



Spring 2024

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

Karina Van Slyke  
*University of North Dakota*

[How does access to this work benefit you? Let us know!](#)

Follow this and additional works at: <https://commons.und.edu/pas-grad-posters>



Part of the [Medicine and Health Sciences Commons](#)

---

### Recommended Citation

Van Slyke, Karina, "Mood Stabilizers vs Stimulants for the Management of Attention-Deficit/Hyperactivity Disorder and Comorbidity Bipolar Disorder" (2024). *Physician Assistant Scholarly Project Posters*. 301. <https://commons.und.edu/pas-grad-posters/301>

This Poster is brought to you for free and open access by the Department of Physician Assistant Studies at UND Scholarly Commons. It has been accepted for inclusion in Physician Assistant Scholarly Project Posters by an authorized administrator of UND Scholarly Commons. For more information, please contact [und.common@library.und.edu](mailto:und.common@library.und.edu).

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

Karina Van Slyke, PA-S

Department of Physician Assistant Studies, University of North Dakota School of Medicine & Health Sciences

Grand Forks, ND 58202-9037

## 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

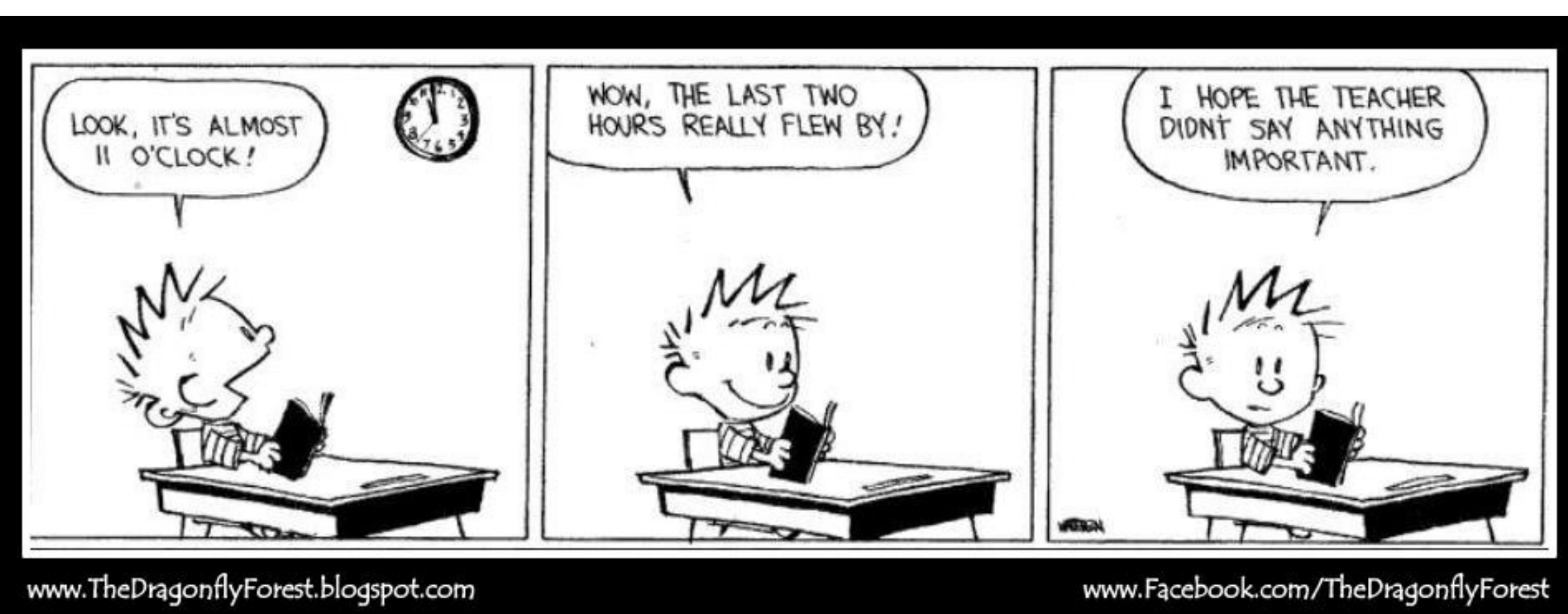
- BD is often associated with prominent mood, aggressive behaviors, and sleep, as well as impulsive behaviors in spending, promiscuity, and substances. ADHD is more often known for fidgeting, disorganized performances due to inattentiveness, forgetfulness, and distractibility (Marangoni et al., 2015).
- 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).
- 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).
- 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).
- 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).

## 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. Unfortunately, these two conditions are commonly mistaken for each other or misdiagnosed all together which further delays treatment for these children.

