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Mood Stabilizers vs Stimulants for the Management of Attention-Deficit/Hyperactivity Disorder and Comorbidity Bipolar Disorder

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By

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Abstract

BD and ADHD share a lot of similar symptoms such as comorbidities, age of onset, chronic, enduring course of illness with interference of vocational, educational, and developmental milestones. There is immense challenge when it comes to differentiating these disorders due to significant overlap and variable courses of psychopathology in children. Providers need to be aware of the medications that are beneficial for each condition separately and which medications can benefit both conditions. Mood stabilizers are commonly used in bipolar disorder while stimulants are a common treatment for ADHD. A literature review was performed using search databases such as PubMed to answer the question of whether mood stabilizers, stimulants, or the combination of the two would have the most positive effect on these two disorders in children. A total of 14 articles fit the criteria for this literature review. The diversity of pharmacological interventions, including mood stabilizers like lithium and divalproex sodium, and atypical antipsychotics such as aripiprazole and risperidone, underscores the complexity of managing this population. The reviewed literature suggests that stimulant medications, such as lisdexamfetamine dimesylate and mixed amphetamine salts, may contribute to an improved quality of life for individuals with comorbid ADHD and BD. This literature review determined that children with BD and comorbid ADHD respond well and show improvement in ADHD symptoms when treated with polypharmacy of a mood stabilizer and a stimulant, with the suggestion that the mood stabilizer be started first before adding the stimulant.

Keywords: attention deficit disorder with hyperactivity, ADHD, bipolar disorder, central nervous system stimulants, antipsychotic agents, anticonvulsants, and piperazines.

Introduction

Bipolar disorder (BD) and attention-deficit hyperactivity disorder (ADHD) are both psychiatric mental conditions that affect many aspects of one's life. BD is often associated with prominent mood, aggressive behaviors, and sleep, as well as impulsive behaviors in spending, promiscuity, and substances. ADHD is more often known for fidgeting, disorganized performances due to inattentiveness, forgetfulness, and distractibility (Marangoni et al., 2015). Comparing and contrasting the two conditions by overlapping symptoms revealed that non-overlapping symptoms have low prevalence and therefore create a challenging differential diagnosis. ADHD is often seen with other comorbidities such as conduct disorder, oppositional defiant disorder, or anxiety disorder. BD already has a high co-occurrence with other psychiatric disorders with around 50% of BD patients being treated for multiple other comorbidities (Altinbas, 2021). These other comorbidities can include ADHD, obsessive-compulsive disorder (OCD), anxiety disorders, personality disorders, and alcohol-substance use disorders (Altinbas, 2021). Much of the research on these conditions shows that the comorbidity of BD in children with ADHD is around 22% and children with BD have an estimated 85% comorbidity of ADHD (Hegerl et al., 2010). Both BD and ADHD are more common in males with the combination of the two conditions being more common in younger subjects. Comorbid BD and ADHD has been shown to have an earlier BD onset and present a chronic BD course with an irritable mood being a more common occurrence.

Early symptoms such as periods of elevated mood, inappropriate sexual behaviors, severe irritability, and decreased sleep can be noted as early as age three in BD and help differentiate these patients from those with ADHD. Symptoms such as suicidal ideation, sadness, and changes in appetite are noted to be discriminators for BD from ADHD around the age of seven. BD is

also associated with physical complaints, bedwetting, and night terrors whereas ADHD cases do not show these symptoms as frequently. Symptoms such as poor frustration tolerance, OCD, anxiety, hyperactivity, short attention span, and impulsivity are common in both BD and ADHD groups and therefore do not discriminate between the two (Marangoni et al., 2015).

Three of the main areas of symptom overlap between BD and ADHD are distractibility, psychomotor agitation, and talkativeness. While both ADHD and BD are known for early insomnia and sleep resistance, BD is more often associated with reduced total sleep time, fragmented sleep, and parasomnias. ADHD children have mood symptoms that stem from difficulties with academics or social aspects of life, while BD children have primary mood symptoms such as mood lability, crying spells, severe irritability, temper tantrums, and dysphoria. When it comes to suicidality, suicidal ideation and attempts are more prevalent in children with BD, while attempts and completed suicide are at increased risk with ADHD. Psychosis along with bizarre behavior is more often seen in youths with BD, not ADHD. BD can show various forms of aggression such as verbal aggression or violent behavior while ADHD is more likely to have physical and verbal aggression stemming from irritability (Marangoni et al., 2015). ADHD in children is associated with more difficulties in academic functioning due to poor concentration and motor control, poor working memory, challenges with time perception, and inattention. ADHD has more neurocognitive deficits that make behavioral responses and brain processing more challenging. The neurocognitive impairment in BD is more commonly studied in the adult population, with difficulties in working and verbal memory, sustained attention, poor problem solving, and diminished executive functioning (Rucklidge, 2006). BD children are more likely to have fluctuating performances at school that vary with their periods of emotional instability. A study by Rucklidge (2006) demonstrated the combined group of BD-

ADHD subjects showed the greatest deficits in the areas of inhibitory control and verbal memory.

Having a positive family history, especially a first-degree relative, increases the risk of having BD to approximately 9%, which is ten times the risk of the general population. Twin studies reviewed showed 58 to 85% heritability of BD while the risk of ADHD heritability is 60 to 80% (Marangoni et al., 2015).

The course of BD can vary depending on episodic or chronic states. Most cases of BD onset experience temperamental mood symptoms and can have a "premorbid" or very symptomatic state. Chronic courses of BD in children often alternate syndromal and subsyndromal phases with those intervals that are symptom-free. Episodic symptoms can vary from no symptoms at all for weeks or months to unremitting symptoms or chronic symptoms for months on end. Those children with ADHD type were more likely to see a course of improvement over time, while the inattention type was linked to negative outcomes and worsened with time or did not improve at all.

Statement of the Problem

BD and ADHD share a lot of similar symptoms such as comorbidities, age of onset, chronic, enduring course of illness with interference of vocational, educational, and developmental milestones. There is immense challenge when it comes to differentiating these disorders due to significant overlap and variable courses of psychopathology in children. Children themselves present as more challenging cases as they are still developing, and the course of the condition can change and evolve with their growth. Children struggling with comorbid ADHD and BD are at increased risk for academic and social difficulties. Clinicians

need to be more thoroughly prepared with data from areas of epidemiology, family history, clinical features, comorbidity, and course of illness. Unfortunately, these two conditions are commonly mistaken for each other or misdiagnosed all together which further delays treatment for these children. Providers need to be aware of the medications that are beneficial for each condition separately and which medications can benefit both conditions. Mood stabilizers are commonly used in bipolar disorder while stimulants are a common treatment for ADHD. Each of these medications has known benefits for one condition, but can they also benefit the other condition at the same time? This area of research is slim, especially pertaining to children and adolescents. Future research is needed to help differentiate ADHD and BD when more complex cases arise and can improve the treatment and overall outcome for these patients.

