comparison	Patients randomized (<i>n</i>)	Patients analyzed (<i>n</i>)	Main findings for ADHD-RS-IV	Risk of bias [27]	Effect size vs. PBO for ADHD-RS-IV total score
Tourette's disorder and other tic disorders						
RCT Allen, 2005 [28]	ATX (< 1.5 mg/kg) vs. PBO	148	ATX: 76 PBO: 72	Significantly greater improvements in total score, inattention, and hyperactivity/impulsivity subscale scores with ATX compared with PBO	Moderate	0.6 (parent:INV)
RCT Scahill, 2001 [44]	GXR (< 4 mg/day) vs. PBO	34	GXR: 17 PBO: 17	Significantly greater improvements in (teacher-rated) total score, inattention, and hyperactivity/impulsivity subscale scores with GXR	Moderate	1.23 (teacher:INV)
Generalized anxiety disorder and major depressive disorder						
RCT Bangs, 2007 [29]	ATX (< 1.8 mg/day) vs. PBO	142	ATX: 72 PBO: 70	Significantly greater improvements in total score from baseline with ATX compared with PBO	Low	0.84 (parent:INV)
RCT Geller, 2007 [34]	ATX (< 1.2 mg/kg) vs. PBO	176	ATX: 55 PBO: 58	Significantly greater improvements in total score (mean difference compared with PBO: - 10.5, $P < 0.001$), inattention, and hyperactivity/impulsivity subscale scores with ATX Significantly higher response rate ($\geq 25\%$ reduction in total score from baseline) with ATX (61.8% vs. 12.1%, $P < 0.001$)	Moderate	1 (INV)
RCT Griffiths, 2018 [35]	ATX (< 1.4 mg/kg) vs. PBO	140	ATX: 38 PBO: 38	Significantly greater improvements in ADHD-RS-IV total score with ATX	Low	0.46 (parent:INV)

NA Not applicable, SMD standardized mean difference; for other abbreviations, see footnote of Table 1

^a Calculated from published data

of treatment-emergent suicidal ideation in patients with comorbid anxiety [34] or comorbid MDD [29] and no exacerbation of depressive symptoms in patients with comorbid MDD [29] who were treated with ATX.

Adverse events reported in case reports of patients receiving MPHs included exacerbation of obsessive behavior [82], visual and/or auditory hallucinations [47, 49, 51, 64], severe agitation, and hyperactivity and/or irritability in three patients with ODD after switching from risperidone to MPHs [85]. Adverse events reported in case reports of patients receiving ATX included Raynaud's phenomenon [65] and onset of mania and auditory hallucinations when a patient titrated up to 40 mg/day [78]. Lethargy, bradycardia, and hypertension were reported in a patient with ADHD and Tourette's disorder who ingested threefold his prescribed dose of GXR [57].

Cardiovascular Parameters and Body Weight

Cardiovascular parameters and body weight were not consistently reported among the studies retrieved and were variable across studies (ESM Table S3). When reported, findings from RCTs were variable and showed that, compared with placebo, patients experienced decreased body weight with AMPs [46], MPHs [61, 71], and ATX [28–30, 32, 34], increased heart rate and/or blood pressure with MPHs [61] and ATX [28–30, 32, 34, 50], and decreased blood pressure and pulse rate with GXR [31, 45] during active treatment (ESM Table S4). Dose-related changes in body weight, blood pressure, and heart rate [60, 61] were reported in patients with tic disorders receiving MPHs during active treatment. However, following 2 years of maintenance therapy, there were no significant changes in expected body weight and, although

significant increases in systolic blood pressure (+6 mmHg) and heart rate (approx. 10 bpm) were reported, none were considered to be clinically relevant [62].

Tic Exacerbation or Onset

Exacerbation or onset of vocal and/or motor tics was reported among several cohort studies and case reports in patients treated with MPHs [79, 80, 88] and ATX [75, 77, 81]. However, findings from several RCTs and a meta-analysis of MPH studies showed that worsening of tic severity or onset of new tics was not different from placebo in patients with comorbid tic disorders who were treated with MPHs or ATX [16, 28, 40, 60–62, 76]. For MPHs, worsening of tic severity was associated with higher drug doses [40, 52] and did not increase in frequency or severity during long-term maintenance therapy [62].

DISCUSSION

This is the first systematic review to conduct a comprehensive assessment of the efficacy and safety of treatments for children and adolescents with ADHD and psychiatric comorbidities. Despite the number of studies retrieved, most meta-analyses and RCTs were focused on the safety of MPHs or the efficacy and safety of ATX. In comparison, there was limited information on the efficacy of MPHs or the efficacy and safety of GXR, and very limited information on the use of AMPs.

