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Using ADHD Medications to Treat Coexisting ADHD and Reading Disorders: A Systematic Review

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Abstract

Attention-deficit/hyperactivity disorder (ADHD), the most common pediatric neurobehavioral disorder, frequently presents with co-existing reading disorders (RD). Despite this, it is unclear whether medication improves symptoms and function in children with comorbid ADHD and RD. We present a systematic review of studies investigating the effects of ADHD medications on ADHD symptoms, academic outcomes, and neuropsychological measures in this important group.

Keywords

Pharmacotherapy; methylphenidate; atomoxetine; pediatric; CNS; psychiatric; cognition; attention-deficit/hyperactivity disorder; ADHD; learning disorders/disabilities; reading disorders/disabilities; dyslexia

Background

Attention-deficit/hyperactivity disorder (ADHD), the most prevalent pediatric neurobehavioral disorder, is present in 7-8% of children.¹⁻³ ADHD is associated with significant impairments in academic, social, and occupational functioning⁴ that are frequently compounded by co-occurring disorders. A recent nationally representative study reported that two-thirds of children with ADHD have a coexisting developmental-behavioral condition, of which the most common was learning disorder (LD).⁵ Of particular importance

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are comorbid reading disorders (RD), as prior studies suggest that 25-48% of children with ADHD have co-existing RD.⁶ The high degree of intersection between ADHD and RD (ADHD+RD) is not surprising given evidence of their common genetic and neuropsychological underpinnings. Twin studies suggest that shared genetic influences account for a portion of the comorbidity between ADHD and reading disorders,⁷⁻⁹ with additional studies pinpointing specific genetic variants that may be linked to ADHD+RD.^{10,11} Furthermore, similar neuropsychological deficits in ADHD and RD highlight the possibility of overlapping neural factors. For example, working memory deficits have been reported in both ADHD and RD.¹²⁻¹⁴ In addition, processing speed issues have been observed in children with ADHD as well as those with reading disorders.¹⁵⁻¹⁸ Rapid automatized naming deficits, which have long been recognized in children with RD,¹⁹ have also been documented in children with ADHD-only.^{20,21}

Although there is abundant evidence of the overlap between ADHD and RD in epidemiologic, genetic, and neuropsychological investigations, the degree of benefit children with coexisting ADHD+RD receive from ADHD-specific medications is less clear.^{22,23} Among parents of children with ADHD, it is known that parental concern about academic performance, which one would expect to be intensified in cases of coexisting ADHD+RD, is linked to medication initiation.²⁴ Therefore, an increased understanding of whether ADHD medications improve symptoms and functioning for this prevalent group has much salience in the clinical setting. Indeed, studies of medication efficacy in children with ADHD and other neurobehavioral comorbidities have reported differential effects compared to what is seen with ADHD-only: methylphenidate, the most commonly prescribed ADHD medication, has lower response rates in children with ADHD and coexisting autism spectrum disorders compared to typically developing children with ADHD.²⁵⁻²⁸ Of note, some clinicians have expressed concern that children with coexisting ADHD and RD may not experience as much improvement in ADHD symptoms with medications as children with ADHD-only, and as a result may be less likely to prescribe medication to this group.²⁹ Effects of ADHD medications on learning in children with ADHD+RD are another important consideration. There is evidence that children with ADHD but no comorbid learning disability demonstrate improvement on some academic skills with medication,³⁰ but the affected skills are limited and these gains may not generalize to those with RD. If a reading disorder in a child with ADHD represents a distinct biologically based condition, it is possible that medical treatment that reduces primary ADHD symptoms may not lead to corresponding improvement in learning. Therefore, we undertook a systematic review of the literature to evaluate the evidence regarding effects of Food and Drug Administration (FDA)-approved ADHD medications (e.g., psychostimulants, atomoxetine, guanfacine, and clonidine) in children with coexisting ADHD+RD on the following domains: 1) ADHD symptoms, 2) academic outcomes, and 3) neuropsychological measures. Due to the sparsity of literature available on this topic, in addition to reviewing double-blind studies comparing medication effects to placebo (PB), we have also included open-label studies which evaluated medication effects by comparing participants' performance on pre- and post-measures.

Search Strategy and Evidence Grading Procedures

This systematic review followed reporting guidelines set out in the preferred reporting items for systematic reviews and meta-analyses (PRISMA³¹) statement. We searched PubMed,³² PsycINFO,³³ Cochrane Database of Systematic Reviews,³⁴ and the Education Resources Information Center (ERIC)³⁵ database for English-language articles published in peer-reviewed journals after 1980 using combinations of the following terms: “ADHD” (encompassing both the acronym and the full term), “learning disabilities,” “learning disorders,” “treatment,” “intervention,” “therapy,” and “medication.” Additional searches were conducted using relevant drug names (methylphenidate, amphetamine, dextroamphetamine, atomoxetine, guanfacine, clonidine). We hand-searched the reference lists of retrieved articles, including review articles and epidemiological studies, to identify any additional relevant references. Searches were conducted independently by two researchers (TF, NE) in order to ensure all relevant records were identified.

The authors reviewed titles, abstracts, and full text to determine relevance for inclusion. We included articles that met the following criteria: (1) clinical trial, (2) children were identified as having both RD and ADHD (identified using the Diagnostic and Statistical Manual of Mental Disorders criteria appropriate for the time at which the study was conducted) (3) participants received treatment with an FDA-approved medication for ADHD, such as methylphenidate or atomoxetine, and (4) treatment efficacy was evaluated using at least one valid outcome measure for ADHD symptoms, academic achievement/skills, or neuropsychological functioning. We excluded studies that enrolled fewer than 10 children with ADHD-RD, or had subjects who also had a comorbid intellectual disability, specific genetic syndrome or autism spectrum disorder (ASD), or who were over 18 years of age.

Two authors (TF, JF, WB, or EC) independently abstracted data from each article using the McMaster Effective Public Health Practice Project Quality Assessment Tool for quantitative studies.³⁶ This tool was annotated for crossover studies using criteria proposed by Ding et al.³⁷ and Mills et al.³⁸ Discrepancies were resolved through consensus. We used Oxford Centre for Evidence-Based Medicine criteria³⁹ to rate each study and assess the overall strength of the body of evidence for treatment recommendations.

Search Retrieval Results

We identified 443 independent records of potential relevance. After applying inclusion and exclusion criteria, we identified 14 treatment studies to be included in this review (Figure 1). Studies focused on the effects of stimulant medications or atomoxetine in children with ADHD and coexisting RD, as we did not identify any studies which focused on clonidine or guanfacine effects in this clinical group. Two studies^{40,41} also included some children who had ADHD and comorbid math disorders or ADHD with both comorbid reading disorders and math disorders.

Stimulant Effects on ADHD Symptoms in Children in ADHD+RD

We identified five controlled clinical trials (CCT) and one cohort analytic open-label study that investigated effects of stimulant medications on ADHD symptoms in children with

ADHD+RD (Table 1), with four studies focusing exclusively on children with coexisting reading disorders⁴²⁻⁴⁵ and two studies including children with documented coexisting mathematics disorders (MD) as well as RD.^{40,41} All studies focused on effects of methylphenidate treatment, except for a non-blinded controlled trial by Tamm et al.⁴³ Tamm et al. employed a protocol providing ADHD behavioral parent training as well as medication treatment with varying agents depending on participant response, yielding a sample treated with methylphenidate (46%), amphetamine and/or dextroamphetamine (42%), atomoxetine (4%) and guanfacine (6%).⁴³ Given that most children in Tamm et al.'s study were treated with psychostimulants, it will be discussed in this section.

Blinded direct observations of ADHD-related behaviors

In a double-blind placebo-controlled (DBPC) crossover trial of children with ADHD+LD (RD and/or MD), methylphenidate led to improvements in directly-observed ADHD-related behaviors.⁴⁰ In this study, Williamson et al.⁴⁰ found that children with ADHD+LD treated with methylphenidate (MPH) were more attentive (Swanson, Kotkin, Alger, M-Flynn, and Pelham [SKAMP] Attention subscale least square mean scores [SE] on MPH=6.5[0.68] vs. on PB=10.7[0.68]; $p < .0001$) and better behaved (SKAMP Deportment subscale least square mean scores [SE] on MPH=3.6[0.70] vs. on PB=8.2[0.71]; $p < .0001$).

