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Child and Adolescent Psychiatry (M Brotman, Section Editor)

Treatment Implications for ADHD Youth with Mood and Anxiety Comorbidity

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Abstract

Purpose of Review There are multiple pharmacological and psychosocial interventions that are tolerable and efficacious for the treatment of attention deficit hyperactivity disorder (ADHD). However, many youth with ADHD have elevated levels of mood and anxiety symptoms that can complicate treatment. In this review, we summarize the relevant treatment studies on the treatment of youth with ADHD and comorbid anxiety or mood disorders.
Recent Findings Treatment of ADHD, specifically CNS stimulants, often translates to reduced irritability in youth with ADHD, but appears to have limited impact on other mood or anxiety symptoms. The presence of ADHD does not appear to reduce the efficacy of pharmacological treatments of mood and anxiety disorders. There is less data on the impact of ADHD on psychosocial treatments for internalizing disorders.
Summary In children with elevated levels of mood or anxiety, ADHD can be safely and effectively treated with either evidence-based pharmacological or psychosocial interventions. However, additional treatments are often needed to achieve significant improvements in other mood or anxiety symptoms.

Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the most common neurobehavioral disorders, affecting 5–7% of school children worldwide [1]. In the USA, up to 11% of youth have been diagnosed with ADHD and over 5% of school children have been prescribed ADHD medication [2]. More money is spent on ADHD care than any other childhood condition, except newborn care [3].

Many children with ADHD also meet criteria for additional behavioral health disorders, with mood and anxiety disorders being some of the most commonly occurring comorbidities [4–6]. Up to 40% of children with ADHD may meet criteria for a mood disorder over their lifetime [4, 5]. In the largest clinical trial of ADHD to date, the Multimodal Treatment Study of ADHD, 6% of participants met criteria for mood disorders at baseline [6]. In clinical samples of depressed adolescents, 13.7% had comorbid ADHD [7]. In addition, childhood ADHD increases the rate for depression in young adulthood, which is mediated by persistent ADHD symptoms and associated impairment [8]. The combination of ADHD, depression, and a disruptive behavior disorder [either oppositional-defiant disorder (ODD) or conduct disorder] appreciably increases the risk for attempted and completed suicide [9, 10]. When comorbid, ADHD typically onsets first suggesting that management of ADHD may help to reduce the risk of future depression [11, 12].

Over the past two decades, there has been appreciable controversy about the association between bipolar disorder and ADHD. When severe persistent irritability is interpreted as a symptom of mania, multiple studies reported elevated rates of bipolar disorder in children with ADHD [13–15]. The labels of severe mood dysregulation (SMD) and then disruptive mood dysregulation disorder (DMDD) [16] were created to describe children with severe persistent irritability and frequent temper outbursts but who did not meet full diagnostic criteria for bipolar disorder. It remains a point of debate if severe persistent irritability is a meaningfully distinct diagnostic entity [17, 18]. It has now been established that chronic irritability, even when severe, is not a meaningful risk factor for mania [19–21], but there is increasing evidence that this presentation is in association with a wide range of impairments that merits intervention [22–24]. Poor frustration tolerance has been suggested to be a key mechanism underlying the relationship between ADHD and depression [25]. It is a core component of SMD and DMDD [26], which have been established as risk factors for both depressive and anxiety disorders [19, 21, 22]. Therefore, treatments preferentially targeting irritability in ADHD youth may reduce the risk for future depression and anxiety disorders, although this has yet to be formally explored.

Epidemiologic studies have demonstrated that 25–50% of children with ADHD have a comorbid anxiety disorder [27, 28]. Rates of anxiety disorders based on parent report in the Multimodal Treatment Study of ADHD exceeded 30% [6]. The combination of ADHD and anxiety is associated with more school and social impairment than ADHD alone [29, 30]. ADHD and other behavioral disorders are both established risk factors for parental divorce; ADHD may be a risk factor for the development of anxiety disorders through increased exposure to stressful life events [31]. For example, elevated rates of posttraumatic stress disorder (PTSD) are seen in patients with ADHD [32], and inattention among adults has been identified as a risk factor for PTSD following trauma [33]. In children, ADHD and other behavioral disorders are associated with worse outcomes following divorce [34]. Concerningly, there are higher rates of separation and divorce among the families of children with ADHD and anxiety (59%) as compared to those children with ADHD alone (27%) and those without a mental health disorder (12%) [35].

There are well-established treatment guidelines for uncomplicated ADHD in the primary care setting [36], which is where the majority of youth receive ADHD care [37]. Internalizing comorbidity is a common reason why children get referred for mental health care as primary care providers report greater comfort treating ADHD than mood or anxiety disorders [38]. The presence of a comorbid mood and anxiety disorders is associated with additional impairment [39], and there is concern that children with comorbid conditions may exhibit lower response rates and increased rates of adverse events [40, 41]. Even subthreshold mood or anxiety symptoms are associated with appreciable impairment that could impact treatment [42]. This narrative review will address the treatment of ADHD youth with mood and anxiety comorbidity.

Methods

Existing literature was ascertained in the English language, published between 1981 and October 2017, using searches of MEDLINE for the following

Table 1. Summary of the selected reviewed studies focus on treatment of ADHD with mood and anxiety comorbidity

Study	Age (years)	*N*	Design	Trial length	Comorbid conditions
ADHD and depressive disorders					
ATX ADHD and comorbid study group et al. 2007 [43]	12–18	142	Multisite, DBRCT	9 weeks	MDD
Daviss et al. 2001 [44]	11–16	24	Open-label trial	8 weeks	MDD or dysthymic disorder
Findling 1996 [45]	10–16	7	Open-label trial	Up to 28 months	MDD
Gammon et al. 1993 [46]	9–17	32	Open-label study	8 weeks	Dysthymia, MDD, and conduct disorders
Golubchik et al. 2013 [47]	8–18	47	Open-label study	12 weeks	Subsyndromal depression based on symptoms count
Kratochvil et al. 2009 [48]	12–17	439	Post hoc analysis of TADS	36 weeks	Major depressive disorder; ADHD not required
ADHD and bipolar disorder					
Chang et al. 2009 [49]	6–17	12	Open-label study	8 weeks	Euthymic BPD I or II on stable med regiment
Findling et al. 2007 [50]	5–17	16	DBRCT	4 weeks	Bipolar disorder (on stable dose of a mood stabilizer)
Hah and Chang 2005 [51]	8–16	7	Case series, retrospective chart review	2–18 months	Bipolar disorder (all but one were on mood stabilizer)
Scheffer et al. 2005 [52]	6–17	40 30	Open-label RCT with crossover trial	8 weeks 4 weeks	Bipolar I or bipolar II disorder
ADHD and irritability/SMD/DMDD					
Bladder et al. 2009 [53]	6–13	74	5 weeks of open-label CNS stimulants and PT followed by 8 weeks of RCT	13 weeks	Disruptive disorder with chronic aggression
Baweja et al. 2016 [54]	7–12	38	Open-label stimulant optimization trial	6 weeks	DMDD
Dickstein et al. 2009 [55]	6–13	45	2-week, single-blind, placebo run-in, followed by DBRCT	8 weeks	SMD
Fernandez De La Cruz et al. 2015 [56•]	7–9.9	579	Post hoc analysis of MTA study	14 months	Mood/anxiety comorbidity not excluded except BPD and serious OCD
TOSCA Study Aman et al. 2014 [57] Gadow et al. 2014 [58] Farmer et al. 2015 [59•]	6–12	168	3 weeks of open-label CNS stimulants and PT then 6 week RCT of risperidone vs placebo	9 weeks	Serious physical aggression