Consistent with the findings from a comprehensive network meta-analysis in children and adolescents with ADHD [13], when reported, treatments were associated with significant improvements in ADHD symptoms during active treatment, regardless of comorbidity. Using clinician-rated composite measures for the change in severity of ADHD core symptoms, the network meta-analyses conducted by Cortese et al. [13] showed that effect sizes (Fig. 2b) were 1.02 for AMPs, 0.78 for MPHs, 0.67 for GXR, and 0.56 for ATX, which confirm the current European and North American recommendations for treatment of ADHD in children and adolescents [9]. Although Cortese et al. did

not analyze treatments by specific comorbidities, they did conduct a sensitivity analysis excluding studies that solely enrolled patients with psychiatric/neurological comorbidities. In general, exclusion of these studies did not change the results, suggesting that comorbidities do not affect the efficacy of treatments for ADHD symptoms [13]. In the current review, which focused especially on children and adolescents with comorbidities, effect sizes for ADHD-RS-IV total scores across all comorbidities ranged from 0.46 to 1.0 for ATX and 0.92 to 2.0 for GXR. Subsequent to this literature review, a pooled analysis of four placebo-controlled RCTs enrolling children and adolescents with ADHD, of whom at least 10% had ODD, has become available [93]. Findings from this analysis showed that dose-optimized GXR was associated with significant improvements in ADHD-RS-IV total scores in patients with and without ODD. The effect sizes for the pooled population were 0.88 and 0.73 for children and adolescents with and without ODD, respectively. A numerically higher effect size for patients with ODD was thought to be due to these patients having greater symptom severity than those without ODD and, therefore, greater capacity for improvement. Although effect sizes based on ADHD-RS-IV were not available for AMPs or MPHs in the current study, effect sizes based on CGI-S from a registry study of MPHs suggest that there may be variation in the effect of MPHs between comorbidities (ADHD only: 0.63; with comorbidities: 0.89; with ODD: 0.58; with anxiety: 1.61) [2]. In addition, a head-to-head comparison of ATX with MPHs [21], which pooled data for 1391 children with ADHD and comorbid ODD from seven RCTs, found no differences in the improvement in ADHD-RS-IV total scores or subscale scores between patients treated with ATX or MPHs.

In the current study, the types of adverse events reported for AMPs, MPHs, ATX, and GXR in children and adolescents with comorbidities were consistent with those reported from studies of children and adolescents predominantly without comorbidities [94–96], and there was no evidence to suggest major differences in the safety and tolerability of treatments by comorbidity. This is consistent with findings from the

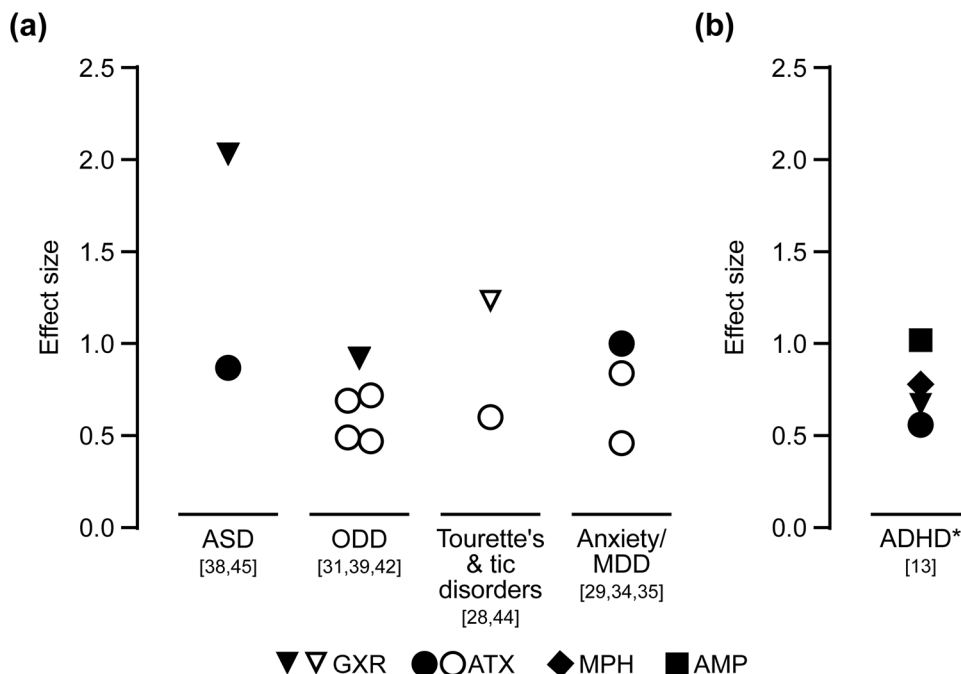


Fig. 2 Summary of effect sizes from **a** included studies for which the effect size (standardized mean difference) was reported [28, 29, 31, 34, 35, 39, 42, 44, 45] or could be calculated [38, 42] for the effect of treatment compared with placebo on ADHD symptoms (ADHD-RS-IV total scores) in children and adolescents with ADHD and at least one of the prespecified comorbidities, and **b** as reported by Cortese et al. [13] for analyses where studies of children with psychiatric and neurological comorbidities were not excluded. Asterisk indicates that the sensitivity analysis suggested that the presence of psychiatric