Research Question

In children and adolescents with comorbid attention-deficit/hyperactivity disorder and bipolar disorder, do mood stabilizers vs stimulants improve the quality of life?

Methods

A literature review was performed using electronic search databases such as PubMed. Keywords and mesh terms were used to narrow down the literature to those discussing ADHD and BD comorbidity and treatment options including stimulants or mood stabilizers. Keywords included attention deficit disorder with hyperactivity, ADHD, bipolar disorder, central nervous system stimulants, antipsychotic agents, anticonvulsants, and piperazines. Results were further refined by limiting articles to those published in the last 20 years. Other filters applied included classical articles, clinical studies, clinical trials, comparative studies, controlled clinical trials,

observational studies, and randomized controlled trials. The search yielded a total of 46 studies. Several studies were excluded because the population age was not in the desired range. This review mainly looked at studies that involved children and adolescents 18 and younger, although some adult studies were included due to limited research available. Some studies were excluded if they dealt with other comorbidities, such as major depressive disorder or conduct disorder. Any studies that involved other combinations of treatment options not pertinent to this review were excluded. Articles were limited to those in the English language. This narrowed the number of studies to seven. References from these studies were also used in the final number of studies utilized for this literature review. A total of 14 articles fit the criteria for this literature review.

Literature Review

Effectiveness of Mood Stabilizers on ADHD and Comorbid BD

State et al. (2004) conducted a retrospective study on the impact ADHD can have on bipolar adolescents when it comes to response to the medications lithium (Li) or divalproex sodium (DVPX). Subjects were chosen if they fit the criteria for bipolar disorder (BD) in DSM-III or DSM-IV and were treated with divalproex sodium or lithium. A total of 42 participants were selected, ages 12 to 19 years old. The clinician in this study was blinded in regard to treatment of the participants. Lithium was the medication treatment for 29 subjects, while divalproex sodium was the treatment used for 13 subjects. A modified Clinical Global Impression Scale (CGI-BP) was used to monitor bipolar disorder and was utilized by the clinician to rate improvement, with data collected from January 1992 to May 1999. Scales were used at admission, day five, day ten, and lastly on the discharge day. Response was considered a

score of one, very much improved, or two, much improved, on the CGI Scale. Adequate serum mood stabilizer levels were to be achieved before assessing response at day five and ten.

Mixed mania was present in 36/42 subjects, and ADHD was found in 14/41 subjects, with one subject not having adequate history for ADHD assessment (State et al., 2004). Thirty-four subjects saw an improved positive response rate (80.9%). Response rates were similar for each treatment group, with 82.7% in the lithium group and 76.9% in the divalproex sodium group (p = 0.656). For some subjects, lithium administration was started at a later date (4.7 days) than those subjects started on divalproex sodium (1.5 days) (p = 0.022). Of those subjects without ADHD, 92.6% (n = 25/27) were responders, while those subjects with ADHD comorbidity had a 57.1% (n = 8/14) response rate (p =0.007). Serum levels taken at discharge day were at a similar percentage for each medication group, 79.3% for lithium and 84.6% for divalproex sodium group. The therapeutic range for divalproex sodium of 50 to 150 μg/mL was achieved at discharge by 11/11 (100%) subjects who had their serum levels obtained. The therapeutic range for lithium of 0.8 to 1.5 mmol/L was achieved at discharge by 16/23 (69.5%) subjects who had their serum levels obtained. State et al. (2004) found there to be no significant difference in the lithium responses compared to the divalproex sodium responses in the subjects with ADHD and the subjects without ADHD. The response rate of those subjects with ADHD was 57.1% (n = 8/14) versus a response rate of 92.6% for those subjects without ADHD (n = 25/27) (p = 0.007). The conclusion of their study showed that adolescents with bipolar disorder and comorbid ADHD have a reduced acute response to the mood stabilizers lithium and divalproex sodium when used as the primary treatment of the manic bipolar phase (State et al., 2004). Some subjects in this study also received concurrent benzodiazepines or antipsychotics during their

hospitalization and therefore presents as a weakness for this study in terms of this literature review.

Tramontina et al. (2009) completed a study looking into the treatment effects of the antipsychotic aripiprazole as a mood stabilizer for children and adolescents with ADHD and comorbid BD. “The presence of ADHD in subjects with juvenile bipolar disorder (JBD) may predict a chronic rather than an episodic course of BD, with an irritable rather than elated mood, higher rates of other disruptive disorders, and a greater psychosocial impairment” (Tramontina et al., 2009, p. 757). Aripiprazole works in the brain by balancing both serotonin and dopamine, both of which could have a positive effect on BD and ADHD. Bipolar disorder and ADHD criteria from the DSM-IV were used to categorize subjects with manic or mixed states in this study. Subjects scoring ≥ 20 on the Young Mania Rating Scale (YMRS) were included in the study. Subjects with an IQ less than 70, any substance abuse, schizophrenia, pervasive developmental disorder, or presenting as a suicide risk were excluded from the study. Subjects who had a diagnosis that could interfere with the research, have used aripiprazole previously, or who have been taking any other medication in the four weeks before the admission of the study were also excluded. A total of 43 subjects met criteria for this study and had an age range of 8-17 years old. The 6-week double-blind study consisted of 18 subjects in the aripiprazole group and 25 subjects in the placebo group. Multiple assessments were used to monitor for symptom improvement, including the YMRS, the Swanson, Nolan and Pelham Scale-Version IV (SNAP-IV), Clinical Global Impressions-Severity of Illness Scale (CGI-S), Child Mania Rating Scale-Parental Version (CMRS-P), Children’s Depression Rating Scale-Revised (CDRS-R), and the Kutcher Adolescent Depression Scale (KADS). The primary outcome measures consisted of the YMRS, SNAP-IV, and weight, which were used at baseline and endpoint. The secondary

outcome measures which were also used at baseline and endpoint were the CGI-S, CMRS-P, CDRS-R, and KADS.