Parent-reported ADHD symptoms

Five studies compared parent ratings of ADHD symptoms on stimulants to baseline or placebo condition ratings in children with ADHD+RD. Kupietz et al. conducted a DBPC trial and found improvements in parent hyperactivity-impulsivity ratings with methylphenidate (mean parent ratings [adjusted for baseline score] for the PB, MPH 0.3mg/kg, MPH 0.5mg/kg, and MPH 0.7mg/kg groups were 2.51, 2.39, 2.36, and 1.8 respectively; main effect of dose $F_{3,40}=4.28$, $p < 0.01$).⁴⁵ However, another DBPC trial of children with ADHD+RD by Tannock et al.⁴² did not observe beneficial effects of methylphenidate on parent-reported inattention or hyperactivity-impulsivity. A non-blinded CCT by Tamm et al.⁴³ documented large beneficial effects of ADHD treatment on parent ADHD symptom ratings ($d=1.1$ and $d=0.8$ for ratings of inattention and hyperactivity-impulsivity respectively). A CCT (not blinded for ADHD symptom assessment) by Williamson et al.⁴⁰ of children with ADHD and coexisting RD and/or MD found that methylphenidate significantly improved (all $p < 0.001$) caregiver ratings of child inattention [Baseline score(SD)=20.8(4.2), Final visit score(SD)=6.0(3.6)], hyperactivity/impulsivity [(Baseline score (SD)=16.1(6.4), Final visit score (SD)=3.4(2.9)], and ADHD total symptoms scores [Baseline score (SD)=36.9(8.4), Final visit score (SD)=9.4(5.7)]. An additional non-blinded cohort analytic study by Dykman et al.⁴⁴ found that methylphenidate had significant positive effects on children with ADHD+RD ($p < 0.001$), with large effect sizes for mean change in parent-rated inattention ($d=1.57$) and hyperactivity/impulsivity ($d=1.14$).

Teacher-reported ADHD symptoms

Five studies compared teacher ratings of ADHD symptoms on stimulants to baseline or placebo condition ratings in children with ADHD+RD. The DBPC trial by Kupietz et al. found a significant main effect of dose on teacher ADHD symptom ratings ($F_{3,35}=11.73$, $p < 0.01$, mean teacher ratings [adjusted for baseline score] for the PB, MPH 0.3mg/kg, MPH

0.5mg/kg, and MPH 0.7mg/kg groups were 2.43, 1.93, 1.85, and 1.62 respectively), indicating a trend for greater improvement with increasing methylphenidate dose which did not vary by symptom domain (i.e., no difference in magnitude of improvements seen for the inattention versus hyperactivity factors).⁴⁵ Intention-to-treat analyses in a DBPC trial of children with ADHD+RD by Tannock et al.⁴² also showed significant albeit modestly sized beneficial effects of methylphenidate on teacher-rated hyperactivity/impulsivity (MPH group adjusted *t* score mean=59.6 vs. PB group adjusted *t* score mean=68.7, *r*=.34, *p*=.04). In contrast, Tannock et al. did not observe significant methylphenidate effects for teacher inattention ratings in intention-to-treat analyses, although additional “as treated” analyses did show improvement with methylphenidate on *both* teacher-rated inattention and hyperactivity/impulsivity (both *ps*<0.01). A non-blinded CCT by Tamm et al. found large effects of ADHD treatment on teacher ADHD symptoms ratings for children with ADHD +RD (*d*=1.4 and *d*=1.0 for improvements in inattention and hyperactivity/impulsivity ratings respectively). A CCT by Williamson et al.⁴⁰ of children with ADHD and coexisting RD and/or MD (not blinded for ADHD symptom assessment) observed that methylphenidate significantly improved teacher ratings of child ADHD total symptom scores [Baseline score(SD)=27.8(12.1), Final visit score(SD)=10.9(11.5), *p*<0.001], with effects on inattention and hyperactivity/impulsivity not reported separately. An additional non-blinded cohort analytic study by Dykman et al.⁴⁴ found that methylphenidate had significant positive effects (*ps*<0.001) on children with ADHD+RD, with large effect sizes for mean change in teacher-rated inattention (*d*=2.19) and hyperactivity/impulsivity (*d*=1.59).

Frequency of positive response to methylphenidate

Two investigations assessed stimulant medication response rates in children with ADHD and RD and/or MD.^{40,41} The DBPC crossover study by Grizenko et al.⁴¹ found that, according to a consensus clinical response rating developed by the research team, the proportion of children with ADHD+LD who responded to methylphenidate was significantly lower than the proportion of methylphenidate responders with ADHD-only (55% vs. 75%, *p*=0.03). However, further analyses showed that the difference was mainly due to poor methylphenidate response in children with ADHD+MD (*p*=0.03), while children with ADHD+RD did not show a differential methylphenidate response compared to those without coexisting RD (*p*=0.33). Methylphenidate response rates were 67% for those with ADHD +RD only, 55% for those with both ADHD+both RD and MD, and 37% for those with ADHD+MD only. The CCT by Williamson et al.,⁴⁰ for which clinician ratings were not blinded, found that 79% of participants with ADHD+LD (both RD and MD included but not analyzed separately) achieved ratings by non-blinded clinicians of “much improved” or “very much improved” with methylphenidate treatment.

Summary of findings

One DBPC trial and the three non-blinded trials observed significant benefits of stimulants on parent-reported ADHD symptom ratings in ADHD+RD samples, while one DBPC trial did not. All identified trials (two DBPC and three non-blinded) documented improvements in teacher ratings of ADHD symptoms with stimulant treatment in children with ADHD +RD. There is evidence from one study that stimulant medication treatment in children with ADHD+RD may improve child attention and behavior when assessed via blinded direct

observations. The available literature also suggests that methylphenidate response rates may be lower in ADHD+MD but not ADHD+RD compared to those with ADHD-only, although this conclusion is based on a single study assessing response rates in ADHD+RD separately from ADHD+MD.

Stimulant Effects on Academic Outcomes in Children in ADHD+RD

We found five controlled clinical trials and two cohort analytic open-label study which investigated stimulant medication effects on academic outcomes in children with ADHD +RD (Table 2), with most studies focusing on methylphenidate effects on reading.

Reading

Five controlled clinical trials^{40-43,46} and one open-label cohort analytic study⁴⁴ investigated effects of stimulant medications on reading outcomes in children with ADHD+RD. A variety of reading-related constructs were evaluated, including decoding, phonological awareness, reading fluency, reading comprehension, and spelling.

Meeting diagnostic criteria for reading disability.—An analysis of data from the landmark Multimodal Treatment of ADHD (MTA) randomized controlled trial by Hechtman et al.⁴⁶ found that among children meeting criteria for ADHD+RD at baseline, there was a borderline significant decrease in likelihood of meeting criteria for RD at the end of the 14 month trial in the rigorously titrated methylphenidate group compared to the community care group (OR[95% CI]=2.03[0.98-4.20], $p=0.055$) and in the combined methylphenidate and behavior treatment group compared to the community care group (OR[95% CI]=3.33[0.92-12.11], $p=0.067$), although the methylphenidate and combined treatment groups showed no advantage over the behavior treatment-only group on this outcome.

Word reading/decoding and phonological awareness.—Effects of methylphenidate on decoding and phonological awareness skills have not been consistent in trials of children with ADHD+RD. In a DBPC trial of children with ADHD+RD, Bental et al.⁴⁷ found significant effects of methylphenidate treatment on word decoding and pseudoword decoding accuracy ($p=0.03$ and $p=0.04$ respectively on Nitzan Diagnostic Battery [NDB] measures) but not on NDB phonemic synthesis or phonemic deletion subtests. In their DBPC trial, Tannock et al.⁴² found significant effects of methylphenidate in ADHD+RD on speech-sound discrimination skills ($F[1, 58]=7.17$, $p=.003$, on the Goldman-Fristoe-Woodcock Sound Analysis subtest], but not word attack or word identification (Woodcock Reading Mastery Tests-Revised [WRMT-R] subtests, Keyword Test, Test of Transfer). In a cohort analytic study, Keulers et al.⁴⁸ found that methylphenidate led to significantly greater improvements in word decoding (assessed on the One Minute Test and Three Minutes Test) and non-word decoding skills (assessed on the Klepel Test) for children with ADHD+RD compared to ADHD-only group. However, in a CCT of children with ADHD+RD by Tamm et al.,⁴³ word reading and pseudoword decoding skills (assessed using the Wechsler Individual Achievement Test-3rd Edition) improved more with a reading skills intervention than with stimulant medication treatment.

Reading fluency.—In their DBPC trial, Williamson et al. found significant benefits of methylphenidate on reading fluency in children with ADHD and RD and/or MD [Dynamic Indicators of Basic Early Literacy Skills reading fluency mean score(SD)=92.6(34.8) with MPH vs. 85.0(38.2) with PB, $p=0.001$].

Reading Comprehension.—Two DBPC trials evaluated effects of methylphenidate on reading comprehension in ADHD+RD. In a sample of children with ADHD+RD, Tannock et al.⁴² found no significant effects of methylphenidate on reading comprehension skills on the WRMT-R. In a sample including children with ADHD+RD and/or ADHD+MD, Williamson et al.⁴⁰ found borderline significant benefits of methylphenidate on reading comprehension [Gray Silent Reading Test mean score(SD)=83.6(14.9) with MPH vs. 78.5(22.3) with PB, $p=0.099$].

Spelling

The DBPC trial of children with ADHD+RD by Bental et al.⁴⁷ did not find significant effects of methylphenidate on spelling accuracy (assessed by copying sentences from the Test of Hand Writing Quality).