Table 1. (Continued)

Study	Age (years)	*N*	Design	Trial length	Comorbid conditions
Waxmonsky et al. 2008 [60]	5–12	101	Post hoc analysis of blinded RCT using crossover design	9 weeks	SMD
Waxmonsky et al. 2016 [61] ADHD and anxiety disorder	7–12	68	RCT	11 weeks	SMD
Abikoff et al. 2005 [62]	6–17	36 (32 stimulants naïve)	Open-label, followed by stabilization	2 weeks +	Anxiety disorder
		25	DBRCT	8 weeks	Anxiety disorder
Diamond et al., 1999 [63]	6–12	91	RCT	4 months	Anxiety disorder
DuPaul et al. 1994 [64]	6–12	40	RCT with crossover design	6 weeks	Comorbid internalizing symptoms
Gadow et al. 2002 [65]	6–13	38	RCT with crossover design	8 weeks	Anxiety disorder, MDD, dysthymic disorder, tics disorder
Geller et al. 2007 [66]	8–17	176	RCT	12 weeks	GAD, SAD, or social phobia
Golubchik et al. 2014 [67]	8–18	21	Open-label	12 weeks	Social phobia
Kratochvil et al. 2005 [48]	7–17 years	173	RCT	8 weeks	Anxiety disorders
MTA 1999 [6]	7–9.9	579	Multisite parallel group, randomized intervention	14 months	Mood/anxiety comorbidity not excluded except BPD and serious OCD
Pliszka 1989 [68]	Mean age 9 years	43	RCT with crossover design	4 weeks	Anxiety disorder
Taylor et al. 1987 [69]	6–10	39	RCT with crossover design	3 weeks	Anxiety disorder
Ter-Stepanian et al. 2010 [70] ADHD, anxiety disorder, and psychotherapy	6–12	267	RCT with crossover design	2 weeks	Depression and anxiety disorders
Costin et al. 2002 [71]	10–12	5	Case series	8 weeks	ODD and anxiety disorder
Halldorsdottir et al. 2015 [72•] (CAMS)	7–17	488	Post hoc analysis of CAMS	6 months	Anxiety disorders- ADHD not required
Jarrett and Ollendick 2012 [73]	8–12	8	Non-concurrent multiple baseline design	6 months	Anxiety disorder
Maric et al. 2015 [74•]	8–18	123	RCT	1 year	Anxiety disorder

Table 1. (Continued)

Study	Medication and daily dose range	ADHD response	Comorbidity response	Tolerability
ADHD and depressive disorders				
ATX ADHD and comorbid study group et al. 2007 [43]	ATX 1.8 mg/kg/day	Improvement on ADHDRS-IV vs placebo (ES=0.84, p=0.001)	No difference in CDRS-R scores vs. placebo (−14.8 vs. −12.8, p=0.34)	No difference in treatment-emergent mania (0 vs. 1.5%), significantly more nausea and weight loss with ATX, no cases of reported suicidal ideation or behavior
Daviss et al. 2001 [44]	Bupropion SR (max of 6 mg/kg/day or 300 mg/day)	Improvement on parents' rating on ARS (p<.0005) but not teachers' (p=0.080) rating	Improvement on parents' (p<0.0005) and childrens' (p=0.016) ratings on MFQ	Generally well tolerated and with no discontinuations because of side effects
Findling 1996 [45]	Fluoxetine up to 60 mg, sertraline up to 100 mg daily, CNS stimulants	Moderate improvement to complete remission in ADHD symptoms	Moderate improvement to complete remission in depressive symptoms	No safety concerns (suicidality, aggressive behavior) or other problematic side effects.
Gammon et al. 1993 [46]	Fluoxetine (20 mg/day), IR MPH (5–20 mg per dose)	Improved ADHD symptoms on CPRS (p<0.0001)	Improved mood symptoms on CDI (p<0.0001)	Improved report card grades (p<0.0001) and global functioning on CGAS (p<0.0001)
Golubchik et al. 2013 [47]	MPH 0.5 to 1.0 mg/kg/day	Improvement in ADHD-RS (p=0.0001)	Improvement on CDRS (p=0.0001)	Positive correlation between the changes CDRS and ADHD-RS total scores (r=0.34, p=0.018)
Kratochvil et al. 2009 [48]	CBT, fluoxetine (10 to 40 mg/d) and combined treatment	No significant treatment-by stimulant use interaction was found (p>0.05).	MDD with ADHD: CBT=FLX=CBT+FLX MDD without ADHD: CBT=FLX<CBT+FLX (p<0.009)	ADHD was not associated with greater dropout; side effects on simultaneous use of stimulants and FLX – not reported
ADHD and bipolar disorder				
Chang et al. 2009 [49]	ATX (mean dose 59.17 mg/day)	Decrease in ADHD-RS-IV scores (p<0.0001, ES 0.73).	NS for YMRS and CDRS	No clear manic or mixed episodes but 2 subjects discontinued due to worsening of mood symptoms
Findling et al. 2007 [50]	1 week each of placebo, IR MPH 5 mg BID, IR MPH10 mg BID,	ADHD-RS-IV total score improvement (p=0.01, ES=0.90) on best dose vs placebo	NS for CDRS-R and YMRS scores	No death or suicides; no clinically significant differences in weight or cardiovascular parameters

Table 1. (Continued)