The results of Tramontina et al. (2009) showed the aripiprazole group had a significant decrease in scores in the YMRS (baseline: 27.22 vs. endpoint: 19.52, p =0.02, ES =0.80), the CGI-S (baseline: 2.05 vs. endpoint: 1.64, p =0.04, ES =0.28), and the CMRS-P (baseline: 21.16 vs. endpoint: 15.52, p =0.02, ES =0.54) at their endpoint assessments in comparison to their baseline. There was no significance found between aripiprazole and the placebo group when measuring for depression in the CDRS-R (16.33 aripiprazole vs. 14.04 placebo, p =0.59) and the KADS (6.72 aripiprazole vs. 5.48 placebo, p =0.19). The placebo groups did not see a significant reduction in endpoint scores. The mean and standard deviation of the final doses of aripiprazole were 13.61 ± 5.37 mg, with the placebo final doses being 15 ± 3.22 mg. The response rate, which consisted of 50% or more improvement in YMRS score, of the aripiprazole group was also significant in comparison to the placebo group (response = 88.9% vs. 52%, p =0.02), although there were more adverse effects noted with the aripiprazole group, such as sialorrhea and somnolence. The measures of weight gain (p = 0.25), BMI (p = 0.49), and SNAP-IV (p = 0.39) showed no significance in comparing aripiprazole to the placebo groups. There was less distractibility (p =0.05) and decreased grandiosity (p =0.01) in those subjects with only irritability alone, with no elated or expansive mood in their presentation. The authors concluded that manic symptoms can be effectively reduced while also improving global functioning with aripiprazole, but that ADHD symptoms were not affected. The fact that Tramontina et al. (2009) utilized a standard assessment scale to monitor ADHD signs and symptoms in their juvenile subjects gave this study strength. The sample size for this study was small which poses as a limitation. Long-term studies on the effects of aripiprazole are needed in the juvenile bipolar

population. Another limitation of this study was due to the lack of assessing environmental factors and how the exposure to things such as family functioning and expressed emotions can impact outcomes of the study.

Risperidone is another antipsychotic medication commonly used as a mood stabilizer for bipolar disorder. Similar to aripiprazole, risperidone works on dopamine and serotonin in the brain. Biederman et al. (2008) set out to prove whether or not risperidone would be effective in treating the symptoms of ADHD in children with comorbid bipolar disorder. Since BD and ADHD have much overlap in their symptomatology, it is possible that risperidone will be effective in treating both disorders. Thirty-one subjects (22 male, 9 female) aged 4-15 years old were selected and fit the DSM-IV criteria for BD, irritable mood for at least seven days, and also had three or four of the seven symptoms of mood disturbance. The study utilized multiple scales for measuring outcomes, which included the CGI-S and improvement CGI-I scales, the ADHD Rating Scale (ADHD-RS), YMRS, and the Kiddie Schedule of Affective Disorders and Schizophrenia Epidemiological Version (KSADS). Cardiac parameters, metabolic parameters, and adverse effects were also measured in this study. A decrease of at least 30% on ADHD-RS and CGI-I score of either one or two had to be obtained to be considered an ADHD responder. ADHD-RS was measured at baseline, week four, and endpoint. CGI-S, CGI-I were obtained at baseline and endpoint. Subjects were started at low doses of risperidone, with the dose increasing weekly based on the subject's response and how they were tolerating the medication. Subjects under 12 years old were started at 0.25 mg/day and increased weekly to a maximum dose of 2.0 mg/day. Those subjects older than 12 years old were started at 0.50 mg/day of risperidone and increased to a maximum dose of 4.0 mg/day (Biederman et al., 2008).

Biederman et al. (2008) study saw improved CGI-I results scoring one or two (much or very much improved) in 68% (n =21) of children with a mean final dose of 1.47 mg/day. Risperidone was shown to improve both mania symptoms in these subjects and ADHD symptoms when comparing baseline to endpoint scores. The ADHD symptoms that showed improvements were hyperactive-impulsive (p <0.05) and inattentive (p <0.05) symptoms. Improvements in CGI-I scores and the ADHD rating scale were seen in only 29% of subjects (n =6). Initial ADHD symptom numbers were higher in those subjects for whom risperidone did not show any manic symptom improvement. One adverse effect of risperidone was weight gain with significant changes from baseline (2.2 ± 2.2 kg; p <0.001). Cardiac and metabolic parameters had no significant differences from baseline to endpoint; however, there was a three-fold increase in prolactin levels (p <0.001). The authors concluded that although risperidone shows improvement in ADHD symptoms in children and adolescents with bipolar disorder, the results are only moderate. (Biederman et al., 2008). This study shows strength because there was improvement in ADHD symptoms in the population being studied. A limitation that the authors mention is the fact that this study was an open study. Studying these disorders in children is not an easy task and this study has strength in making that first step in the right direction. Future double-blind trials will be needed to further assess these medications and their effects on ADHD and BD.

Effectiveness of Stimulants on ADHD and Comorbid BD

Galanter et al. (2003) completed a study that investigated the effects of stimulants on ADHD children with or without manic symptoms. Previous studies have expressed concern that stimulants may cause an increase in mania symptoms in bipolar disorder. Their study attempted

to exclude children with bipolar disorder, but ultimately this was not the case due to the limitations of the resources the researchers had at their disposal in order to separate those with manic symptoms from those with bipolar disorder.

A total of 270 children, ages 7-9.9 years old, were used in the Galanter et al. (2003) study. The ethnicity of the subjects included Caucasian, African American, Black Hispanic, non-Black Hispanic, Asian American/Pacific Islander, mixed, and other. Subjects were grouped into four categories: Diagnostic Interview Schedule for Children (DISC) mania proxy-positive (n =29), DISC mania proxy-negative (n =260), Child Behavior Checklist (CBCL) mania proxy-positive (n =32), or CBCL mania proxy-negative (n =257). In total, 10% of subjects (n =29) fit the criteria for DISC mania proxy-positive, 11.1% of subjects (n =32) fit in the category of CBCL mania proxy-positive, and seven subjects (n =7) fulfilled the criteria for both positive proxies. The DISC and CBCL proxies and SNAP, which is an acronym of the developer's names and measures ADHD symptoms, were completed at baseline by the participants' primary guardian and teacher. Teachers and guardians used the 16-item Conners, Loney, and Milich (CLAM) scale to track participants' ADHD symptoms daily. The CLAM scale has subscales of Aggressive/Defiant (A/D), Inattentive/Overactive (I/O), and Mixed (I/O+A/D). Teachers and guardians were also to monitor the occurrence of 10 common adverse events of methylphenidate (MPH) and their severity using the Pittsburgh Side Effect Rating Scale (Galanter et al., 2003).

Response and adverse effects were not affected by the absence or presence of either proxy in this study. The adverse effects were similar for both the proxy subjects and the nonproxy subjects. The results showed a positive MPH response in ADHD children with mania symptoms over the 1-month titration trial. ADHD symptoms of attention, aggression, and impulsivity saw improvement in children with mania proxy. In conclusion, there was no increase

in irritability or increased adverse effects in ADHD children with manic symptoms when treated with the stimulant MPH (Galanter et al., 2003).