Mathematics

We identified two DBPC trials^{40,42} and one cohort analytic open-label trial⁴⁴ which investigated effects of methylphenidate on math outcomes in children with ADHD+RD. In a DBPC crossover trial of children with ADHD and coexisting RD and/or MD, Williamson et al.⁴⁰ found significant benefits of methylphenidate on math computation skills [Permanent Product Math Test arithmetic problems correct least squares mean score(SD)=95.7(3.2) with MPH vs. 76.7(3.2) with PB, $p<0.0001$]. Tannock et al.⁴² also found that methylphenidate had significant beneficial effects on arithmetic skills ($F(1, 55)=7.79$, $p=.01$, on Wide Range Achievement Test-Revised) in a DBPC trial of children with ADHD+RD. Similarly, an open label study of children with ADHD+RD by Dykman et al.⁴⁴ found beneficial effects of methylphenidate on arithmetic performance (20-minute task consisting of addition and subtraction problems, $d=0.26-0.34$, $p<0.01$).

Handwriting

In a DBPC crossover trial of children with ADHD and coexisting RD and/or MD, Williamson et al.⁴⁰ found significant benefits of methylphenidate on handwriting [Test of Handwriting Skills-Revised mean score (SD)=90.0 (21.2) with MPH vs. 85.7(21.1) with PB, $p=0.0001$].

Summary of findings

Effects of stimulant medications on reading skills have been mixed in prior studies of children with ADHD+RD. Although only three studies have assessed effects of methylphenidate on math performance in children with ADHD+RD, all documented significant improvement in computation performance with treatment. The single available trial evaluating methylphenidate effects on handwriting in children with ADHD+RD showed positive treatment effects.

Stimulant Effects on Neuropsychological Outcomes in Children in ADHD

+RD

We identified three DBPC crossover trials^{40,45,47} and one open-label cohort analytic study⁴⁸ that investigated effects of methylphenidate on neuropsychological outcomes in children with ADHD+RD (Table 2).

Paired-associate learning

In their DBPC trial of children with ADHD+RD, Kupietz et al. found that methylphenidate reduced errors in paired-associate learning at higher doses (0.5mg/kg and 0.7mg/kg) at the end but not beginning of the trial (end of trial mean errors [adjusted for baseline] on PB, MPH 0.3mg/kg, MPH 0.5mg/kg, and MPH 0.7mg/kg 2.6, 2.8, 1.8, and 1.0 respectively; dose*time interaction $F_{3,41}=3.34$, $p<0.05$).⁴⁵

Rapid automatized naming skills

In a DBPC trial that evaluated effects of methylphenidate on children with ADHD+RD, Bental et al.⁴⁷ reported beneficial effects of active treatment compared to PB on the Rapid Automatized Naming test of digits ($t=-0.214$, $p=0.04$).

Reaction time variability

In a DBPC crossover trial of children with ADHD and coexisting RD and/or MD, Williamson et al.⁴⁰ found significant benefits of methylphenidate on reaction time variability [Test of Variables of Attention mean score(SD)=87.4(26.7) with MPH vs. 63.2(21.9) with PB, $p<0.0001$].

Visual attention and task-switching

An open-label trial of children with ADHD+RD by Dykman et al.⁴⁴ documented improvements with methylphenidate on visual task-switching (Trail Making Test-Trails B, $ES=0.29$, $p<0.001$) but not visual attention (Trail Making Test-Trails A, $p>0.05$).

Visual processing speed and sustained attention

Two open-label studies of children with ADHD+RD have assessed effects of methylphenidate on visual processing speed (using the Weschler Intelligence Scale for Children-Revised Coding subtest), and both found beneficial effects. Keuler et al.⁴⁸ documented large beneficial effects of methylphenidate on visual processing speed ($\eta_p^2=0.52$, $p<0.001$), as did Dykman et al.⁴⁴ ($ES=1.06$, $p<0.001$). Keuler et al.⁴⁸ also found large significant effects of methylphenidate on a sustained visual attention cancellation task in children with ADHD+RD ($\eta_p^2=0.56$, $p<0.001$ for attention accuracy and $\eta_p^2=0.43$, $p<0.001$ for attention speed on the Bourdon-Vos Test).

Visual-spatial working memory

In a DBPC trial of ADHD+LD (RD and/or MD), Williamson et al.⁴⁰ reported benefits of methylphenidate on visual spatial working memory using the Wide Range Assessment of Memory and Learning task [Finger Windows Forwards mean score(SD)=12.8(4.3) with

MPH vs. 11.0(3.2) with PB, $p=0.002$; Finger Windows Backwards mean score(SD)=9.7(3.6) with MPH vs. 8.6(4.3) with PB, $p=0.02$].

Additional neuropsychological constructs

In a small sample of children with ADHD+RD (N=25), Bental et al.⁴⁷ did *not* find significant effects of methylphenidate on response inhibition, planning, rule abstraction/set-shifting, verbal fluency, and verbal working memory, as assessed using the following measures: the Matching Familiar Figures Test, Porteus Maze, Wisconsin Card Sorting Test, Animal Retrieval and Food Retrieval Tests, listening sentence span test, and listening numbers span test. Similarly, Kupietz et al. did not observe improvements in short term visual memory (assessed via Sprague and Sleator's Short-term Memory task) with methylphenidate in ADHD+RD.⁴⁵

Summary of findings

The few available publications on children with ADHD+RD assessing effects of stimulant medications on neuropsychological functioning suggest that methylphenidate may have benefits on paired-associate learning, rapid automatized naming skills, reaction time variability, sustained attention, visual processing speed, visual-spatial working memory, and visual task-switching, but more studies are needed to confirm these results.

Atomoxetine Effects on ADHD Symptoms in Children in ADHD+RD

We identified three independent samples investigating atomoxetine effects on ADHD symptoms in children with ADHD+RD, two of which were examined in DBPC trials^{49,50} and one which was examined in cohort analytic open-label studies.^{51,52}

Parent-reported ADHD symptoms

Effects of atomoxetine on parent-reported ADHD symptoms in children with ADHD+RD were assessed in three samples.⁴⁹⁻⁵² All studies reported significant improvements in parent ratings of ADHD symptoms. Medium to large effect sizes (ES) were observed in the DBPC trials, and large ES were seen in the open-label trials. Specifically, in the DBPC crossover trial by de Jong et al.,⁴⁹ parent-reported ADHD symptoms diminished after taking atomoxetine in children with ADHD+RD (medium to large ES of $\eta_p^2=0.23$, $p=0.01$). In a DBPC trial by Wietecha et al.,⁵⁰ atomoxetine led to significantly greater improvement than PB in parent ratings of inattentive, hyperactive-impulsive, and ADHD total symptom scores ($ps=0.02$ to 0.002 , $d=-0.40$ to -0.53). In an open label cohort reported on by both Sumner et al.⁵² and Shaywitz et al. (2014),⁵¹ for the ADHD+RD group, improvements with atomoxetine were seen in parent-reported inattentive, hyperactive-impulsive, and ADHD total symptom scores (all $ps<0.001$), with improvement ES ranging from $d=1.12$ to 2.27 [mean change from baseline to endpoint in inattentive, hyperactive-impulsive, and total symptom scores was -10.5 , -7.7 , and -17.7 respectively].

Teacher-reported ADHD symptoms

We identified only one study evaluating the effects of atomoxetine on teacher ratings of ADHD symptoms in ADHD+RD. In a DBPC trial by Wietecha et al.,⁵⁰ atomoxetine led to

significantly greater improvement than PB in teacher ratings of ADHD inattentive symptom scores ($p=0.02$, $d=-0.68$) for children with coexisting RD, but there was no significant atomoxetine-related improvements in teacher-reported hyperactive-impulsive or ADHD total symptom scores.

Summary of findings

In children with ADHD+RD, atomoxetine had significant beneficial effects on parent ratings of inattentive and hyperactive-impulsive symptoms in three independent samples, with larger effect sizes seen in open-label than in placebo-controlled trials. Significant effects of atomoxetine on teacher ratings of inattention but not hyperactivity-impulsivity were also observed in the single study which evaluated this outcome.

Atomoxetine Effects on Academic Outcomes in Children in ADHD+RD

We found three independent trials (two DBPC and one cohort analytic open label trial)^{49,51-53} in which academic outcomes of atomoxetine treatment in ADHD+RD were evaluated. Each of the three trials evaluating effects of atomoxetine on specific academic outcomes focused on reading-related outcomes, with none reporting effects on additional outcomes such as mathematics.