Study	Medication and daily dose range	ADHD response	Comorbidity response	Tolerability
	and IR MPH15 mg BID			
Hah and Chang 2005 [51]	ATX (mean dose 53 mg/day)	6/7 subjects improved	No episodes of hypomania or mania	Adverse effects of atomoxetine included sedation, nausea, and decreased appetite
Scheffer et al. 2005 [52]	Divalproex sodium (median dose 750 mg/day)	NS for change in CGI-I scores during open-label; only 7.5% had significant improvement in ADHD symptoms	YMRS scores decreased ($p<0.0001$); 80% subjects achieved ≥50% reduction in YMRS scale	No significant side effects
	MAS (5 mg by mouth b.i.d.) vs placebo	CGI I scores greater for MAS ($p<0.0001$)	NS for YMRS	No significant side effects
ADHD and irritability/SMD/DMDD				
Bladder et al. 2009 [53]	RCT phase: divalproex (mean dose 567 mg daily) or placebo	Larger decrease in ADHD symptom ratings on Conners' Global Index restless-inattentive subscale scores ($p=0.01$) aggression: significantly higher rate of remission (57%) on divalproex vs. placebo (15%) during RCT	Not reported	Stimulant treatment was associated with anxiety, fingernail biting, and suppressed appetite; divalproex treatment was associated with treatment-emergent sadness ($p=0.07$) and trouble falling asleep ($p=0.08$)
Baweja et al. 2016 [54]	Dose range of 0.71–1.03 mg/kg/day MPH equivalents	Significant reduction in ADHD symptoms ($p<0.05$, ES=0.95)	Significant decline is CDRS-R (ES 0.61), DBD-RS (ES=0.95), and irritability (ES=0.58), but NS for YMRS	Significant decline in the crabby/irritable score PSERS ($p<0.05$), no significant changes on the PSERS mood score and total score
Dickstein et al. 2009 [55]	Lithium 300 mg twice daily (target steady state level of 0.8–1.2 mmol/L)	Not reported	Significant clinical improvement during the placebo run-in 45% of subjects; NS for group differences on CGI, CGAS, YMRS, CDRS, and PANSS factor 4	Two subjects randomized to lithium discontinued—one due to clinical worsening and the other due to homesickness. Otherwise lithium was tolerable
Fernandez De La Cruz et al. 2015 [56•]	Medication management vs. intensive behavioral treatment vs. combined group vs. community care	Not reported	Change over time: med (ES 0.63), behavioral treatment (ES=0.42), combined (ES=0.82), and community care (ES=0.48)	Irritability did not moderate response to treatment of ADHD.

Table 1. (Continued)

Study	Medication and daily dose range	ADHD response	Comorbidity response	Tolerability
TOSCA Study Aman et al. 2014 [57] Gadow et al. 2014 [58] Farmer et al. 2015 [59•]	Risperidone (mean dose 1.65 mg)	Greater reduction with risperidone for odd severity (p=0.002, Cohen's d= 0.27), and aggressive behavior (ABS reactive aggression subscale ES=0.29, p −0.01) but not ADHD (ES=0.13), or CD symptoms (ES=0.09)	NS on withdrawn dysphoric on NCBRF	Comorbid anxiety did not moderate any effect of treatment (p>0.05); trouble falling asleep was more common AE for CNS stimulants; elevated prolactin levels, GI upset; and weight gain (1.8 kg at over 9 weeks) with risperidone
Waxmonsky et al. 2008 [60]	BMOD (no, low, high) with IR MPH (0.15, 0.3, 0.6 mg/kg TID)	Significant reduction in ADHD symptoms by counselor rating and behavior counts (p<0.001)	34% reduction in YMRS ratings (p<0.001) and 31% reduction in CDRS-R (p<0.001) with BMOD + IR MPH treatment in SMD subjects	No difference in side effects between SMD and non-SMD youth
Waxmonsky et al. 2016 [61]	ADHD med+novel behavioral therapy vs. community-based psychosocial treatment and ADHD meds	No group differences in ADHD symptoms (DBD-RS) as both groups significantly declined over time	Significantly greater improvement in parent-rated irritability (DBD-RS, ES= 0.63), significant change in mood symptoms (YMRS+CDRS-R, ES=0.51) for subjects who attended majority of sessions	No manic episode, 2 incidences of suicidal ideation (1 per group), no incidents involved a self-harm attempt
ADHD and anxiety disorder				
Abikoff et al. 2005 [62]	MPH titration in open-label, mean dose of MPH 39.63 mg and MAS-XR 25 mg	81% had positive ADHD response; significant reductions seen in stimulant naïve (p<.001)	Around 19% participants no longer had impairing anxiety after treatment of their ADHD	Improvement (p=0.05) in trouble sleeping (40%) vs. at the beginning of stabilization (50%).
	Fluvoxamine (mean dose 145.4 mg) vs placebo	NS for SNAP scores	NS for PARS scores with both groups improving over time	No differences in restlessness, behavioral activation, or mood lability
Diamond et al., 1999 [63]	IR MPH (0.7 mg/kg) vs. placebo	NS for parent or teacher IOWA Connors (p>0.5)	Not reported	No differential response between groups on any side effects measures
DuPaul et al. 1994 [64]	IR MPH BID (5, 10, 15 mg) vs. placebo	50% of children in high internalizing group (anxiety) did not improve classroom behavior on TSCRS total score and academic measures, while	Not reported	Children with high comorbid internalizing symptoms may have higher risk for an adverse medication response as compared to those with

Table 1. (Continued)

Study	Medication and daily dose range	ADHD response	Comorbidity response	Tolerability
		85% improved on low and borderline internalizing groups		low and borderline internalizing symptoms
Gadow et al. 2002 [65]	2 weeks each placebo, IR MPH (0.1, 0.3, and 0.5 mg/kg)	Anxiety or depression symptoms did not moderate response to MPH	Not reported	No significant relationship (rs=0.15) between baseline anxiety/depression symptoms and adverse drug effects
Geller et al. 2007 [66]	ATX 1.8 mg/kg/day vs. placebo	Improvement in the ADHD-RS with ATX (ES=0.8, $p<0.001$).	Improvement on ATX for anxiety (PARS, ES=0.4, $p<0.010$)	Atomoxetine was well tolerated; decreased appetite more common with ATX ($p<0.001$)
Golubchik et al. 2014 [67]	IR MPH (0.5–1 mg/kg)	Reduction in ADHD symptom scores ($p<0.0001$); improvement in ADHD symptoms correlated with improvement in social phobia. ($r=0.45$, $p=0.038$)	Significant reduction social anxiety on LSAS-CA ($p=0.013$), as well as the school-related items of LSAS-CA ($p=0.011$)	MPH was well tolerated. No reported intolerable side effects
Kratochvil et al. 2005 [48]	FLX+ATX vs. ATX+ placebo (concomitant use of ATX in the last 5 weeks)	NS as both groups improved over time	NS as both groups improved on mood and anxiety symptoms over time	No difference in completion rates and discontinuation rates, increased blood pressure ($p=0.008$), and pulse ($p=0.008$) in ATX+FLX
MTA 1999 [6]	Medication management vs. intensive behavioral treatment vs. combined group vs. community care	Med, combined group>community care, behavioral therapy, and parent-rated anxiety predicted an improved response to behavioral treatment for ADHD.	SSRS internalizing symptoms combined group>community care, behavioral therapy, med	Anxiety did not predict a poorer response to stimulant medication
Pliszka 1989 [68]	IR MPH: low dose (0.25 to 0.40 mg/kg) and high dose (0.45 to 0.70 mg/kg) and placebo	Significant improvement on Iowa CTRS with MPH ($p<0.0001$); anxiety predicted reduced response to MPH and increased response to placebo	Not reported	Impact of mood/anxiety on tolerability of MPH not reported
Taylor et al. 1987 [69]	IR MPH up to 30 mg daily and placebo	69% showed improvement vs. 26% on placebo on global judgment of severity ($p<0.01$)	NS on "tension anxiety" factor of the Conners Rating Scale	Higher levels of anxiety were associated with poor response on CTRS ($p<0.05$)