Armstrong and Kapolowicz (2023) noted the lack of information on how monotherapy with a stimulant will affect these disorders. Although the subjects they studied are adults, the information is still valuable. The two subjects used in their study, a 49-year-old female and a 27-year-old male, both met the DSM-V criteria for BD and ADHD. Mixed amphetamine salts (MAS) long-acting version were used for both subjects. The 49-year-old female subject experienced more manic episodes and major depressive disorder (MDD) symptoms, leaning more towards a bipolar II diagnosis. After two weeks on MAS 20 mg daily, this subject reported that her anxiety symptoms had decreased, she felt an improvement in her overall mood, and she reported being able to accomplish more throughout her days. She denied any manic episodes during the first two weeks of the trial. The next interview with the subject was at six months, where she reported more feelings of depression in the past two months. Due to the depression symptoms, Armstrong and Kapolowicz (2023) decided to add escitalopram 10 mg daily in addition to the MAS. At the eighth month of treatment, this subject showed improvements in her mood once again. At the initial interview, the patient scored a 15 on the patient health questionnaire (PHQ-9), which is a depression scale. She scored a 10 on the generalized anxiety disorder (GAD-7) scale at the initial interview. At the completion of the trial, this subject showed immense improvement in her scores, resulting in a score of four on the PHQ-9 and a three on the GAD-7. No mania episodes were reported for this subject during the entire eight-month trial, where before this trial she used to experience mania symptoms multiple times a month (Armstrong and Kapolowicz, 2023).

The 27-year-old male in Armstrong and Kapolowicz's (2023) study exhibited manic episodes, lasting up to four days at a time, around six times per year. This subject did not show symptoms of MDD but rather hypomanic episodes. His main symptoms of depression consisted of oversleeping, a lack of motivation, and a continual absence of energy. This subject also had thoughts of self-harm. The Adult ADHD self-report scale was utilized for ADHD symptoms alongside the DSM-V criteria for ADHD. There are six main dark boxes on the Adult ADHD self-report scale, and this subject presented with a mark in every one of those boxes. At the initial interview, this subject scored a 15 on the PHQ-9 and a 14 on the GAD-7. This subject saw improved symptoms and continued to have positive outcomes throughout the 6-month trial on 20 mg of MAS. There were no hypomania or symptoms of depression reported, with his mood also improving and his motivation increasing. This subject saw a decrease in his oversleeping and denied any problems with sleeping while on MAS. This subject also reported consistency with these symptoms during the study and denied any "wearing off" or "kicking in" feelings on the MAS. The final interview with this subject saw great improvement in his scores, with a PHQ-9 of zero and a GAD-7 of zero. The Adult ADHD Self-Report Scale was also administered again at the final interview, and this time the subject had no marks in the six dark boxes (Armstrong and Kapolowicz, 2023).

The results of the study by Armstrong and Kapolowicz (2023) demonstrated that each subject saw improvement in their bipolar symptoms and ADHD symptoms when taking 20 mg of MAS daily without the assistance of a mood stabilizer. This study showed that symptoms of mania and hypomania can both be improved with monotherapy of MAS, with both subjects effectively seeing a decrease in episodes experienced during the trial. The authors concluded that more research is needed on the outcome of long-term treatment of BD and comorbid ADHD with

MAS or other psychostimulants without the addition of a mood stabilizer. This study only gave insight into a short-term treatment with MAS, and therefore the results cannot be generalized for long-term therapy. Data was acquired from only two subjects which poses as a limitation in this study. A limitation that the authors noted as to why these results were obtained might be because the subjects could have atypical ADHD symptoms that are more closely associated with bipolar disorder without actually having a BD diagnosis. The authors also suggested the outcomes could be due to the subjects having BD with comorbid ADHD, which resulted in manic symptoms decreasing when treated with a psychostimulant, which is similar to other case reports. In conclusion, this study demonstrated that psychostimulants can be an effective therapy for manic or hypomanic symptoms of BD and comorbid ADHD. They noted that these two subjects, although they met the criteria for BD and ADHD in the DSM-V, had some atypical presentations of BD and ADHD, and therefore the results of this study may not be applicable to other cases of these disorders (Armstrong and Kapolowicz, 2023). A strength of this study is that it can apply to children and adolescents, as both case subjects noticed ADHD and BD symptoms begin when they were children, and the symptoms continued throughout their adolescent years and into adulthood.

McIntyre et al. (2013) completed a study to answer the question of what sort of effect adjunctive therapy with lisdexamfetamine dimesylate (LDX) has on metabolic and anthropometric parameters. They also sought to determine what effect LDX has on the severity of ADHD symptoms in adults diagnosed with BD. This study consisted of 45 adults who participated in a 4-week, open-label, phase IV study that involved flexible doses of adjunctive LDX. Subjects were recruited from the mood disorder psychopharmacology unit at the University Health Network. Subjects had to meet the DSM-IV-TR criteria for either bipolar I or

bipolar II and the ADHD criteria, with the adult ADHD diagnosis being confirmed via the Mini International Neuropsychiatric Interview (MINI Plus 5.0). The MINI Plus 5.0 criteria consisted of determining if the subject had at least six or more ADHD symptoms prior to the age of seven and the age of nine, or if they exhibited more symptoms during adulthood. The Wender Utah Rating Scale was the self-reporting tool utilized for childhood ADHD, and the ADHD Self-Report Scale was used to report on adult ADHD symptoms. The bipolar disorder of each subject must also be stable, meaning that they are non-rapid cycling, and there are no significant hypo/manic symptoms present. Table 1 shows the eligibility criteria required to participate in this study and the criteria used to exclude subjects from the study. Subjects were to continue with any pharmacotherapy and/or psychosocial involvement they were receiving for BD, such as treatment with mood stabilizers, antidepressants, anxiolytics/hypnotics, and antipsychotics. These treatments were not to be modified nor should any new treatments be started, besides the addition of LDX to their current regimen for the purpose of McIntyre et al.'s (2013) study.

Table 1

Eligibility and exclusion criteria from McIntyre et al. (2013) study on the effects of lisdexamfetamine dimesylate (LDX) on metabolic and anthropometric parameters in adults with bipolar I/II and comorbid ADHD.

Eligibility Criteria	Exclusion criteria
• Status: Outpatient • Age: 18-55 years • Male or female • Confirmed diagnosis of bipolar I/II disorder and comorbid ADHD via the MINI Plus 5.0 and DSM-IV-TR • A reliable birth control method used • Young Mania Rating Scale (YMRS) score: ≤12 • Clinical Global Impression Severity (CGI-S): <6 • Able and willing to provide written informed consent	• Focus of clinical attention is on a primary Axis I psychiatric diagnosis other than bipolar I/II disorder and comorbid ADHD • In the past 12 months, current rapid cycling course of illness • Current psychotic symptoms as part of bipolar I disorder • Within the past 3 months: active alcohol, illicit and/or other substance abuse • Current and clinically unstable medical condition • Inability to understand and engage in the process of informed consent • Inability to cooperate with study procedures (attending follow-up visits, study treatment orders) • Presence of known allergies or hypersensitivity to LDX

	• History of destabilization when exposed to psychostimulant medication • Current high risk of suicide • Current treatment of corticosteroids • Electroconvulsive therapy in the last 1 year • Current participation in a separate clinical research study involving an investigation

ADHD, attention-deficit hyperactivity disorder; MINI, mini international neuropsychiatric interview