Reading

Effects of atomoxetine on reading in children with ADHD+RD were evaluated in two DBPC^{49,53} and one open-label^{51,52} trial. In their DBPC crossover trial of children with ADHD+RD, De Jong et al. did not observe significant improvements in lexical decision-making (distinguishing real words and pseudowords) with atomoxetine.⁴⁹ In the DBPC trial by Shaywitz et al. (2017),⁵³ children with ADHD+RD did have significantly greater improvement in elision skills (the ability to remove phonological segments from spoken words to form other words) on the Comprehensive Test of Phonological Processing (CTOPP) with atomoxetine compared to PB ($p<0.02$, $d=0.50$). However, this study did not find significant effects of atomoxetine on any of their eight other CTOPP outcomes, seven Woodcock Johnson III reading-related outcomes (including both reading decoding and reading comprehension measures), five Gray Oral Reading Test-4 outcomes, and three Test of Word Reading Efficiency outcomes.⁵³ In contrast, in their open-label studies evaluating the same cohort of children with ADHD+RD, Shaywitz et al. (2014)⁵¹ and Sumner et al.⁵² documented significant improvements with atomoxetine on Kaufman Test of Educational Achievement (K-TEA) Reading Decoding, Reading Comprehension and Reading Composite measures. Specifically, these groups found a K-TEA Reading Decoding improvement $d=0.53$ (mean change in score +5.6 from pre to post, $p<0.01$), a Reading Comprehension improvement $d=0.35$ (mean change in score +9.8 from pre to post, $p<0.001$), and a Reading Composite improvement $d=0.45$ (mean change in score +8.1 from pre to post, $p<0.001$).

Spelling

The effect of atomoxetine on spelling in children with ADHD+RD was evaluated in one DBPC⁵³ and one open-label trial. Significant improvements in spelling with atomoxetine were not seen in either study.^{52,53}

Summary of findings

There is little to no evidence regarding beneficial effects of atomoxetine on reading outcomes in children with ADHD+RD in DBPC studies, although significant improvements in reading decoding and comprehension with atomoxetine were seen in an open-label trial. Neither of the two studies assessing atomoxetine effects on spelling found significant beneficial effects.

Atomoxetine Effects on Neuropsychological Outcomes in Children in ADHD +RD

Three trials (two DBPC^{49,50} and one open-label^{51,52}) investigating effects of atomoxetine on neuropsychological outcomes in children with ADHD+RD were identified. The neuropsychological constructs evaluated included response inhibition, verbal working memory, and visual-spatial working memory.

Response inhibition

One study evaluated atomoxetine effects on response inhibition in children with ADHD +RD. In a DBPC crossover trial by de Jong et al.,⁴⁹ borderline significant effects ($p=0.07$) of atomoxetine on response inhibition were observed for the ADHD+RD group, with faster reaction times on the Stop Signal Paradigm seen while on atomoxetine versus PB.

Verbal working memory

One DBPC⁵⁰ and one open-label trial^{51,52} evaluated atomoxetine effects on verbal working memory in ADHD+RD. Using the Working Memory Test Battery for Children [WMTB-C], the open-label trial by Shaywitz et al. (2014) and Sumner et al.^{51,52} found significant benefits of atomoxetine on the Phonological Loop Working Memory domain (based on the Digit Recall, Word List Matching, Word List Recall and Non-word List Recall subtests, standard score mean change=20.2 [SE 8.9], $p=.05$), while a DBPC trial by Wietecha et al.⁵⁰ did *not*. These studies also documented conflicting results on the WMTB-C Central Executive Working Memory domain (based on the Listening Recall, Counting Recall and Backwards Digit Recall subtests): the DBPC trial⁵⁰ found that atomoxetine led to significantly greater improvement compared to PB ($p=0.01$, $d=0.68$), while the open-label trial did not observe significant effects of atomoxetine on this domain.^{51,52}

Visual-spatial working memory

Two DBPC^{49,50} and one open-label trial^{51,52} evaluated effects of atomoxetine on verbal working memory in ADHD+RD. In their DBPC crossover trial, de Jong et al.⁴⁹ found that visual-spatial working memory (assessed on the Corsi Block Tapping Test) improved with atomoxetine compared to PB (ES medium to large as $\eta_p^2=0.13$, $p=0.01$) in children with

ADHD+RD. However, in another DBPC trial⁵⁰ as well as an open-label trial^{51,52} in children with ADHD+RD, atomoxetine did *not* improve visual-spatial working memory (assessed using the WMTB-C Visuospatial Sketchpad score, which is based on Block Recall and Mazes Memory subtests).

Summary of findings

Effects of atomoxetine on verbal and visual-spatial working memory were mixed in studies of children with ADHD+RD. The single study assessing atomoxetine effects on response inhibition in ADHD+RD found borderline significant beneficial effects.

Overall Strength of Evidence

The limited body of evidence suggests that treatment with ADHD medication can be associated with some improvements in ADHD symptoms, select academic outcomes, and specific neuropsychological impairments in children with co-existing ADHD and RD. Medication effects were generally more robust for ADHD symptoms than for academic or neuropsychological outcomes. We found largely consistent evidence that these two medications can improve ADHD symptoms in coexisting ADHD and RD, with the quality of the available studies rated as moderate to strong for methylphenidate (Oxford Centre for Evidence-Based Medicine³⁹ level 2b for four studies and 1b- for two studies) and as moderate for atomoxetine (Oxford level of 2b for three trials). Notably, the evidence for atomoxetine rests primarily on studies of parent-reported symptom ratings, with only one trial documenting beneficial effects on teacher symptom ratings, while beneficial effects of methylphenidate were observed on teacher symptom ratings in five studies and on blinded direct behavior observations in one study. In the case of academic outcomes, there was consistent evidence across the few available studies that methylphenidate can improve math computation performance in children with ADHD+RD, with the quality of available studies generally rated as moderate (Oxford level of 2b for three studies). On the other hand, we found weak evidence for improvement in reading outcomes with methylphenidate (inconsistent findings across studies) and atomoxetine (inconsistent findings across studies) in this group. There is emerging evidence that methylphenidate can improve performance on select neuropsychological measures in children with ADHD+RD, but the quality of evidence is considered to be weak at this time due to the identification of only 1-2 studies investigating each domain. We did not find evidence suggesting improvement in neuropsychological test performance with atomoxetine in the few available ADHD+RD trials (inconsistent or negative findings).

Limitations of the Available Evidence

As noted by the tempered strength of evidence ratings, these findings should be interpreted with caution given the sparsity of the available literature and its numerous limitations. We endeavored to capture these limitations systematically by abstracting data from each study using the EPHPP Quality Assessment Tool.³⁶ The “Comments” columns in Tables 1-6 highlight notable sources of bias in individual studies. Special attention should be paid to patterns of weakness across studies. For example, among the nine studies assessing stimulant effects in ADHD+LD, three excluded children with a prior history of stimulant

intolerance or poor response,⁴⁰⁻⁴² thus likely overestimating the beneficial effects of methylphenidate. The predominance of Caucasian participants (or a lack of reporting of participants' racial backgrounds) also constrains generalizability of the methylphenidate study findings. In addition, all of the trials evaluating atomoxetine effects in ADHD+RD were funded by and study authors had affiliations with Eli Lilly and Company (Indianapolis, IN), the manufacturer of Strattera (atomoxetine branded formulation), which may represent a perceived conflict of interest. However, given that public agencies often lack the capacity to fund studies needed to further understanding of medication effects, it should be noted that studies sponsored by pharmaceutical companies can fill this important gap and thereby help to improve clinical care. There is also a risk that reported atomoxetine effects are inflated given the degree of attrition (<80% completed the trial)^{50,53} or failure to report level of drop-out⁴⁹ in the DBPC studies, as poor response is a primary reason for withdrawal from medication trials. By and large, both methylphenidate and atomoxetine studies were also of relatively short duration, with only the stimulant trial by Hechtman et al. assessing medication treatment longer than one year (e.g., 14 months),⁴⁶ while a longer observation period is likely needed to capture changes in academic skills that accrue over time. The extreme heterogeneity of the academic and neuropsychological measures employed also makes it difficult to draw conclusions across studies. Even when common measures were employed across studies, differences in analytic methods and inconsistent reporting of effect sizes hamper efforts to compare or pool findings.