Table 1. (Continued)

Study	Medication and daily dose range	ADHD response	Comorbidity response	Tolerability
Ter-Stepanian et al. 2010 [70]	BID IR MPH (0.5 mg/kg)	69.6% were rated as good responders; internalizing symptoms did not moderate response to IR MPH	Presence of anxiety disorder was associated with poor responders (OR 0.38, p=0.03)	Not reported
ADHD, anxiety disorder, and psychotherapy				
Costin et al. 2002 [71]	Cognitive-behavioral family-based intervention	Not reported	No significant change in parent reported CBCL and child reported R-CMAS psychopathology	Adherence was high
Halldorsdottir et al. 2015 [72•] (CAMS)	CBT alone (14 sessions), sertraline (up to 200 mg per day) CBT and sertraline, CBT and placebo	Not reported	ADHD predicted poorer immediate treatment response to child-focused-CBT and reduced remission rates 6 months post treatment	No moderating effects of ADHD were found for the pharmacotherapy
Jarrett and Ollendick 2012 [73]	10 weeks of parent management training for ADHD and family-based CBT for anxiety	Reduced ADHD symptoms (p<0.01) in the treatment phase but symptoms remained clinically elevated	Significant change in anxiety symptoms (p<0.01); anxiety declined to subclinical range 1 month post treatment	87.5% families completed the entire 10-week session
Maric et al. 2015 [74•]	Child cognitive-behavioral therapy (CCBT) versus family CBT (FCBT)	Significant improvement in ADHD symptoms, (effect estimates ranging 0.72 to 1.87)	ADHD symptoms did not moderate treatment response for either treatment; high ADHD FCBT>CCBT; low ADHD FCBT=CCBT	

ABS, Antisocial Behavior Scale; *ADHD*, attention deficit hyperactivity disorder; *ADHD-RS-IV*, ADHD Rating Scale-IV; *AE*, adverse effect; *ARS*, ADHD Rating Scale; *ATX*, atomoxetine; *BID*, twice (two times) a day; *BMOD*, behavior modification therapy; *BPD*, bipolar disorder; *CAMS*, Child/Adolescent Anxiety Multimodal Study; *CBT*, cognitive behavioral therapy; *CBCL*, child behavior checklist; *CDI*, Children's Depression Inventory; *CGAS*, Children's Global Assessment Scale; *CDRS*, Children's Depression Rating Scale; *CDRS-R*, Children's Depression Rating Scale-Revised; *CGI-I*, Clinical Global Impression–Global Improvement Scale; *CPRS*, Comprehensive Psychopathological Rating Scale; *CTRS*, Conners Teacher Rating Scale; *DBD-RS*, Disruptive Behavior Disorders Rating Scale; *DBRCT*, double-blind randomized controlled trial; *DMDD*, disruptive mood dysregulation disorder; *ES*, effect size; *GAD*, generalized anxiety disorder; *IR*, immediate release; *LSAS-CA*, Liebowitz Social Anxiety Scale for Children and Adolescents; *MAS*, mixed amphetamine salts; *MAS-XR*, mixed amphetamine salts extended release; *MDD*, major depressive disorder; *MFQ*, mood and feelings questionnaire; *MPH*, methylphenidate; *MTA*, Multimodal Treatment Study of Children With ADHD; *NCBRF*, Nisonger Child Behavior Rating Form; *NS*, non-significant; *OCD*, obsessive compulsive disorder; *PARS*, Pediatric Anxiety Rating Scale; *PSERS*, Pittsburgh Side Effect *Rating Scale*; *PT*, parent training; *SAD*, separation anxiety disorder; *SMD*, severe mood dysregulation; *RCT*, randomized controlled trial; *SANP Scale*, Swanson, Nolan and Pelham Scale; *SSRS*, social skills rating system; *TADS*, Treatment for Adolescents with Depression Study; *TID*, three times a day; *TOSCA*, Treatment of Severe Child Aggression; *TSCRS*, Teacher Self-Control Rating Scale; *YMRS*, Young Mania Rating Scale

categories: attention deficit hyperactivity disorder, depression, anxiety disorder, bipolar disorder, disruptive mood dysregulation disorder, severe mood dysregulation, irritability, children, adolescence, youth, non-stimulant, pharmacotherapy, drugs, CNS stimulants, medication, and psychotherapy. References from identified articles were also reviewed to ensure that all relevant papers were included. Table 1 provides a summary of the published treatment studies for children with ADHD and comorbid mood and anxiety issues.

Results

Treatment of ADHD and mood disorder

Pharmacological intervention of ADHD and mood disorder

ADHD and depressive disorders

There has been little formal investigation of the responsiveness to CNS stimulants in children with ADHD and major depression with no controlled data. In a case series ($N=7$), no improvement in ADHD symptoms was observed during fluoxetine or sertraline monotherapy, and stimulants did not appear to provide observable antidepressant effects. However, adjunctive treatment with stimulants and antidepressant was well tolerated and combination therapy was effective in improving both depressive and ADHD symptoms [45]. In an open-label study, fluoxetine (20 mg/day) was combined with methylphenidate to treat 32 children and adolescents with ADHD with comorbid mood [78% had dysthymia, 18% had major depressive disorder (MDD)] and conduct disorders. All patients showed a positive therapeutic response—reduced symptom levels, improved report card grades, and enhanced global functioning. No unusual adverse effects from the combination were encountered [46]. In another open-label study, among 47 youth with ADHD and subsyndromal depression [baseline Children's Depression Rating Scale-Revised (CDRS-R) score 40.9 ± 12.0], there was significant decrease in both ADHD Rating Scale (ADHD-RS) and CDRS-R scores with methylphenidate (p's<0.0005). A significant positive correlation was found between the changes in the CDRS-R and the ADHD-RS scores ($r=0.34$, $p=0.018$) [47].