Cited Source: McIntyre, R.S., Alsuwaidan, M., Soczynska, J.K., Szpindel, I., Bilkey, T.S., Almagor, D., Woldeyohannes, H.O., Powell, A.M., Cha, D.S., Gallaugher, L.A., & Kennedy, S.H. (2013). The effect of lisdexamfetamine dimesylate on body weight, metabolic parameters, and attention deficit hyperactivity disorder symptomatology in adults with bipolar I/II disorder. *Human Psychopharmacology,* 28(5), 421-427. https://doi.org/10.1002/hup.2325

In the first week, all subjects were started on 30 mg/day of LDX. Weeks two through four allowed for flexible dosing of adjunctive LDX between 30-70 mg/day, with tolerability taken into consideration. Waist circumference, weight, and body mass index (BMI) were the primary outcome measures examined for significant differences between baseline and endpoint values. There were many secondary outcome measures in the study by McIntyre et al. (2013), which included total cholesterol (TC) and fractionation, triglycerides, fasting blood glucose, and metabolic peptides such as leptin, ghrelin, adiponectin, resistin, and insulin. Scales that were used as part of the secondary outcome measures were the ADHD Rating Scale (ADHD-RS), CGI-Severity and Improvement (CGI-S and CGI-I), Conners' Adult ADHD Rating Scales (CAARS), Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) and the Adults with ADHD Quality of Life Scale (AAQoL). The ADHD-RS and the CAARS along with the primary outcome measures of BMI, weight, and waist circumference were administered on a weekly basis. The AAQoL was administered to subjects first at baseline, followed by week two, and lastly at endpoint interview. The Q-LES-Q was administered at baseline and the endpoint. Safety measures were completed throughout the study, reporting on vital signs, physical examination, adverse events, and electrocardiograms. The Columbia-Suicide Severity Rating Scale (C-SSRS) along with the CGI-S and the CGI-I were also administered for safety

assessment. The YMRS and the Mongomery-Åsberg Depression Rating Scale (MADRS) were assessed every week. Hypo/mania was carefully monitored for and defined by two successive interviews consisting of YMRS scores >12 and/or having a YMRS score >12 at the endpoint interview or requiring treatment for symptoms of hypo/mania. If any subjects were to experience symptoms of mood destabilization such as a score of six or seven on the CGI-I scale, then they were withdrawn from the trial (McIntyre et al., 2013).

Out of the 45 original subjects in the McIntyre et al. (2013) trial, only 40 of them received adjunctive treatment with LDX. There were five subjects excluded from the study, with four withdrawn due to different non-participatory reasons, and one discontinued because a medical condition that was uncontrolled was identified. Thirty-eight subjects recorded baseline measures and at least one following assessment measure. The criteria for adult ADHD confirmed by the MINI and the clinician-diagnosis were both met by 31 subjects, with the remaining seven subjects only meeting the criteria for adult ADHD via clinician-diagnosis. Three of the seven subjects did not adequately fit the child-onset ADHD criteria as defined by the Wender Utah Rating Scale. A total of 7/38 subjects recalled previous psychostimulant exposure. The results of the effect of LDX on metabolic parameters and clinical outcome measures are shown in Table 2 and Table 3. The parameters with a p-value <0.05 were shown to be statistically significant. At the final interview, the mean dose of LDX was 60±10 mg/day. McIntyre et al. (2013) separately analyzed the weight of individuals and noted the results showed the overweight/obese subjects had a significant decrease in BMI (p <0.001), while the healthy weight subjects with a BMI between 18.6-24.9 kg/m^2 did not show a significant difference in BMI (p =0.105) over the timeline.

Table 2

Effect of lisdexamfetamine dimesylate (LDX) on metabolic parameters.

	Baseline		Week 4		*p*-value	Effect size
	M	SD	M	SD		
BMI (kg/m^2)	28.46	5.78	27.89	5.71	<0.001*	0.53
Weight (kg)	83.97	19.57	82.30	19.36	< 0.001*	0.53
Waist circumference (cm)	98.54	17.42	97.35	16.98	0.001*	0.43
Waist-to-hip ratio (m)	0.90	0.09	0.89	0.08	0.056	0.25
Pulse (beats/min)	68.13	13.24	78.51	13.60	< 0.001*	0.50
Systolic blood pressure (mmHg)	115.34	12.80	119.91	11.96	0.053	0.24
Diastolic blood pressure (mmHg)	75.30	8.96	78.99	9.23	0.003*	0.38
Glucose (mmol/l)	4.64	0.43	4.67	0.59	0.739	0.00
Insulin (pmol/l)	39.94	31.18	35.00	28.40	0.250	0.05
Total cholesterol (mmol/l)	4.92	0.96	4.67	0.90	0.011*	0.19
LDL (mmol/l)	3.03	0.74	2.88	0.73	0.044*	0.12
HDL (mmol/l)	1.37	0.30	1.30	0.26	0.015*	0.18
Triglycerides (mmol/l)	1.14	0.61	1.07	0.40	0.382	0.03
Ghrelin (pg/ml)	35.77	13.72	39.59	23.68	0.485	0.02
Adiponectin (pg/ml)	1.31 X 10^7	6.85 X 10^6	1.25 X10^7	7.18 X 10^6	0.708	0.01
Resistin (pg/ml)	15292.73	4620.18	17339.93	6345.92	0.124	0.08
Leptin (ng/ml)	7.62	6.89	5.51	5.19	0.047*	0.12

BMI, body mass index; LDL, low density lipoprotein; HDL, high density lipoprotein. *$p < 0.05$

Cited Source: McIntyre, R.S., Alsuwaidan, M., Soczynska, J.K., Szpindel, I., Bilkey, T.S., Almagor, D., Woldeyohannes, H.O., Powell, A.M., Cha, D.S., Gallaugher, L.A., & Kennedy, S.H. (2013). The effect of lisdexamfetamine dimesylate on body weight, metabolic parameters, and attention deficit hyperactivity disorder symptomatology in adults with bipolar I/II disorder. *Human Psychopharmacology,* 28(5), 421-427. https://doi.org/10.1002/hup.2325

Table 3

Effect of lisdexamfetamine dimesylate (LDX) on clinical outcome measure.