Medication Effects on ADHD Symptoms in ADHD+RD versus ADHD-only

Despite these limitations, the available literature can help clinicians and families to understand the benefits that medication may confer upon children with ADHD+RD, and how this may compare to what is seen in children with ADHD-only. The body of evidence does suggest that, as with ADHD-only, that methylphenidate and atomoxetine can effectively reduce ADHD symptoms in children with ADHD+RD. However, whether methylphenidate response rates and effect sizes are similar in ADHD+RD and uncomplicated ADHD is not completely clear. Methylphenidate response rates in ADHD+RD were similar to what is observed in more general pediatric ADHD samples (77%)^{54,55} in studies by Williamson et al⁴⁰ (79%) and Grizenko et al⁴¹ (67%), while the ATX studies did not assess response rates. The observed magnitudes of effect in the studies reviewed were not consistently equivalent to the large effect size seen for methylphenidate ($d=1.0$) and the medium to large effect size seen for atomoxetine ($d=0.63$)⁵⁶ in children with uncomplicated ADHD. Effect sizes were varied in the few DBPC trials assessing impact of methylphenidate on core ADHD symptoms in ADHD+RD: one trial observed large effect sizes for reductions in teacher- and parent-reported ADHD symptoms at the highest administered methylphenidate dose (0.7mg/kg)⁴⁵ and another found improvements of large effect size for direct observations of attention and deportment,⁴⁰ while a third found only modestly size methylphenidate-related improvements in teacher hyperactivity-impulsivity ratings and no significant effects on teacher- and parent-rated inattention or parent-rated hyperactivity-impulsivity in intent-to-treat analyses.⁴² In the two DBPC trials assessing atomoxetine's impact on ADHD symptoms in ADHD+RD, one trial found medium⁵⁰ and another found medium to large⁴⁹ effects sizes for parent ratings of ADHD symptoms, while

the single trial assessing impact on teacher symptom ratings found medium to large effect sizes for inattention and no significant effects for hyperactivity-impulsivity.⁵⁰

Medication Effects on Academic Outcomes in ADHD+RD versus ADHD-only

Our review of studies focused on children with coexisting ADHD and RD found mixed methylphenidate effects on reading measures, consistent beneficial methylphenidate effects on math outcomes, and little evidence for beneficial atomoxetine effects on reading outcomes. The methylphenidate math-related findings in ADHD+RD samples are consistent with findings in ADHD-only samples, for which a recent meta-analysis documented beneficial effects of methylphenidate on math productivity and accuracy.³⁰ We are unable to find a point of comparison for methylphenidate's mixed effects on phonological processing outcomes in ADHD+RD samples due to the paucity of prior research on these outcomes in children with uncomplicated ADHD. Our review found little evidence regarding medication effects on *long-term* academic outcomes in children with ADHD+RD other than a borderline significant reduced likelihood of participants maintaining their RD status after 14 months of stimulant medication treatment in the MTA trial.⁴⁸ Intriguingly, some prior research focused on academic functioning in ADHD-only samples *over years* has shown that youth who take stimulant medication may have some improvements in standardized academic achievement test scores.⁵⁷⁻⁶⁰ However, all of the long-term studies in uncomplicated ADHD samples are limited by their lack of control for some important potential confounding variables. Unlike methylphenidate, there has been little prior study of either short-term or long-term atomoxetine effects on standardized academic achievement test outcomes in uncomplicated ADHD samples,^{23,61,62} so it is not possible to provide further contextualization of the findings in ADHD+RD samples.

Medication Effects on Neuropsychological Outcomes in ADHD+RD versus ADHD-only

Neuropsychological test performance has long been of interest as a marker for how medications may scaffold brain functioning in children diagnosed with ADHD, although the association between performance on neuropsychological tests and real-world academic and behavioral functioning is limited.⁶³⁻⁶⁵ Given the compounded difficulties experienced by children with coexisting ADHD and RD, clinicians and families are eager to understand the potential of ADHD medications to ameliorate execution dysfunction in this group. As has been observed in many but not all studies of children with uncomplicated ADHD,^{54,66-69} the few available studies of medication effects on neuropsychological functioning in ADHD +RD provide some evidence that methylphenidate may improve rapid automatized naming, sustained attention, reaction time variability, and paired associate learning, as well as visual-spatial working memory, processing speed, and task-switching. Methylphenidate-related improvements in certain of these neuropsychological domains may be particularly salient for improving academic functioning in children with ADHD+RD. For example, rapid automatized naming deficiencies, weaknesses in sustained attention, slow processing speed, and working memory deficits have all been implicated in RD.^{17,70,71} Compared to methylphenidate, improvements in executive functioning in ADHD+RD do not appear to be

as robust with atomoxetine. Although studies in ADHD-only samples show an emerging pattern that atomoxetine may improve working memory⁷²⁻⁷⁵ and response inhibition,^{72,76,77} the available literature in ADHD+RD did not provide convincing documentation of atomoxetine's beneficial effects on these domains, as effects were either mixed or borderline significant.

Future Directions

Collectively, the studies included in this review provide some insights into the potential for medication treatment to improve both core ADHD symptoms as well as specific skills related to academic achievement in reading and math in children with ADHD+RD. Nevertheless, future research is required to address challenges with the existing literature, as well as broader questions about the relationship between attention and learning disorders, and the extent to which treatment can ameliorate academic underachievement in children with coexisting ADHD and RDs.

Future intervention studies investigating treatment effects in ADHD+RD should enroll children who are treatment naïve, or who are enrolled without knowledge of prior treatment response, to avoid biases that may arise by excluding children with a history of poor response to a specific medication. Similarly, additional intervention studies should focus on children who have ADHD along with the same, well-defined deficit (e.g., impaired phonological awareness) rather than a heterogeneous array of different deficits related to reading, so that the precise impact of medication can be evaluated. The studies cited in this review demonstrate that medication may differentially impact academic performance in the various domains (e.g., reading versus math). This presumably reflects the differing extent to which attention concentration and the various executive functions are directly related to the task. For example, the most consistent finding related to medication treatment and academic functioning in uncomplicated ADHD samples is improvement in speed of completing schoolwork. Work speed may be more related to performance of some academic tasks (e.g., math computation worksheets) than others (e.g., demonstrating reading comprehension through expository writing). Determining the extent to which medication may improve the academic performance of children with ADHD+RD beyond improving speed and demonstration of rote skills is critically needed. In particular, written expression is an important area for future investigation: some studies suggest it is the most challenging academic domain for children with ADHD, as it depends heavily on organization and initiation as well as attention and concentration. Furthermore, because many children with ADHD have academic impairment in multiple academic domains, treatment response for various combinations of learning problems should be characterized. Future studies should also expand beyond investigation of methylphenidate and atomoxetine effects in ADHD+RD to investigate the impact of amphetamine-, guanfacine-, and clonidine-based preparations.

Moreover, because medication may impact academic functioning by improving learning in response to instruction and practice over time, long-term treatment studies in children with ADHD+RD are needed. Study duration must be sufficient to permit assessment of changes in specific academic skills, which are unlikely to change significantly in weeks or even months. It will also be important to conduct studies that combine ADHD medication

treatment with evidence-based educational interventions for specific learning difficulties, such as phonologically based reading instruction. Ultimately, improving care for children with coexisting ADHD and RD will require clinical effectiveness studies that evaluate long-term academic achievement as a function of baseline ADHD/RD status, as well as medication treatment and educational interventions received over time.

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Figure 1. PRISMA diagram of the article selection process.

ADHD = Attention-deficit/hyperactivity disorder

ADHD+LD = Coexisting attention-deficit/hyperactivity disorder and learning disorder

ASD = Autism spectrum disorder

LD = Learning disorder

RD = Reading disorder

Table 1. Clinical Trials Evaluating Effects of Stimulants on ADHD Symptoms in Children with Coexisting ADHD and Reading Disorder

Source and Study Design	Sample Size of Children with ADHD+LD and Characteristics	Duration and Dose of Medication Treatment	Efficacy Measures	Findings	Comments	Oxford Quality Rating
Dykman RA et al (1991) Cohort analytic ^a	-N=82 had ADHD+RD -7-11 years old -Analyzed sample was 100% male and Caucasian -RD criteria: IQ 90 AND WRAT reading and spelling subtest SS <90	-4 week trial -Treatment with low MPH dose (0.3mg/kg BID) and high MPH dose (0.6mg/kg BID)	-Parent- and teacher-reported ADHD symptom ratings (Conners questionnaires and ADD behaviors listed in DSM-III)	-Parent-rated and teacher-rated IA and HI symptoms improved with MPH.	-Data on MPH effects analyzed for only 78% (N=64) of the ADHD+RD group	2b
Grizenko N et al (2006) Randomized, DBPC crossover trial	-N=42 had ADHD+LD (N=22 had RD+MD, N=12 had RD, N=8 had MD) -8-12 years old -85% male, race not specified -RD criteria: WRAT reading performance 2 years or more below grade level -MD criteria: WRAT math performance 2 years or more below grade level	-2 week trial (1 week of MPH and 1 week of PB) -MPH dose was 0.25mg/kg BID	-Consensus clinical response rating made by blinded research team based on parent- and teacher-reported ADHD symptom ratings, direct behavior observations, and neuropsychological test of sustained attention	-Children with ADHD +MD had lower MPH response rates than children with ADHD-only, while the ADHD+RD and ADHD-only groups did not differ in MPH response rates.	-Children with a prior history of MPH intolerance were excluded	2b ^c
Kupietz S et al (1988) Controlled clinical trial ^b with DBPC methodology	-N=58 had ADHD+RD -7-13 years old -% male and racial not specified -RD criteria: met DSM-III criteria for developmental RD and had reading grade level (based on composite score from the PIAT, GMRT, and DST) indicating an achievement rate 75% of typical achievement rate	-28 week trial -Children were randomly assigned to 1 of 4 conditions: PB, MPH 0.3 mg/kg, MPH 0.5 mg/kg, or MPH 0.7 mg/kg	-Parent-reported HI symptom ratings (Conners Abbreviated Rating Scale) -Teacher-reported ADHD symptom ratings (Conners Teacher Rating Scale)	-Parent-rated HI symptoms improved with MPH. -Teacher-rated IA and HI symptoms improved with MPH.	-Data on MPH effects analyzed for 81% of the sample (N=47)	1b-
Tamm L et al (2017) Controlled clinical trial ^b	-N=78 had ADHD+RD -Grades 2-5 -68% male and 71 -RD criteria: IQ 70 AND SS <90 on WJIII Letter Word Identification subtest, Word Attack subtest, or Basic Reading Skills composite.	-16 week trial -Ultimate/final medications prescribed were MPH for 46%, amphetamine and/or dextroamphetamine for 42%, atomoxetine for 4%, and guanfacine for 6% (mean doses not reported)	-Parent- and teacher-reported ADHD symptom ratings (SNAP-IV)	-Parent-rated and teacher-rated IA and HI symptoms improved with medication treatment (88% received stimulants).	-Families also attended an average of 4.8 behavior training sessions in addition to child receiving ADHD medication	1b-
Tannock R et al (2018) Controlled clinical trial ^b with DBPC methodology	-N=65 had ADHD+RD -7-11 years old -75% male and 90% Caucasian -RD criteria: IQ>80 AND SS on 2 reading subtests [WRAT-3 Reading, WRMT-R Word Identification, WRMT-R Word Attack] at least 1.5 SD below age level or SS on all 3 reading subtests at least 1 SD below age level	-4 month trial -Maximum MPH dose was 0.7mg/kg BID or 20mg BID (whichever achieved first), mean dose not specified	-Parent- and teacher-reported ADHD symptom ratings (Conners' Rating Scales-Revised)	-Beneficial effects of MPH were seen for teacher HI but not IA ratings in intention-to-treat analyses. -Beneficial effects of MPH were seen for teacher HI and IA ratings in as-treated analyses.	-Children with a history of poor response to stimulant medications excluded -20% of sample changed MPH/PB conditions: 8 changed from PB	2b ^c