Atomoxetine is FDA approved for the treatment of ADHD in children, adolescents, and adults. It has been one of the more extensively studied agents in youth with comorbid depression [43, 48]. In a multisite, double-blind, 9-week randomized placebo-controlled trial of atomoxetine (max of 1.8 mg/kg/day) in 142 adolescents with ADHD and MDD, significant improvement on scores on the ADHD Rating Scale-IV (ADHDRS-IV) was seen with active drug (−13.3 vs. −5.1, ES=0.84). No group differences were seen in depressive symptoms (CDRS scores −14.8 vs. −12.8). There was no difference between atomoxetine and placebo groups in the rates of treatment-emergent mania (0 vs. 1.5%) or worsening of depressive symptoms (7.0 vs. 5.8%) [43]. In an 8-week, double-blind, placebo-controlled trial of fluoxetine among children ($N=173$) with ADHD and a depressive disorder (45.7% met criteria for MDD), children were randomly assigned to fluoxetine or placebo, then after week 3, all received atomoxetine. Both

groups experienced a significant reduction in ADHD and depressive symptoms over time, but there were no between-group differences. Likewise, completion rates for the two groups were similar. The combination group had greater increases in blood pressure and pulse [48]. Atomoxetine does carry a black box warning label stating that in youth, atomoxetine may be associated with increased rates of suicidal thoughts and actions versus placebo [75].

An open-label trial of bupropion sustained release (SR) in adolescents (N = 24, age range 11–16) with ADHD and MDD showed that both disorders remitted after 8 weeks at a maximum dose of 6 mg/kg/day or 300 mg/day. Bupropion SR was generally well tolerated, and no one discontinued medication because of side effects [44]. In addition, a prospective case-control and a nationwide longitudinal cohort study have found evidence of a protective effect of ADHD pharmacotherapy on future mood disorders that persisted after adjusting for potential sociodemographic, and clinical confounders [76, 77].

There is also the question as to whether the presence of ADHD alters the response to antidepressants. In a large randomized, placebo-controlled trial of paroxetine in adolescent MDD, patients with comorbid ADHD were found to have significantly lower response rates to both placebo and paroxetine [78]. However, these results are difficult to interpret in light of the weak efficacy and tolerability data for paroxetine for the treatment of depression in children and adolescents, leading to recommendations to not use this agent in children [79]. In the Treatment for Adolescents with Depression Study (TADS), participants with MDD and ADHD showed no statistically different response for depressive symptoms to cognitive behavioral therapy (CBT), fluoxetine therapy, or combined treatment. When comparing within diagnostic groups, combined treatment produced superior improvement ($p < 0.009$) in depressive symptoms than either monotherapy for youth with MDD but not ADHD. The preferential improvement of combined therapy for depressive symptoms was not seen in youth with ADHD. ADHD was not associated with greater dropout (27.4 vs. 25.5% without ADHD) during the 36-week treatment [80].

These joint results demonstrate that ADHD can be safely treated in the presence of ADHD, but it does not acutely lead to improved mood. The presence of stabilized ADHD does not appear to reduce the efficacy of treatments of depressive disorders.

ADHD and pediatric bipolar disorder or chronic persistent irritability

The treatment literature is complicated by the field's shifting diagnostic formulation of bipolar disorder. Much of this work was conducted when severe persistent irritability was viewed as a sufficient criterion for bipolar disorder. Therefore, it is not clear if these results would translate to children or teens who meet full diagnostic criteria for The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [16], bipolar disorder or would now better apply to children meeting criteria for DMDD or SMD.

Scheffer and colleagues conducted an 8-week open-label trial of divalproex sodium, followed by a 4-week randomized, double-blind, placebo-

controlled crossover trial of mixed amphetamine salts (MAS) in participants ages 6 to 17 years with bipolar disorder. In this study, presence of either elation or grandiosity was required to differentiate mania from ADHD and other behavioral problems. Results showed that MAS safely and effectively treated ADHD symptoms (CGI improvement score, $p < 0.0001$) after manic symptoms were stabilized with divalproex sodium [52].

Findling and colleagues investigated the efficacy and tolerability of immediate release methylphenidate in a 4-week, double-blind, placebo-controlled trial in youths ages 5–17 who met DSM-IV criteria for bipolar disorder and ADHD and were on a set dose of a mood stabilizer. They were randomized to 1 week each of placebo, and three different doses of IR methylphenidate dosed twice a day. The IR methylphenidate was well tolerated and produced large reductions (Cohen's $d = 0.90$) in ADHD symptoms. There was no significant change in CDRS-R or Young Mania Rating Scale (YMRS) scores [50].

There are no published controlled clinical studies that have evaluated the efficacy of atomoxetine at treating ADHD symptoms in patients with comorbid bipolar disorder. In a case series of seven children on mood stabilizers, atomoxetine was well tolerated and all but one patient demonstrated significant improvement on ADHD symptoms [51]. In a larger open-label study by the same group, atomoxetine was associated with large reductions in ADHD but mood symptoms [49].

While there is a general paucity of controlled data for CNS stimulants for the treatment of ADHD in youth with mood disorders, there is a rapidly expanding literature based for the use of CNS stimulants for the treatment of irritability, including youth meeting criteria for SMD or DMDD. In the Multimodal Treatment Study of ADHD, CNS stimulants were associated with large reductions in symptoms of ADHD and moderate reductions in levels of parent-rated irritability. For irritability, study-based medication treatment outperformed behavioral treatment but not community-based medication treatment. Multimodal treatment led to the greatest reductions in irritability over the 14 months of study-based treatment [56•]. Irritability did not moderate the level of ADHD symptom improvement. In a post hoc analysis of a double-blind crossover study using low, medium, and high doses of IR methylphenidate, CNS stimulants were equally efficacious for treating ADHD in youth with and without SMD symptoms. SMD symptoms improved as ADHD improved [60]. In a prospective open-label trial of stimulants in youth with ADHD and SMD, both methylphenidate and amphetamine (AMPH) preparations were well tolerated by children and associated with clinically significant reductions in externalizing symptoms but only mild improvements in mood. Most participants still exhibited significant global impairment after the CNS stimulant was optimized, suggesting the need for additional treatment [54].

In a randomized, controlled trial of children with ADHD and severe aggression, parent training and open-label optimization of the CNS stimulant led to significant reductions in aggression, ADHD symptoms, and other behavioral problems. However, after 3 weeks, most participants still manifested elevated levels of aggression and were randomly assigned to blinded risperidone or placebo. Risperidone at a mean dose of 1.65 mg/day led to moderate but variable improvement in aggressive behaviors [57].