	Baseline		Week 4		*p*-value	Effect Size
	M	SD	M	SD		
MADRS	8.78	6.54	5.89	7.66	0.035*	0.26
YMRS	1.26	2.02	0.84	1.62	0.589	0.08
ADHD-RS	37.68	7.95	12.65	13.03	< 0.001*	0.74
CAARS	133.16	27.46	72.19	33.93	< 0.001*	0.76
AAQoL	40.86	13.84	62.58	16.56	< 0.001*	0.51
Q-LES-Q (% max)	42.94	28.93	50.28	25.70	< 0.001*	0.40
CGI-S	4.50	0.66	2.67	1.12	< 0.001*	0.75

CGI-I	3.28 (week 1)	0.91 (week 1)	2.11	1.33	< 0.001*	0.57

MADRS: Montgomery–Åsberg depression rating scale; YMRS: Young mania rating scale; ADHD-RS: Attention deficit hyperactivity disorder self-report scale; CAARS: Conners' adult ADHD rating scales; AAQoL: Adults with ADHD quality of life scale; Q-LES-Q: Quality of life enjoyment and satisfaction questionnaire; CGI-S: Clinical global impression-severity; CGI-I: Clinical global impression-improvement. *$p < 0.05$

Cited Source: McIntyre, R.S., Alsuwaidan, M., Soczynska, J.K., Szpindel, I., Bilkey, T.S., Almagor, D., Woldeyohannes, H.O., Powell, A.M., Cha, D.S., Gallaugher, L.A., & Kennedy, S.H. (2013). The effect of lisdexamfetamine dimesylate on body weight, metabolic parameters, and attention deficit hyperactivity disorder symptomatology in adults with bipolar I/II disorder. *Human Psychopharmacology,* 28(5), 421-427. https://doi.org/10.1002/hup.2325

Certain items on MADRS contributed to the final score, such as the significant improvement in concentration (p <0.001), inner tension (p =0.023), and lassitude (p =0.013). The appetite item (p =0.007) on MADRS decreased over the timeline. At the time of the baseline interview, there was one subject who reported thoughts of suicide, but their subsequent visits displayed no such thoughts on the C-SSRS. Two subjects reported suicidal ideation during week one although there was no intent to act on these thoughts, with subsequent visits resulting in no such reports. The adverse effects most reported in week one were dry mouth (n =5), anxiety/nervousness (n =6), and anorexia (n =5). At the endpoint, adverse effect reports were decreased for anxiety/nervousness (n =1), and persistent for anorexia (n =4) and dry mouth (n =3). Irritability (n =5) and insomnia (n =5) were reported most during week two, with each showing a decline in reports by week four (irritability n =2; insomnia n =1) (McIntyre et al., 2013).

The general conclusion from the McIntyre et al. (2013) study is that there are beneficial effects of adjunctive LDX on multiple metabolic parameters, BMI, and body weight when used as a short-term treatment for adults with bipolar I/II and comorbid ADHD. Overall, the adjunctive LDX was tolerated well by the subjects in the study and had mitigating effects on ADHD symptom and depressive severity. There was no induction of mood destabilization or hypo/manic symptomatology present in the subjects of this study. The most significant decreases over the timeline were seen in the fasting TC, HDL, LDL, and BMI. There was a suggestion that

the decrease in leptin levels may be related to the reduction in body weight. This study had strength in its number of participants and in its broad range of outcome measures. The limitations of the study are due to its open-label method and its brief trial period. The results of this study cannot be generalized for long-term use of LDX, since there is a possibility that hypo/manic episodes may be induced with longer treatment periods. It is also possible that the change in appetite behavior LDX has could affect energy expenditure and/or consummatory behavior, neither of which were evaluated in this study. This study provided strong results on the effect of LDX adjunctive therapy but did not go into detail on what other medications each subject was already taking and how this may have played a role in the outcomes. We know that some of the subjects were already on medication for BD, but the study does not clarify how many subjects were affected and how long they may have been on these other medications. Continued research is required to study the effects of long-term treatment with LDX on subjects with ADHD and comorbid BD. Since the comorbidity of ADHD and BD is higher in children, further research should also focus on lengthier treatment periods of stimulants in children with ADHD and comorbid BD. Subsequent studies must evaluate the effect of stimulant monotherapy on BD and comorbid ADHD, without the involvement of other medications such as bipolar stabilizers.

Effectiveness of Combination Pharmacotherapy for ADHD and Comorbid BD

Findling et al. (2007) conducted a 4-week double-blind study that set out to answer the question of whether adding methylphenidate (MPH) to mood stabilizers, already prescribed to treat children and adolescents with ADHD symptoms and bipolar disorder, would be both safe and effective in decreasing the ADHD symptoms. There were twenty children and adolescents selected for this study, but only sixteen completed the trial. Adverse effects such as urticaria and

increased liver transaminases caused two subjects to drop out of the trial. The other subjects who did not complete the study did so due to hospitalization and a lack of adherence. The twelve males and four females were recruited from a bipolar disorder treatment study and also from a Midwestern academic medical center. The ages range from 5 to 17 years old, with all meeting criteria for both the bipolar spectrum and ADHD, which was confirmed by a board-certified child psychiatrist. The majority of the subjects were white/non-Hispanic, with the remainder being three Hispanics and one African American. Exclusion criteria included active neurological conditions or medical conditions related to mood symptoms, pervasive developmental disorders, mental retardation, the inability to swallow pills, and pregnant females. Any person with a history of alcohol or substance abuse/dependence were also excluded from the study. Nursing mothers, any significant neurological or medical illness, significant mania symptoms or depression during the week prior to enrollment, and any person on TCA, antipsychotic medication, or with suicidal ideation, were also excluded from this study. The study consisted of all the subjects starting a mood stabilizer one week prior to the start of the MPH doses: 12 received DVPX and Li, three received DVPX, and one received Li monotherapy. Most of the participants were also part of an open-label study by Findling et al. (2003, 2005b), where they were being treated with Li in combination with DVPX. The participants were grouped based on which six possible dosing orders they received, with each containing a placebo, 5 mg MPH, 10 mg MPH, and 15 mg MPH. Participants' dosing order was randomly generated in a numbers table with counterbalancing so that each dose order was utilized in the study (Findling et al., 2007).

Multiple scales were used as measurement tools for this study. These measurements were conducted at baseline and each week before the next dose change. For ADHD symptomatology,

the ADHD Rating Scale-IV (ARS-IV) was used. The Conners Parent Rating Scale (CPRS-48) was used for learning problems and psychosomatic symptoms, among others; CDRS-R measured specific mood states; and YMRS measures symptoms of mania. The CGI-S assessed overall illness severity. Parents and subjects were to monitor side effects using the Side Effects Behavior Monitoring Scale. Lastly, plasma concentrations of the mood-stabilizing agents were monitored, as were blood pressure, pulse, and weight (Findling et al., 2007).

Fifteen patients had ADHD-combined type, one patient had ADHD-inattentive type, fourteen patients had bipolar I disorder, one patient had bipolar II disorder, and one patient had bipolar NOS. The results of the study showed no significance between the best dose once weight was adjusted between the age groups (p =0.452). Between the best dose week and the placebo week, there was a significant difference ($p < 0.05$). There was significance found between these best dose weeks in comparison to baseline ($p < 0.05$). A large effect size was noted between the placebo and the best dose week, resulting in less symptom behavior and a positive therapeutic benefit (Cohen's d = 0.90 (95% CI 0.23-1.58)). Higher doses were noted to have an even larger effect size on the outcome in comparison to the placebo. The following subscales of the ARS-IV were found to be significant when comparing the best dose week to placebo: impulsivity/hyperactivity (p =0.02), inattentiveness (p =0.005), and ARS-IV total scores (p =0.01). Best dose week also showed significant differences on the CPRS-48 in the following three subscales in comparison to placebo week: conduct problem ($p = 0.05$), impulsive hyperactive ($p = 0.02$), and hyperactivity index ($p = 0.02$). However, there was no significant change in subscales of anxiety ($p = 0.45$), learning problems ($p = 0.08$), or psychosomatic symptoms ($p = 0.98$). The CDRS-R and YMRS scores showed no significance between the best dose week and placebo week ($p > 0.05$). The CGI-S scale, on the other hand, did result in a

significant difference between the best dose week and placebo week, showing less psychiatric symptomatology ($p < 0.01$). This significance increased as the dose increased in comparison to baseline (baseline vs. 15 mg, $p < 0.001$). Blood pressure (systolic $p = 0.15$; diastolic $p = 0.78$), pulse ($p = 0.95$), and weight ($p = 0.54$) showed no significant change from baseline to the end of the study (Findling et al., 2007).