Source and Study Design	Sample Size of Children with ADHD+LD and Characteristics	Duration and Dose of Medication Treatment	Efficacy Measures	Findings	Comments	Oxford Quality Rating
Williamson D et al (2014) Controlled clinical trial ^b with DBPC crossover methodology	-N=46 had ADHD+LD (N=31 had RD, N=9 had MD, N=6 had RD +MD) -9-12 years old -69% male and 40% minority (African American or Hispanic) -RD criteria: scores 1-2 SD below the mean on the CTOPP Elision subtest and the GORT-4 fluency subtest -MD criteria: scores 1-2 SD below the mean on the WIAT-II-A Numerical Operations subtest	-6 week trial -MPH was titrated upward until clinician rated children as "much" or "very much" improved: best dose was 18mg for 13%, 36mg for 26% and 54mg for 61% of ADHD+LD group	-Non-blinded parent- and teacher-reported ADHD symptom ratings (ADHD Rating Scale-IV) -Blinded direct observations of behavior (SKAMP)	-No beneficial effects of MPH were seen for parent IA or HI ratings in either intention-to-treat or as-treated analyses. -Parent-rated and teacher-rated IA and HI symptoms improved with MPH (according to unblinded ratings). -79% of participants with ADHD+LD achieved clinician ratings of "much" or "very much" improved with MPH treatment. -Children with ADHD +LD were more attentive and better behaved when treated with MPH according to blinded direct observations.	-No correction for multiple comparisons -Children with a history of stimulant non-response excluded	2b ^c

^aNaturalistic, open label study, with pre- and post-measures

^bDescribed as randomized by authors but classified as a controlled clinical trial rather than a randomized control trial due to lack of detail regarding randomization procedures

^cQuality rating downgraded from 1b due to exclusion of children with history of poor response to stimulants

ADD=attention deficit disorder

ADHD=attention-deficit/hyperactivity disorder

BID=twice a day

CTOPP=Comprehensive Test of Phonological Processing

DBPC=Double-blind placebo-controlled

DSM III=Diagnostic and Statistical Manual of Mental Disorders-3rd Edition

DST=Decoding Skills Test

GMRT=Gates-MacGinitie Reading Test

GORT-4=Gray Oral Reading Test-4th edition

HI= hyperactivity/impulsivity

IA=inattention

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LD=Learning disorder

MPH=methylphenidate

PB=placebo

PIAT=Peabody Individual Achievement Test

RD=Reading disorder

SD=Standard deviation

SKAMP=Swanson, Kotkin, Alger, M-Flynn, and Pelham

SNAP-IV=Swanson Nolan and Pelham

SS=Standard score

WIAT-II-A=Wechsler Individual Achievement Test-2nd Edition-Abbreviated

WJIII=Woodcock Johnson III Tests of Achievement

WRAT=Wide Range Achievement Test

WRMT-R=Woodcock Reading Mastery Tests-Revised

Table 2.

Clinical Trials Evaluating Effects of Stimulants on Academic Outcomes in Children with Coexisting ADHD and Reading Disorder

Source and Study Design	Sample Size of Children with ADHD+LD and Characteristics	Duration and Dose of Medication Treatment	Efficacy Measures	Findings	Comments	Oxford Quality Rating
Bental B et al (2008) Controlled clinical trial ^b with DBPC crossover methodology	-N=25 had ADHD+RD -7-11 years old -100% male, race not specified -RD criteria: <25th percentile in both NDB single word decoding and text reading subtests, or <15th percentile on either one	-Trial with single MPH dose -MPH dose was 0.3-0.4 mg/kg	-Word and non-word decoding accuracy (NDB) -Spelling (NDB) -Phonemic synthesis and deletion (NDB)	-MPH improved word and non-word decoding accuracy but not spelling accuracy, phonemic synthesis, or phonemic deletion.	-No correction for multiple comparisons	1b-
Dykman RA et al (1991) Cohort analytic ^a	-N=82 had ADHD+RD -7-11 years old -Analyzed sample was 100% male and Caucasian -RD criteria: IQ 90 AND WRAT reading and spelling subtest SS <90	-4 week trial -Treatment with low MPH dose (0.3mg/kg BID) and high MPH dose (0.6mg/kg BID)	-20-minute arithmetic task with addition and subtraction problems	-MPH improved arithmetic performance.	-Data on MPH effects analyzed for only 78% (N=64) of the ADHD+RD group	2b
Hechman L et al (2005) Randomized controlled trial	-N=82 had ADHD+RD at study baseline (N=576 for whole sample) -7-9 years old -Whole sample: 80% male, 61% Caucasian -RD criteria: discrepancy between IQ and WIAT reading SS at the 5% significance level	-14 month trial -Children randomized to get rigorously titrated MPH (mean=38 mg/kg/day), combined MPH (mean=31 mg/kg/day), + behavior parent training, behavior parent training only, or usual community care (67% got ADHD medications: among those on MPH, mean=23 mg/kg/day)	-Meeting criteria for reading disorder (discrepancy between ability and reading achievement at the 5% significance level, as measured by the WISC-III and WIAT)	-Among those with LD at baseline, there was a borderline significant decrease in likelihood of meeting criteria for LD at the end of the trial in: 1) the MPH group compared to the community care group, 2) in the combined (MPH + behavior parent training) group compared to the community care group, 3) the behavioral parent training group compared to the community care group.	-Data was from the Multimodal Treatment Study of Children with ADHD (landmark trial of MPH efficacy in pediatric ADHD)	1b
Keulers EH et al (2007) Cohort analytic ^a	-N=24 had ADHD+RD (N=9 had ADHD-only) -7-13 years old -71% male, race not specified -RD criteria: met DSM-IV criteria for RD and not improving in reading skills despite adequate remedial instruction for at least 6 months	-Study duration varied between 0.3 to 1.4 years -Mean MPH dose was 0.48 mg/kg/day	-Word reading/decoding (EMT and DMT) -Non-word decoding (Klepel Test)	-MPH produced larger improvements in word decoding and non-word decoding skills in the ADHD+RD than the ADHD-only group.	-Duration between pre- and post-assessments varied from 0.3 to 1.4 years -Limited description of inclusion criteria and MPH dosing protocol	2b
Tamm L et al (2017) Controlled clinical trial ^b	-N=78 had ADHD+RD -Grades 2-5 -68% male and 71% African American -RD criteria: IQ 70 AND SS <90 on WJIII Letter Word Identification	-16 week trial -Ultimate/final medications prescribed were MPH for 46%, AMPH and/or DEX for 42%, ATX for 4%, and	-Word Reading and Pseudoword Decoding (WIAT-3)	-Word reading and pseudoword decoding skills improved more with a reading intervention than with medication treatment.	-Families also attended an average of 4.8 behavior training sessions in addition to child receiving ADHD medication	1b-