Augmentation with risperidone was superior to placebo in reduction of ADHD and oppositional-defiant disorder symptoms and associated impairment; however, clinical improvement was context specific and effect sizes ranged from small to moderate [58]. Similarly, promising results have been found in a controlled trial of Depakote following dose optimization of CNS stimulants and parent training [53]. However, lithium did not outperform placebo in this population [55]. Given the links between irritability and depression as well as the high rates of anxiety disorders in irritable youth [21, 22, 26, 81], antidepressants are also being explored for treatment of severe mood dysregulation and then disruptive mood dysregulation disorder [82]. However, no results have been published to date. In the Multimodal Treatment Study of ADHD, behavioral treatment was associated with significant reductions in irritability over time (ES = .42) [56•], and intensive behavioral treatments for ADHD have been found to be equally effective in ADHD youth with and without SMD symptoms [60]. However, these joint results are limited by the lack of extended no-treatment group. Waxmonsky and colleagues conducted a randomized trial of an integrative group therapy for children with SMD and ADHD employing parallel parent and child sessions over 11 weeks. The joint treatment package was associated with greater reduction in parent-rated irritability than with CNS stimulants plus community-based psychosocial treatment. In those completing the majority of sessions, significant improvement in other mood symptoms was seen as measured by the CDRS-R and YMRS [61].

There is emerging evidence that psychosocial and pharmacological treatments for ADHD reduce irritability without worsening other mood symptoms. CNS stimulants also appear to be a safe and tolerable treatment for ADHD in youth with stabilized bipolar disorder.

Treatment of ADHD and anxiety disorder

Pharmacological intervention of ADHD and anxiety disorder

Compared to mood disorders, there has been more investigation of the treatment of youth with ADHD and anxiety. Early work found that anxiety was associated with reduced response to IR methylphenidate as measured by blinded parent and teacher ratings [64, 69]. In a double-blind, placebo-controlled, crossover trial of methylphenidate among 43 children with ADHD, response rate to CNS stimulants was higher in the non-anxious youth while response to placebo was higher in anxious youth. Anxiety status did not impact tolerability [68]. More recently, in a double-blind, placebo-controlled, 2-week medication trial of methylphenidate, Ter-Stepnian and colleagues found that children with ADHD who have comorbid anxiety exhibited a decreased response to IR methylphenidate on parent and teacher ratings (0.5 mg/kg) vs. those without anxiety [70]. However, other studies including double-blinded RCTs found comparable levels of response to IR methylphenidate in anxious and non-anxious youth [63, 65]. In the Multimodal Treatment Study of ADHD, anxiety did not predict a poorer response to stimulant medication and parent-rated anxiety predicted an improved response to behavioral treatment for ADHD. However, child (self)-rated anxiety did not predict response to any type of treatment [6].

Several studies have examined the impact of CNS stimulant treatment of ADHD on the change in anxiety symptoms. In a study among children with ADHD and comorbid anxiety disorder, open-label optimization of CNS stimulants was robustly effective for improving ADHD. Approximately one in five participants no longer had impairing anxiety after treatment of their ADHD. The remaining 80% were randomly assigned to fluvoxamine (mean dose 145.4 mg) or placebo for 8 weeks. While combined treatment was well tolerated, fluvoxamine did not outperform placebo [62]. In an open-label study of methylphenidate (0.5–1 mg/kg) among children with ADHD and comorbid social phobia, improvement in ADHD symptoms correlated with a parallel improvement in social phobia [67].

Atomoxetine has been safely used in children with ADHD and comorbid anxiety disorders. Geller and colleagues randomized 176 youth to atomoxetine (up to 1.8 mg/kg per day) or placebo for 12 weeks. There was a significantly greater improvement in the ADHD-RS score for patients with atomoxetine versus that for placebo (ES = 0.8, $p < 0.001$). Milder but still significant benefits of atomoxetine were seen for anxiety (ES = 0.4, $p < 0.010$) on the clinician-administered Pediatric Anxiety Rating Scale [66]. In a double-blind study comparing atomoxetine plus placebo with atomoxetine plus fluoxetine, anxiety and ADHD symptoms improved to a comparable degree across both treatment groups (mean change for atomoxetine plus fluoxetine vs. atomoxetine: on MASC total score – 13.4 vs. – 11.3, on ADHD-RS score – 24 vs. – 20.5) [48].

There is mixed evidence for the effectiveness of CNS stimulants for improving ADHD symptoms in youth with comorbid anxiety disorders although the largest ADHD treatment study to data did find them to be an efficacious ADHD treatment in this population. Atomoxetine has been found to be a tolerable and effective treatment for improving ADHD in children with anxiety, with some data supporting a concurrent reduction in anxiety.

Psychological intervention of ADHD and anxiety disorder

There are well-established psychosocial treatments for pediatric anxiety that have been studied in ADHD youth. Costin et al. examined the role of an 8-week, cognitive-behavioral, family-based intervention for five boys ages 10–12 with ADHD, oppositional-defiant disorder, and anxiety disorder. While satisfaction and adherence were high, there were no changes on symptomatology [71]. A second study examined the efficacy of a joint psychosocial intervention integrating parent management for ADHD with family-based CBT for anxiety in a 10-week study of eight children ages 8–12 with ADHD and an anxiety disorder. There was significant and clinically meaningful improvements in ADHD and anxiety symptoms at 1-week post treatment, but only anxiety symptoms declined into the subclinical range. At 6-month follow-up, treatment effects were maintained and ADHD symptoms also fell to subclinical range [73]. Neither study employed an active comparator.

In a Child/Adolescent Anxiety Multimodal Study (CAMS) of 488 children ages 7–17, ADHD predicted poorer immediate treatment response to child-focused CBT and as well as reduced remission rates 6 months post treatment. No moderating effects of ADHD were found for the pharmacotherapy [72•]. Maric and colleagues found a family-based anxiety treatment to be more effective in ADHD youth than a child-based treatment, with no differences

between interventions for children low in ADHD symptoms [74•]. In the Treatment of Severe Childhood Aggression (TOSCA) study, comorbid anxiety symptoms did not moderate any effect on treatment, which included CNS stimulants, parent training, and risperidone [59•]. However, psychosocial treatments were given jointly with medication, so it was not possible to examine effects separately for each treatment modality.

Discussion

Uncomplicated ADHD is typically treated in primary care settings and responds to a wide range of treatments [6, 36]. However, a sizable percentage of youth with ADHD have comorbid mood and anxiety disorders that can complicate treatment. We summarized the relevant treatment studies published over the past 30 years (see Table 1) for anxiety, mood disorders, and irritability/SMD/DMDD in youth with ADHD. The majority of the studies support that existing treatments for ADHD and internalizing disorders can be safely used in youth with these complex presentations, and that ADHD symptoms meaningfully improve with treatment. The impact of treatment on internalizing symptoms is more variable, with the largest reductions seen for irritability and the smallest for depressive symptoms.