The authors discussed that MPH, along with a mood stabilizer such as Li, DVPX, or a combination of the two, resulted in the safe and effective use of MPH for the treatment of children and adolescents with ADHD and comorbid bipolar disorder. They were not able to determine if a specific dose of MPH was most effective in comparison to the placebo due to the small sample size of this study. However, the authors concluded that when a psychostimulant medication is combined with a mood stabilizer, there is no destabilization of bipolar illness. The combined treatment of MPH and a mood stabilizer can be beneficial for children and adolescents who have ADHD and bipolar disorder (Findling et al., 2007).

This study has strength in that it was a placebo-controlled, double-blinded study. For how small the study population was, the authors did a good job of having some variety in the demographics of the subjects. The small sample size of just sixteen subjects must be taken into account when generalizing the results of this study. The fact that this study only lasted four weeks can also limit the study's applicability since it is such a short-term study and there can be no long-term safety conclusions drawn. Another weakness of the study is that subjects were only on a mood stabilizer for five days before starting their MPH doses. Again, the short time frame limits the results.

A 6-month study on how children and adolescents with BD respond to combination pharmacotherapy was completed by Kowatch et al. (2003). As stated previously, children with

BD have a high comorbidity of ADHD, with some studies showing as high as 98% comorbidity. In this particular study, which contained 35 subjects, ages 7-18, the rate of comorbid ADHD combined with BD was 80%. Oppositional defiant disorder was seen in 38% of these subjects, and 17% of the subjects had anxiety disorder. Therefore, the results of this study pertained mostly to the larger group of comorbid BD and ADHD children. Children with schizophrenia, autistic disorder, obsessive-compulsive disorder, and substance abuse were excluded from this study. At the start of the study, subjects had to score at least 14 or greater on the Young Mania Rating Scale (Y-MRS). Through the study, this scale was used to monitor for improvement. Every two or three weeks, the subjects would be rated on the Y-MRS, the Clinical Global Impression-Bipolar Scale, side effects, and the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version (K-SADS), focusing on the mania and depression sections. In order to keep track of ADHD symptoms, they were also rated on the Children's Clinical Global Assessment (CGAS) scale (Kowatch et al., 2003).

The children in Kowatch et al. (2003) were all started with a singular mood stabilizer in the first acute phase of the treatment plan. By the end of the acute phase, subjects were either "responders" or "nonresponders." If subjects responded in the acute phase, they stayed on that course of medication for the remainder of the trial. For those who did not respond to monotherapy, they were either given an additional mood stabilizer and either an antidepressant, stimulant, or antipsychotic medication. The extension phase consisted of 15 subjects being treated with one mood stabilizer, and 20 subjects were in the second category of combination pharmacotherapy with one of the previously mentioned medications in addition to two mood stabilizers. The results showed that of the 20 subjects who participated in the combination therapy, 80% responded positively to treatment. The combination therapy responders consisted

of the following: 2/35 were taking two mood stabilizers and an antidepressant; 4/35 had an antipsychotic and two mood stabilizers; and 12/35 subjects were on a stimulant in combination with two mood stabilizers (Kowatch et al., 2003). There was a 92% positive improvement in ADHD symptoms in the 12 out of 13 subjects who were given two mood stabilizers and a stimulant. Of the 15 subjects treated with monotherapy of only one mood stabilizer, there was a 92% response rate. The mood stabilizers utilized were lithium with a 66.7% response, carbamazepine with a 57% response, and divalproex sodium with an 80% response. The researchers concluded that bipolar children and adolescents do respond to polypharmacy, which is similar to how adults with BD respond to combined pharmacotherapy. Age, gender, severity, and previous exposure to psychotropic medications did not differ when comparing the monotherapy mood stabilizer group to the combination therapy group. The researchers also determined that children with BD and comorbid ADHD respond well and show improvement in ADHD symptoms when treated with a mood stabilizer and a stimulant. The authors suggest that combination therapy is vital for children and adolescents with these comorbidities and that therapy should consist of a mood stabilizer first before adding the stimulant (Kowatch et al., 2003).

Scheffer et al. (2005) began their study in search of answers pertaining to whether psychostimulants can be an effective therapy in children with BD I or II and comorbid ADHD when these children are first mood stabilized with divalproex sodium. Forty subjects between the ages of six and 17 participated in this study. Participants had to have a ≥14 Youth Mania Rating Score and also meet DSM-IV criteria for ADHD and bipolar I or II. Approximately 77.5% of the subjects were bipolar I, and 22.5% were bipolar II. Subjects also needed to exceed the normal score of the hyperactivity index on the Conners' teacher and parent rating scales to qualify for

the study. The Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) was used to clinically verify diagnoses. The study was broken up into two parts: an 8-week trial of divalproex sodium to treat manic symptoms first and monitor for any effect on ADHD symptoms; followed by a 4-week double-blind trial where subjects were randomized into groups of either mixed amphetamine salts or a placebo group. Only 30 subjects participated in the 4-week crossover trial. Outcome measures utilized in this study were the YMRS, mainly for manic symptoms, and CGI-I for measuring ADHD symptoms.

Scheffer et al. (2005) study resulted in a 50% or greater reduction in YMRS scores in 32 subjects during the first 8 weeks of taking only divalproex sodium. The decrease of 0.001 points per week in the CGI improvement scores were not significant (p =0.96). The improvement in ADHD symptoms with only divalproex sodium was noted in three subjects whose CGI improvement scores were either very much improved or much improved (score of one or two, respectively). There was a significant difference between the mixed amphetamine salts group and the placebo group of the crossover trial when measuring ADHD symptoms, with mixed amphetamine salts being more effective (p <0.0001). The authors noted there was no increase in manic episodes or significant side effects in those participating in the crossover trial. The authors compared the mania responses of the YMRS and the ADHD responses of the CGI-I and found no significant relationship between the two (p =0.10). Scheffer et al. (2005) concluded that children with bipolar disorder and comorbid ADHD show poor management of ADHD symptoms with only divalproex sodium. Although BD and ADHD share some common characteristics, they are still two distinct disorders and need to be treated as such. Children with these comorbid disorders can be effectively treated using divalproex sodium for manic symptom stabilization, followed by adjunctive treatment with mixed amphetamine salts. The two main strengths of this study are that

it is a double-blind, placebo-controlled trial where the combination of ADHD and BD in children was monitored for symptom improvement with stimulant and mood stabilization treatment, and secondly, that the results demonstrated that these disorders can be safely treated with divalproex sodium and MAS. Limitations of this study were due to MAS doses being fairly small and therefore the results might have been subpar. Had the dose of MAS been increased to maximal efficacy, the results may have been greater, but there also could have been greater associated manic symptoms. The authors also noted that the divalproex sodium doses were not increased to maximal effect and therefore subject's mania symptoms could have been more controlled. All the subjects in the study were selected from a single medical center and therefore the generalizability of the results are limited. Although this trial length was longer than others, it is still considered short-term and therefore further long-term trails are needed.