Source and Study Design	Sample Size of Children with ADHD+LD and Characteristics	Duration and Dose of Medication Treatment	Efficacy Measures	Findings	Comments	Oxford Quality Rating
Tannock R et al (2018) Controlled clinical trial ^b with DBPC methodology	subtest, Word Attack subtest, or Basic Reading Skills composite. -N=65 had ADHD+RD -Ages 7-11 years old -75% male and 90% Caucasian -RD criteria: IQ>80 AND SS on 2 reading subtests [WRAT-3 Reading, WRMT-R Word Identification, WRMT-R Word Attack] at least 1.5 SD below age level or SS on all 3 reading subtests at least 1 SD below age level	guanfacine for 6% (mean doses not reported) -4 month trial -Maximum MPH dose was 0.7mg/kg BID or 20mg BID (whichever achieved first), mean dose not specified	-Speech-sound discrimination (GFW Sound Analysis subtest) -Word attack and word identification (WRMT-R) TOT -Passage comprehension (WRMT-R) -Arithmetic (WRMT-R)	-MPH improved speech-sound discrimination and arithmetic performance, but not word attack, word identification, decoding, or passage comprehension.	-Children with a history of poor response to stimulant medications excluded	2b ^c
Williamson D et al (2014) Controlled clinical trial ^b with DBPC crossover methodology	-N=46 had ADHD+LD (N=31 had RD, N=9 had MD, N=6 had RD +MD) -9-12 years old -69% male and 40% minority (African American or Hispanic) -RD criteria: scores 1-2 SD below the mean on the CTOPP Elision subtest and the GORT-4 fluency subtest -MD criteria: scores 1-2 SD below the mean on the WIAT-II-A Numerical Operations subtest	-6 week trial -MPH was titrated upward until clinician rated children as "much" or "very much" improved: best dose was 18mg for 13%, 36mg for 26%, and 54mg for 61% of ADHD+LD group	-Handwriting (THS-R) -Math computation (PERMP) -Reading Fluency (DIBELS) -Reading Comprehension (GSRT)	-MPH improved reading fluency, handwriting, and math computation skills, and had borderline significant beneficial effects on reading comprehension.	-No correction for multiple comparisons -Children with a history of stimulant non-response excluded	2b ^c

^aNaturalistic, open label study, with pre- and post-measures

^bDescribed as randomized by authors but classified as a controlled clinical trial rather than a randomized control trial due to lack of detail regarding randomization procedures

^cQuality rating downgraded from 1b due to exclusion of children with history of poor response to stimulants

ADHD=attention-deficit/hyperactivity disorder

AMPH=Amphetamine

ATX=Atomoxetine

DBPC=Double-blind placebo-controlled

DEX=Dextroamphetamine

DIBELS=Dynamic Indicators of Basic Early Literacy Skills

DMT=Three Minutes Test

DSM-IV=Diagnostic and Statistical Manual for Mental Disorders-4th edition

EMT=One Minute Test

GFW=Goldman-Fristoe-Woodcock

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GORT-4=Gray Oral Reading Test-4th edition
GSRT – Gray Silent Reading Test
KT=Keyword Test
LD=Learning Disorder
MD=Math Disorder
MPH=Methylphenidate
NDB=Nirzan Diagnostic Battery for Reading Performance in Hebrew
PB=Placebo
PERMP – Permanent Product Math Test
RD=Reading disorder
SS=Standard score
THRS-R=Test of Handwriting Skills-Revised
TOT=Test of Transfer
WIAT=Wechsler Individual Achievement Test
WISC=Weschler Intelligence Scale for Children
WJIII=Woodcock Johnson III Tests of Achievement
WRAT=Wide Range Achievement Test
WRMT-R=Woodcock Reading Mastery Tests-Revised

Table 3. Clinical Trials Evaluating Effects of Stimulants on Neuropsychological Outcomes in Children with Coexisting ADHD and Reading Disorder

Source and Study Design	Sample Size of Children with ADHD +LD and Characteristics	Duration and Dose of Medication Treatment	Efficacy Measures	Findings	Comments	Oxford Quality Rating
Bental B et al (2008) Controlled clinical trial ^b with DBPC crossover methodology	-N=25 had ADHD+RD -7-11 years old -100% male, race not specified -RD criteria: <25th percentile in both NDB single word decoding and text reading, or <15th percentile on either one	-Trial with single MPH dose -MPH dose was 0.3-0.4 mg/kg	-Planning (PM) -Rapid digit naming (RAN) -Response inhibition (MIFFT) -Rule abstraction/set-shifting (WCST) -Verbal fluency (ART and FRT) -Verbal working memory (LNS and LSS)	-MPH improved rapid digit naming but not planning, response inhibition, rule abstraction/set-shifting, verbal fluency, or verbal working memory.	-No correction for multiple comparisons	1b-
Dykman RA et al (1991) Cohort analytic ^a	-N=82 had ADHD+RD -7-11 years old -Analyzed sample was 100% male and Caucasian -RD criteria: IQ 90 AND SS<90 on WRAT reading and spelling subtests	-4 week trial -Treatment with low MPH dose (0.3mg/kg BID) and high MPH dose (0.6mg/kg BID)	-Visual attention (TMT Trials A) -Task-switching (TMT-Trails B) -Visual-spatial processing speed (WISC-R Coding subtest)	-MPH improved visual-spatial processing speed and task-switching, but not visual attention.	-Data on MPH effects analyzed for only 78% (N=64) of the ADHD+RD group	2b
Keulers EH et al (2007) Cohort analytic ^a	-N=24 had ADHD+RD (N=9 had ADHD-only) -7-13 years old -71% male, race not specified -RD criteria: met DSM-IV criteria for RD and not improving in reading skills despite adequate remedial instruction for at least 6 months	-Study duration varied between 0.3 to 1.4 years -Mean MPH dose was 0.48 mg/kg/day	-Sustained attention (BVT) -Visual processing speed (WISC-R Coding subtest)	-MPH improved sustained attention and visual processing speed in both the ADHD+RD and ADHD-only groups.	-Duration between pre- and post-assessments varied from 0.3 to 1.4 years -Limited description of inclusion criteria and MPH dosing protocol	2b
Kupietz S et al (1988) Controlled clinical trial ^b with DBPC methodology	-N=58 -7-13 years old -% male and race not specified -RD criteria: met DSM-III criteria for developmental RD and had reading grade level (based on composite score from the PIAT, GMRT, and DST) indicating an achievement rate 75% of typical achievement rate	-28 week trial -Children were randomly assigned to 1 of 4 conditions: PB, MPH 0.3 mg/kg, MPH 0.5 mg/kg, MPH 0.7 mg/kg	-Paired-associate learning (Kupietz task) -Short term visual memory (Sprague and Sleator STM task)	-MPH reduced errors in paired-associate learning at higher MPH doses (0.5mg/kg and 0.7mg/kg) at the end but not beginning of the trial. -MPH did not improve short term visual memory.	-Data on MPH effects analyzed for 81% (N=47) of the sample	1b-
Williamson D et al (2014) Controlled clinical trial ^b with DBPC crossover methodology	-N=46 had ADHD+LD (N=31 had RD, N=9 had MD, N=6 had RD+MD) -9-12 years old -69% male and 40% minority (African American or Hispanic) -RD criteria: scores 1-2 SD below the mean on the CTOPP Elision subtest and the GORT-4 fluency subtest	-6 week trial -MPH was titrated upward until clinician rated children as "much" or "very much" improved: best dose was 18mg for 13%, 36mg for 26%, and 54mg for 61% of ADHD+LD group	-Reaction time variability (TOVA) -Visual working memory (WRAML Finger Windows Forwards and Backwards)	-MPH improved reaction time variability and visual-spatial working memory.	-No correction for multiple comparisons -Children with a history of stimulant non-response excluded	2b ^c

Source and Study Design	Sample Size of Children with ADHD +LD and Characteristics	Duration and Dose of Medication Treatment	Efficacy Measures	Findings	Comments	Oxford Quality Rating
-MD criteria: scores 1-2 SD below the mean on the WIAT-II-A Numerical Operations subtest						

- ^a Naturalistic, open label study, with pre- and post-measures
- ^b Described as randomized by authors but classified as a controlled clinical trial rather than a randomized control trial due to lack of detail regarding randomization procedures
- ^c Quality rating downgraded from 1b due to exclusion of children with history of poor response to stimulants

ART=Animal Retrieval Test

BVT=Bourdon-Vos Test

CTOPP=Comprehensive Test of Phonological Processing

DSM=Diagnostic and Statistical Manual for Mental Disorders

DST=Decoding Skills Test

FRT=Food Retrieval Test

GMRT=Gates-MacGinitie Reading Test

LD=Learning Disorder

LNS=Listening Number Span

LSS=Listening Sentence Span

MD=Math Disorder

MPH=Methylphenidate

MFFT=Matching Familiar Figures Test

NDB=Nizan Diagnostic Battery for Reading Performance in Hebrew

PB=Placebo

PIAT=Peabody Individual Achievement Test

PM=Porteus Maze

RAN= Rapid Automatized Naming

RD=Reading Disorder

SS=Standard Scores

STM=Short-term Memory

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TMT=Trail-Making Test
TOVA=Test of Variables of Attention
WCST=Wisconsin Card Sorting Test
WIAT-II-A=Wechsler Individual Achievement Test-2nd Edition-Abbreviated
WISC-R=Wechsler Intelligence Scale for Children-Revised
WRAML – Wide Range Assessment of Memory and Learning
WRAT=Wide Range Achievement Test