Depressive disorders

Compared to anxiety, there is a relative paucity of data supporting how to manage ADHD comorbid with a depressive disorder. Similar to anxiety, some of the best data is for atomoxetine with clear evidence of effect for ADHD but at best limited support for the treatment of depression [43, 48]. Atomoxetine does carry a black box warning for inducing new or worsening suicidal ideation or self-harm behaviors, but the collective studies support its safety in youth with depressive disorders. The incidence of expressed suicidal ideation or self-harm attempts was under 1% in the atomoxetine registry trials. These rates are not elevated compared to those reported in children treated with CNS stimulants for ADHD [75] and are lower than those seen in antidepressant trials in youth [83].

CNS stimulants have not been well studied in youth with depression but have shown effectiveness as an augmenting agent for antidepressants in adults [84, 85], suggesting they be a possible option. In addition, studies in youth with subthreshold mood symptoms and ADHD document that ADHD treatments are tolerable and are associated with at least mild decreases in mood symptoms [53, 54, 60]. While bupropion has controlled data to support its efficacy for pediatric ADHD, its effects are somewhat modest compared to those of CNS stimulants [86]. There is no controlled data to support its efficacy for pediatric depression. As with all FDA-approved antidepressants, it carries a black box warning for new onset or worsening suicidal ideation or behavior. Tricyclic antidepressants have been found to be effective for the treatment of ADHD but have appreciable safety concerns and limited efficacy data for pediatric depression. Serotonin and norepinephrine reuptake inhibitors have not been found to be effective for the treatment of pediatric ADHD [87].

Given the lack of pediatric data, clinicians should not expect that the treatment of ADHD will routinely improve comorbid depressive symptoms. Fortunately, TADS found that in teens, either CBT or fluoxetine may be effective for treatment of depression [80]. Compared to other agents for depression, fluoxetine has a robust database leading to FDA approval for major depression and a long half-life, making it a good first choice for adolescents with ADHD who may be prone to limited medication compliance. The finding that CBT was more effective in ADHD than non-ADHD youth was surprising and opposite what was seen in CAMS. TADS results are limited by the small size of the ADHD subgroup and the milder severity of depressive symptoms in the ADHD subset [80]. However, CBT has been adapted for use as a treatment for adult ADHD [88] so it is possible that the CBT in TADS may have enhanced ADHD symptom control; however, this would not explain the different results between TADS and CAMS. Study differences could be due to the age of the patients where over 70% of participants in CAMS were under the age of 13, while the mean age was 14.6 in TADS. Moreover, adolescents volunteering for an intensive treatment study for depression may be fairly motivated for treatment, limiting the generalizability of results. TADS also had a more intensive parent component than CAMS, which could have buffered the impact of ADHD symptoms.

Selective serotonin reuptake inhibitors (SSRIs) have been associated with increased restlessness, and treatment of mood symptoms may unleash preexisting impulsivity that was inhibited by anxiety, especially in settings outside of the home. Neither of these changes would be suggestive of medication-induced mania or worsening of mood unless manifesting with other mood symptoms such as decreased sleep need or increased irritability. The risk of adverse emotional responses to any medication working in the CNS should always be reviewed with patients and parents, as tolerability can never be assumed.

The Texas Medication Algorithm Project (TMAP) recommends initial treatment with stimulants for children with ADHD and a comorbid depressive disorder, except when the child is actually suicidal or psychotic [89]; however, there remains little data to guide clinicians about sequencing treatments for ADHD and depression. Suicidal ideation or any self-harm behaviors should always be directly assessed and never assumed that it is just an impulsive statement stemming from the ADHD. Some studies observed a protective effect of ADHD treatment on future depression [76, 77], so a patient's risk for depressive symptoms should be considered when making a decision to continue ADHD treatment or not.

Bipolar disorder

CNS stimulants carry a warning for inducing mania or psychoses. However, several studies have found that stimulants are safe and effective for the treatment of ADHD in children and adolescents with bipolar disorder once mood symptoms have been stabilized with medication [50, 52]. A meta-analysis of the pharmacological treatment of mania in youth indicated that those with comorbid ADHD tended to be less responsive than those without ADHD [90]. However, it may be that many of those cases with ADHD and bipolar disorder would now be reclassified as DMDD, where some mood stabilizers have not proved to be efficacious. Therefore, these results should not be interpreted as a

clear indication that pediatric bipolar disorder + ADHD is less responsive to established mood-stabilizing treatments. There are only a few evidence-based psychosocial interventions for pediatric bipolar disorder. Many of the participants in these trials had ADHD, and these interventions did show benefit for reducing ADHD symptoms [91, 92], making them reasonable treatment options when available.

There is little debate that mania needs to be treated first and that any consideration of treating ADHD should not occur until after the mania has stabilized. In children in whom the mania diagnosis is less clear (only aggression, irritability, and mood lability) and the presence of ADHD is well established, then a CNS stimulant trial would be a reasonable first step given their capacity to improve irritability, established safety profile, and ease of use.

Irritability

The assessment and treatment of irritability in children with ADHD has been a topic of great interest over the past few years [22]. There is a clear signal that psychosocial and pharmacological treatments for ADHD reduce irritability with generally good tolerability. The combination of these two modalities may be the most efficacious for reducing irritability [54, 56•, 61]. These joint results suggest the value of first optimizing treatment for ADHD prior to considering other medication classes. If still needed, both valproate [53] and atypical antipsychotics [57] but not lithium [55] have been found to improve irritability in youth with SMD/DMDD. Given the high rates of comorbid anxiety in youth with ADHD and SMD/DMDD, the efficacy and tolerability of effective anxiolytic treatments in children should also be explored. Currently, the NIMH is conducting a trial examining the effects of addition of citalopram on stimulants medication but results are pending [93].

Anxiety disorder

There is a solid, albeit mixed evidence base for the treatment of ADHD in children with anxiety, mostly examining social phobia, generalized anxiety, and separation anxiety disorders. Early studies largely examined the impact of IR methylphenidate in small samples, with several finding that medication could exacerbate anxiety symptoms. However, the largest ADHD clinical trial to date (the Multimodal Treatment Study of ADHD) found no evidence of this negative effect, and most recent work has found that treatment of ADHD is associated with improved anxiety symptoms [6, 48, 62, 67, 94]. ADHD treatment may indirectly reduce anxiety by decreasing the number of anxiogenic situations at home, school, and with peers experienced by the patient. Besides IR methylphenidate, atomoxetine has been the most studied agent, with all trials showing that it can improve ADHD without exacerbating anxiety symptoms and some finding evidence of reduced anxiety symptoms [48, 66]. Compared to other ADHD agents, atomoxetine has a delayed onset and higher rates of nonresponse [95], so it may not always lead to optimization of ADHD symptom control. There has been little formal investigation of extended released versions of methylphenidate or AMPH in anxious youth.