Discussion

Collectively, these studies highlight the ongoing efforts to understand and refine treatment approaches for individuals with comorbid ADHD and BD. The diversity of pharmacological interventions, including mood stabilizers like lithium and divalproex sodium, and atypical antipsychotics such as aripiprazole and risperidone, underscores the complexity of managing this population. State et al. (2004) concluded that adolescents with bipolar disorder and comorbid ADHD have a reduced acute response to the mood stabilizers lithium and divalproex sodium. Tramontina et al. (2009) determined that manic symptoms in children and adolescents can be effectively reduced while also improving global functioning with the mood stabilizer aripiprazole, but that ADHD symptoms were not affected. The study by Biederman et al. (2008) demonstrated that the mood stabilizer risperidone did improve both mania symptoms

and ADHD symptoms in children, with improvements of ADHD seen with symptoms of hyperactive-impulsive and inattentive. Although the results by Biederman et al. (2008) show a positive improvement in ADHD symptoms and BD symptoms, the results are only moderate. Each of these studies on mood stabilizers had strength in their population size considering the young age of the subjects being studied. The study by State et al. (2004) included a longer period of research whereas the other two studies in this section were short-term. The literature reviewed suggests the importance of individualized treatment plans, considering the unique presentation of symptoms and treatment responses in children and adolescents with comorbid ADHD and BD. Continued research in this area is crucial for optimizing treatment outcomes and enhancing the overall quality of life for individuals facing the challenges of these co-occurring conditions.

Previous studies have expressed concern that stimulants may cause an increase in mania symptoms in bipolar disorder. The reviewed literature suggests that stimulant medications, such as lisdexamfetamine dimesylate and mixed amphetamine salts, may contribute to an improved quality of life for individuals with comorbid ADHD and BD. Galanter et al. (2003) concluded that a 1-month titration trail with methylphenidate (MPH) had a positive response in ADHD children with mania symptoms. The ADHD symptoms that saw the most improvement were attention, aggression, and impulsivity. Galanter et al. (2003) did not show any increased irritability or increased adverse effects in ADHD children with manic symptoms when treated with the stimulant MPH. Armstrong and Kapolowicz (2023) showed similar results with positive improvement in anxiety symptoms and overall mood, with no manic or hypomanic episodes reported throughout the trail of mixed amphetamine salts (MAS). Each subject saw improvement in their bipolar symptoms and ADHD symptoms when taking MAS daily without the assistance of a mood stabilizer. McIntyre et al. (2013) demonstrated that adjunctive

lisdexamfetamine dimesylate (LDX) can have beneficial impact on metabolic parameters, such as BMI and body weight, as well as mitigating effects on ADHD symptoms and depressive severity. A limitation of this study was due to the fact that subjects could already be taking other medications but did not go into detail as to what these medications may be or how they could have affected the results. It had strength in its number of participants and its broad range of outcome measures and the demonstration that no mood destabilization or hypo/manic symptomatology was present. The positive effects observed in symptom management without significant adverse effects on other parameters underscore the potential benefits of stimulant treatment in addressing the unique challenges posed by the co-occurrence of ADHD and BD. Further research is required to study the effects of long-term treatment of stimulants in children and adolescents with comorbidity of ADHD and BD.

Combination therapy studied by Findling et al. (2007) demonstrated that MPH, along with a mood stabilizer such as Li, DVPX, or a combination of the two, resulted in the safe and effective use of MPH for the treatment of children and adolescents with ADHD and comorbid BD. Higher doses of MPH were noted to have larger effect size resulting in less symptom behavior and a positive therapeutic benefit. Symptom subscales that were noted to have significant improvement were impulsivity/hyperactivity and inattentiveness. No significant change was noted in the subscales of anxiety or psychosomatic symptoms. Similar to other article results, this study noted that when a stimulant medication is combined with a mood stabilizer, there is no destabilization of bipolar disorder. Kowatch et al. (2003) concluded that children given two mood stabilizers and a stimulant saw 92% positive improvement in ADHD symptoms. However, this study also resulted in a 92% response rate in 15 subjects who were treated with monotherapy of only one mood stabilizer. Divalproex sodium had the largest

response rate, followed by lithium, and then carbamazepine. The researchers determined that children with BD and comorbid ADHD respond well and show improvement in ADHD symptoms when treated with polypharmacy of a mood stabilizer and a stimulant, with the suggestion that the mood stabilizer be started first before adding the stimulant. Scheffer et al. (2005) showed similar results to State et al. (2004), concluding that children with BD and comorbid ADHD show poor management of ADHD symptoms with monotherapy of divalproex sodium. Similar to other articles in this literature review, Scheffer et al. (2005) noted there was no increase in manic episodes or significant side effects in children treated with divalproex sodium and adjunctive mixed amphetamine salts. This reviewed literature indicated that combination therapy involving mood stabilizers and stimulants holds promise for improving the quality of life for individuals with comorbid ADHD and bipolar disorder. The synergistic effects of these medications in addressing the diverse symptomatology of both disorders highlight the importance of individualized and comprehensive treatment approaches in managing the complex challenges associated with comorbidity. These findings demonstrate the need for further studies to assess treatment of ADHD symptoms in children and adolescents with bipolar disorder comorbid with ADHD.

Conclusion

Applicability to Clinical Practice

The information provided in the literature review demonstrates that ADHD and bipolar disorder, although they have similar overlap in symptoms, are two separate disorders and need to be evaluated as such. Children with comorbid ADHD and bipolar disorder show improvement in some symptoms of each disorder with mood stabilizer monotherapy and with stimulant

monotherapy. The greatest improvement in symptoms and therefore quality of life seems to arise from polypharmacy with both a mood stabilizer and a stimulant for those children diagnosed with comorbid ADHD and bipolar disorder. It is important for medical providers to understand both conditions and be able to differentiate the symptoms of each in order to provide the best care for each patient as an individual. Further long-term treatment studies are needed in order to have a better understanding of how these medications can affect children with comorbid ADHD and bipolar disorder as they grow and progress into adulthood.

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