comorbidities did not significantly affect the results when studies of children with psychiatric and neurological comorbidities were excluded. Filled symbols indicate investigator-rated ADHD-RS-IV scores; open symbols indicate parent- or teacher-investigator-rated ADHD-RS-IV scores. *ADHD* attention-deficit hyperactivity disorder, *ADHD-RS-IV* ADHD Rating Scale IV, *AMP* amphetamine, *ASD* autism spectrum disorder, *ATX* atomoxetine, *GXR* guanfacine extended-release, *MDD* major depressive disorder, *MPH* methylphenidate, *ODD* oppositional defiant disorder

Italian National ADHD Registry study [94], which showed no consistent pattern for an increased rate of adverse events for children and adolescents with and without comorbidities. Furthermore, the sensitivity analysis in the Cortese et al. [13] network meta-analysis showed a slight improvement in tolerability for ADHD medications when studies that solely enrolled children and adolescents with psychiatric or neurological comorbidities were excluded. Although AMPs, MPHs, ATX, and GXR are associated with changes in body weight and/or cardiovascular factors [94–96], these factors were not well reported across the RCTs, particularly for AMPs and MPHs, which is likely to have contributed to reporting bias. In addition,

although two crossover RCTs [43, 50] reported no significant differences between MPHs or ATX compared with placebo for changes in heart rate or blood pressure in children with autism spectrum disorder, these studies enrolled fewer than 25 patients and were not likely to be sufficiently powered for cardiovascular events. Despite this, a recent claims-based analysis from the USA assessed the risk of serious cardiovascular events in children with ADHD (2.2 million) or autism spectrum disorder (326,221) who had been prescribed psychostimulants or ATX [97]. Findings from these large cohorts of children aged 3 to 18 years showed no increased risk of serious cardiovascular events in either cohort. As demonstrated by the exacerbation or

onset of adverse events, including tics, obsessive thoughts, and agitation, reported in the case reports and cohort studies of children and adolescents receiving MPHs and ATX, the ability of children and adolescents with comorbidities to tolerate ADHD treatment in clinical practice was based on many factors, including the dose level and formulation (i.e., sustained or immediate release), whether doses were fixed or titrated, and individual responses. The results from these smaller reports are consistent with those from long-term clinical practice studies, such as the Italian National ADHD Registry study [94], and emphasize the need for ADHD treatments to be individualized to patients and prescribed at the lowest effective dose, as well as supporting current guidelines [7, 10, 11] that selection of pharmacotherapy should depend on the ability of patients to tolerate treatment and whether ADHD or the comorbidity or comorbid symptoms are to be treated first.

The key strength of this review was that it focused on studies of children and adolescents with multiple comorbidities in addition to ADHD, and therefore represents the large proportion of patients with ADHD who require complex management strategies. In addition, most of the eligible placebo-controlled RCTs had a low to moderate risk of bias. However, the outcomes of this review are limited because very few studies were available that assessed efficacy using the primary ADHD core symptom rating scale, ADHD-RS-IV, and there was a high level of heterogeneity among the studies in the efficacy and safety outcomes reported. In particular, patient discontinuation is an important measure of the safety and tolerability of pharmacological treatments and may contribute to study bias. However, we were not able to include this measure because very few of the eligible studies reported dropout rates or reported dropout rates consistently between dose titration and dose maintenance. In addition, because there were very few studies that directly compared the efficacy and safety of ADHD treatments between children and adolescents with and without comorbidities, we were limited in the comparisons that we could make. It is important to acknowledge that, in addition to ADHD symptom response to treatment, an assessment

of functional outcomes and comorbid symptoms are needed to comprehensively manage patients with comorbid ADHD. This is demonstrated by the diverse number of rating scales that were reported as the primary efficacy measure in this study (see Table 1). These scales ranged from those designed to measure ADHD symptom frequency, severity, and improvement to those specific to one symptom and those that included items associated with comorbid symptoms and functional outcomes [24]. As our objective was to compare treatment response specifically with respect to the severity of ADHD symptoms, we focused especially on the ADHD-RS-IV because it is a validated measure of treatment response for which a minimal clinically important difference has been defined [25].

CONCLUSIONS

Overall, findings from this systematic review showed that there is limited information available from placebo-controlled RCTs on the efficacy of drug treatments in reducing ADHD symptoms, in terms of ADHD-RS-IV in children and adolescents with ADHD and psychiatric comorbidities. The available evidence suggests that the safety profiles of the treatments assessed are consistent with the profiles in children without comorbidities. However, further studies are required to support evidence-based drug selection for children with ADHD and comorbidities and, in particular, there is a need for studies that compare the efficacy and safety of treatments in children and adolescents with and without comorbidities and between treatments.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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