Results are mixed as to how ADHD impacts the treatment of anxiety. One small study found only mild benefit of SSRIs for improving anxiety in children with ADHD [62], but the large multisite CAMS found no evidence of reduced

response to SSRIs in children with ADHD [72•]. There has been little formal investigation of the capacity of anxiety treatments to reduce the need for subsequent ADHD treatment, but a recent meta-analysis found a significant protective effect of CNS stimulants for ADHD on future anxiety (RR = 0.86) when compared with placebo, with evidence of dose-dependent effects [94].

There are numerous well-established psychosocial interventions for pediatric anxiety with effects at least as robust as those seen with medication [96]. CBT is the most well-researched intervention for pediatric anxiety. As CBT requires a fair level of patient engagement, sustained attention, and task persistence, it has been theorized that children with ADHD may be less responsive to CBT [72•, 80]. In the CAMS, there was a signal of reduced efficacy for CBT in youth with ADHD [72]. A more recent study among youth (ages 8–18) with ADHD and anxiety found preferential response to psychosocial interventions for anxiety employing a family component versus those only engaging the patient [74•]. Interestingly, in the Multimodal Treatment Study of ADHD, elevated levels of parent-rated anxiety were found to predict a preferential response to behavioral treatments for ADHD. However, it is possible that some parents may identify the restless, irritability, or negative affect seen with ADHD as anxiety symptoms. Therefore, the findings of the Multimodal Treatment Study of ADHD may not translate to children with recurrent worry or other internalized anxiety symptoms [6, 27].

The TMAP drew on ADHD experts to publish a consensus algorithm for the treatment of ADHD that also addressed management of comorbidity [89]. The results of this review suggest that it is reasonable to start with initial treatment of ADHD, consistent with the findings of TMAP. The response to pharmacological treatments for ADHD can be assessed more quickly than that for antidepressant medication as most ADHD medications have a relatively quick onset. In addition, there are numerous well-established rating scales for ADHD that can be filled out by parents and teachers [97]. Behavioral treatments for ADHD may also improve anxiety. If impairing anxiety persists after treating ADHD, then use of CBT, antidepressants, or both would be reasonable options. The combination of SSRIs and CNS stimulants or SSRIs with non-stimulants has been found to be tolerable [48, 62, 80]. While AMPH does have mild serotonergic effects, their combination with SSRIs is considered safe [98, 99]. Several SSRIs are potent 2D6 inhibitors, which may increase levels of atomoxetine, but elevated blood levels of atomoxetine are not routinely associated with diminished tolerability [100]. Children prone to somatic anxieties may find the on/off effects of CNS stimulants challenging to tolerate. Therefore, if a child's anxiety primarily manifests through physical symptoms, then CNS stimulants with a long therapeutic duration, non-stimulants, behavioral treatments, or treatment of the anxiety before ADHD may be preferred.

Side effect or symptom?

A variety of adverse emotional responses have been reported to be a side effect of ADHD medications [101, 102]. Yet, mood and anxiety symptoms are common in youth with ADHD [103] and failure to measure these constructs before initiation of treatment for ADHD can lead to interpreting comorbid symptoms as treatment-induced adverse events. Therefore, we recommend use of structured side effect scales, such as the Pittsburgh Side Effect Rating Scale [104] or

Barkley Side Effects Rating Scale [105] that query common mood symptoms such as irritability, anxiety, or social withdrawal. As is the case with motor/verbal tics [106], studies that have employed these measures at baseline have found that rates of internalizing symptoms do not meaningfully increase with ADHD medication and in some cases, actually improve [54, 60, 107].

With CNS stimulants, a dose can be safely withheld to examine the temporal association between medication and symptoms. Many of these "side effects" do not turn out to be causally related to the medication once they are systematically assessed. Still, it is important to recognize that any psychotropic medication can be associated with adverse emotional effects. Any complaint of adverse emotional effects should be explored. Rates of adverse emotional side effects with ADHD medications are higher in younger children [108] and those with autism spectrum disorder [109]. Starting at the smallest available dose and increasing the dose gradually is recommended in these populations. Tolerability of CNS stimulants may improve with age. Therefore, it is reasonable for clinicians to reconsider CNS stimulant for a child if it has been over a year since they last used a medication in this class, and if the initial side effects were not severe.

Worsening mood or anxiety symptoms that onset later in the day may be associated with loss of the therapeutic effects of CNS stimulants. If this appears to be the pattern, then switching to a longer acting formulation or combination of an alpha agonist and a CNS stimulant to extend duration may be reasonable. Clinicians should also consider psychosocial interventions for comorbid internalizing symptoms, particularly since the long-standing assumption that ADHD symptoms would interfere with counseling efficacy is not well supported by the literature [6, 80], with the possible exception of child-focused interventions lacking an intensive parent component.

Conclusion

ADHD commonly presents with symptoms of mood and anxiety. These comorbid symptoms produce additional impairment and place children at greater risk for future morbidity. Therefore, it is imperative to assess and treat mood and anxiety disorders in youth with ADHD. The extant literature suggests that ADHD can be safely treated with either pharmacological or behavioral treatments in the presence of mood and anxiety disorders. There are mixed results about the impact of treating ADHD on mood and anxiety symptoms, with anxiety and ADHD being the most well-studied comorbidity. While more work is needed, treating ADHD appears to lead to moderate to large reductions in irritability but at best mild reductions in depressive symptoms. The presence of ADHD does not appear to reduce the efficacy of pharmacological treatments for the internalizing disorder. There is less data on the impact of ADHD on psychosocial treatments for internalizing disorders, but at least in adolescents, ADHD does not appear to meaningfully impact efficacy.

There has been little formal investigation of sequencing effects in children with ADHD and mood or anxiety disorders to guide clinicians. When pharmacological treatment is being considered, it may be reasonable to start with ADHD, given the ease of administration and relatively quick onset of most ADHD medications unless there is clear evidence that the anxiety or mood

disorder is associated with a greater level of impairment, as would be the case with mania. Psychosocial treatments are evidence-based and tolerable interventions for pediatric ADHD, anxiety, and mood disorders and can be tailored to the individual needs of complex patients. They should always be considered as an initial treatment option versus being reserved for medication non-responders. By using both psychopharmacologic and psychosocial interventions in a flexible manner, clinicians will have a wide variety of tools for management of complex cases.

Compliance with Ethical Standards

Conflict of Interest

Dr. R. Baweja declares that he has no conflict of interest. Dr. Waxmonsky, in the past 3 years, received research funds from NIH and Pfizer and served as a consultant for Noven Pharmaceuticals, IronShore, Purdue Pharma, and NLS Pharma.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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