Table 4. Clinical Trials Evaluating Atomoxetine Effects on ADHD Symptoms in Children with Coexisting ADHD and Reading Disorder

Source and Study Design	Sample Size of Children with ADHD +LD and Characteristics	Duration and Dose of Medication Treatment	Efficacy Measures	Findings	Comments	Oxford Quality Rating
de Jong CG et al (2009) Controlled clinical trial ^a with DBPC crossover methodology	-N=20 had ADHD+RD -8-12 years old -75% male, race not reported -RD criteria: 15 months delay on 2 or more reading tests [One Minute Test, Pseudo-word Reading Test, or Text Reading Test]	-8 week trial -Mean dose was 1.11 mg/kg/day	-Parent-reported ADHD symptom ratings (ADHD Rating Scale IV)	-Parent-rated ADHD total symptom scores improved with ATX (effects on IA and HI not reported separately).	-Only post hoc analyses adjusted for multiple comparisons -# of study drop-outs in ADHD+RD group not reported	2b
Shaywitz BA et al (2014) + Sumner CR et al (2009) (shared cohort) Cohort analytic ^c	-N=36 had ADHD+RD -10-16 years old -67% male and 67% Caucasian -RD criteria: IQ 80 and 22 point discrepancy between IQ score and K-TEA Reading Composite SS	-16 week trial -Dose was 1.0 mg/kg/day to 1.4 mg/kg/day (mean dose not reported)	-Parent-reported ADHD symptom ratings (ADHD Rating Scale IV)	-Parent-rated ADHD IA, HI, and total symptom scores improved with ATX.		2b
Wietecha L et al (2013) Controlled clinical trial ^a with DBPC methodology	-N=124 had ADHD+RD -10-16 years old -Whole sample: 62% male and 73% Caucasian -RD criteria: IQ 80 AND 1) SS <90 on any WJIII reading subtest (Basic Reading, Letter Word Identification, or Word Attack) or 2) 22 point discrepancy between IQ and SS on any WJIII reading subtest	-16 week trial -Dose was 1.0 mg/kg/day to 1.4 mg/kg/day (mean dose not reported)	-Parent- and teacher-reported ADHD symptom ratings (ADHD Rating Scale IV)	-Parent-rated IA, HI, and ADHD total symptom scores improved with ATX. -Teacher-rated IA symptoms scores improved with ATX but HI and ADHD total symptom scores did not.	-No correction for multiple comparisons -Only 76% (N=94) of participants completed the study's controlled trial phase -Same cohort as Shaywitz BA et al (2017) [See Table 4]	2b

^aDescribed as randomized by authors but classified as a controlled clinical trial rather than a randomized control trial due to lack of detail regarding randomization procedures

^bQuality rating downgraded from 1b due to <80% of participants completing study or failure to report # of study drop-outs

^cNaturalistic, open label study, with pre- and post-measures

ADHD=attention-deficit/hyperactivity disorder

ATX=atomoxetine

DBPC=Double-blind placebo-controlled

HI= hyperactivity/impulsivity

IA=inattention

IQ=intelligence quotient

K-TEA=Kaufman Test of Educational Achievement

WJIII=Woodcock Johnson III Tests of Achievement

SS=Standard score

RD=Reading disorder

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Table 5.

Clinical Trials Evaluating Atomoxetine Effects on Academic Outcomes in Children with Coexisting ADHD and Reading Disorder

Source and Study Design	Sample Size and Characteristics	Duration and Dose of Medication Treatment	Efficacy Measures	Findings	Comments	Oxford Quality Rating
Shaywitz BA et al (2014) + Sumner CR et al (2009) (shared cohort) Cohort analytic ^a	-N=36 had ADHD+RD -Ages 10–16 years old -67% male and 67% Caucasian -RD criteria: IQ 80 and 22 point discrepancy between IQ score and K-TEA Reading Composite SS	-16 week trial -Dose was 1.0 mg/kg/day to 1.4 mg/kg/day (mean dose not reported)	-Reading Decoding, Comprehension, and Composite scores (K-TEA) -Spelling scores (K-TEA)	-Reading decoding, comprehension, and composite scores improved with ATX. -Spelling did not improve with ATX.		2b
Shaywitz S et al (2017) Controlled clinical trial ^b with DBPC methodology	-N=124 had ADHD+RD -10–16 years old -Whole sample: 62% male and 73% Caucasian -RD criteria: IQ 80 AND 1) SS <90 on any WJIII reading subtest (Basic Reading, Letter Word Identification, or Word Attack) or 2) 22 point discrepancy between IQ and SS on any WJIII reading subtest	-16 week trial -Dose was 1.0 mg/kg/day to 1.4 mg/kg/day (mean dose not reported)	-Word Identification, Word Attack and Passage Comprehension (WJIII) -Spelling (WJIII) -Phonological Processing (CTOPP) -Oral reading (GORT-4) -Reading fluency (TOWRE)	-Elision skills improved with ATX. -None of the 25 other academic outcomes assessed improved with ATX.	-No corrections for multiple comparisons -Only 76% (N=94) of participants completed the study's controlled trial phase -Same cohort as Wietecha L et al (2013) [Tables 4 & 6]	2b ^c

^aNaturalistic, open label study, with pre- and post-measures

^bDescribed as randomized by authors but classified as a controlled clinical trial rather than a randomized control trial due to lack of detail regarding randomization procedures

^cQuality rating downgraded from 1b due to <80% of participants completing study

ADHD=attention-deficit/hyperactivity disorder

ATX=atomoxetine

CTOPP=Comprehensive Test of Phonological Processing

DBPC=Double-blind placebo-controlled

GORT-4=Gray Oral Reading Tests-4

K-TEA=Kaufman Test of Educational Achievement

RD=Reading Disorder

SS=Standard score

TOWRE=Test of Word Reading Efficiency

WJIII=Woodcock Johnson III Tests of Achievement

Table 6.

Clinical Trials Evaluating Atomoxetine Effects on Neuropsychological Outcomes in Children with Coexisting ADHD and Reading Disorder

Source and Study Design	Sample Size and Characteristics	Duration and Dose of Medication Treatment	Efficacy Measures	Findings	Comments	Oxford Quality Rating
de Jong CG et al (2009) Controlled clinical trial ^b with DBPC crossover methodology	-N=20 had ADHD+RD -8-12 years old -75% male, race not reported -RD criteria: 15 months delay on 2 or more reading tests [One Minute Test, Pseudo-word Reading Test, or Text Reading Test]	-8 week trial -Mean dose was 1.11 mg/kg/day	-Visual-spatial working memory (Const Block Tapping Test) -Inhibition (Stop Signal Paradigm) -Lexical decision-making (Lexical Decision Task)	-Visual-spatial working memory improved with ATX. -Borderline significant improvement in inhibition observed with ATX. -Lexical decision accuracy and speed did not improve with ATX.	-Not all analyses adjusted for multiple comparisons -# of study drop-outs in ADHD+RD group not reported	2b ^c
Shaywitz BA et al (2014) + Sumner CR et al (2009) (shared cohort) Cohort analytic ^a	-N=36 had ADHD+RD -10-16 years old -67% male and 67% Caucasian -RD criteria: IQ 80 and 22 point discrepancy between IQ score and K-TEA Reading Composite SS	-16 week trial -Dose was 1.0 mg/kg/day to 1.4 mg/kg/day (mean dose not reported)	-Phonological loop working memory, central executive working memory, and visual spatial working memory (WMTB-C)	-Phonological loop working memory improved with ATX. -Central executive and visual-spatial working memory did not improve with ATX.		2b
Wietecha L et al (2013) Controlled clinical trial ^b with DBPC methodology	-N=124 had ADHD+RD -10-16 years old -Whole sample: 62% male and 73% Caucasian -RD criteria: IQ 80 AND 1) SS <90 on any WJIII reading subtest (Basic Reading, Letter Word Identification, or Word Attack) or 2) 22 point discrepancy between IQ and SS on any WJIII reading subtest	-16 week trial -Dose was 1.0 mg/kg/day to 1.4 mg/kg/day (mean dose not reported)	-Phonological loop working memory, central executive working memory, and visual spatial working memory (WMTB-C)	-Central executive working memory improved with ATX. -Phonological loop and visual-spatial working memory did not improve with ATX.	-No corrections for multiple comparisons -Only 76% (N=94) of participants completed the study's controlled trial phase -Same cohort as Shaywitz BA et al (2017) [See Table 5]	2b

^aNaturalistic, open label study, with pre- and post-measures

^bDescribed as randomized by authors but classified as a controlled clinical trial rather than a randomized control trial due to lack of detail regarding randomization procedures

^cQuality rating downgraded from 1b due to failure to report # of study drop-outs

ADHD=attention-deficit/hyperactivity disorder

ATX=atomoxetine

DBPC=Double-blind placebo-controlled

K-TEA=Kaufman Test of Educational Achievement

RD=Reading Disorder

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SS=Standard score

WMTB-C=Working Memory Test Battery for Children

WJIII=Woodcock Johnson III Tests of Achievement

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