## 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?



## Literature Review

### Effectiveness of Mood Stabilizers on ADHD and Comorbid BD

- Thirty-four subjects saw an improved positive response rate (80.9%). 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). 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.
- Tramontina et al. (2009) used a total of 43 subjects and with an age range of 8-17 years old. The results showed the aripiprazole group had a significant decrease in scores in the YMRS (p = 0.02, ES = 0.80), the CGI-S (p = 0.04, ES = 0.28), and the CMRS-P (p = 0.02, ES = 0.54) at their endpoint assessments in comparison to their baseline.
- Biederman et al. (2008): Thirty-one subjects aged 4-15 years old; The study saw improved CGI-I results scoring 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.

### Effectiveness of Stimulants on ADHD and Comorbid BD

- A total of 270 children, ages 7-9.9 years old, were used in the Galanter et al. (2003) study. 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. There was no increase in irritability or increased adverse effects in ADHD children with mania symptoms when treated with the stimulant MPH (Galanter et al., 2003).
- The two subjects used in Armstrong and Kaplowicz (2023) study, a 49-year-old female and a 27-year-old male, both met the DSM-V criteria for BD and ADHD. This study showed that symptoms of mania and hypomania can both be improved with monotherapy of MAS, while also showing improvement in their bipolar symptoms and ADHD symptoms.
- McIntyre et al. (2013) study consisted of 45 adults who participated in a 4-week, open-label, phase IV study that involved flexible doses of adjunctive LDX. The general conclusion from the 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. See Table 3.

### 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. The ages range from 5 to 17 years old.
- There was significance found between the best dose weeks in comparison to baseline (p < 0.05) and between best dose week and the placebo week (p < 0.05). The following subscales showed significant differences when comparing the best dose week to placebo week: ARS-IV impulsivity/hyperactivity (p = 0.02), inattentiveness (p = 0.005), and ARS-IV total scores (p = 0.01); CPRS-48 conduct problem (p = 0.05), impulsive hyperactive (p = 0.02), and hyperactivity index (p = 0.02); CGI-S scale showing less psychiatric symptomatology (p < 0.01) (Findling et al., 2007).
- Kowatch et al. (2003) completed a study containing 35 subjects, ages 7-18. 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 either an additional mood stabilizer and either an antidepressant, stimulant, or antipsychotic medication in addition to two mood stabilizers.
- 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 (Kowatch et al., 2003).
- Scheffer et al. (2005) utilized forty subjects between the ages of six and 17 in their study. 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.
- 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). 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.

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

## Discussion

- 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 symptoms.
- 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.
- 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.
- 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 mania symptoms when treated with the stimulant MPH.
- 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.
- 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.
- This study noted that when a stimulant medication is combined with a mood stabilizer, there is no destabilization of bipolar disorder.
- 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.
- 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.

## Applicability to Clinical Practice

- 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.

## References

Altinbas K. (2021). Treatment of Comorbid Psychiatric Disorders with Bipolar Disorder. *Noro psikiyatri arsivi*, 58(Suppl 1), S41-S46. <https://doi.org/ezproxyr.med.und.edu/10.29399/npa.27615>

Armstrong, C., & Kaplowicz, M. R. (2023). Mixed Amphetamine Salts Without a Mood Stabilizer for Treating Comorbid Attention-Deficit Hyperactivity Disorder and Bipolar Disorder: Two Case Reports. *Military medicine*, 188(5-6), e1316-e1319. <https://doi.org/ezproxyr.med.und.edu/10.1093/milmed/usab305>

Biederman, J., Hammerness, P., Doyle, R., Joshi, G., Alkardi, M., & Mick, E. (2008). Risperidone treatment for ADHD in children and adolescents with bipolar disorder. *Neuropsychiatric disease and treatment*, 4(1), 203-207. <https://doi.org/ezproxyr.med.und.edu/10.2147/ndt.s1992>

Findling, R. L., Short, E. J., McNamara, N. K., Demeter, C. A., Stansbrey, R. J., Gracious, B. L., Whipkey, R., Manos, M. J., & Calabrese, J. R. (2007). Methylphenidate in the treatment of children and adolescents with bipolar disorder and attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, 46(11), 1445-1453. <https://doi.org/ezproxyr.med.und.edu/10.1097/chi.0b013e31814b8d3b>

Galanter, C. A., Carlson, G. A., Jensen, P. S., Greenhill, L. L., Davies, M., Li, W., Chuang, S. Z., Elliott, G. R., Arnold, L. E., March, J. S., Hechtman, L., Pelham, W. E., & Swanson, J. M. (2003). Response to methylphenidate in children with attention deficit hyperactivity disorder and mania symptoms in the multimodal treatment study of children with attention deficit hyperactivity disorder titration trial. *Journal of child and adolescent psychopharmacology*, 13(2), 123-136. <https://doi.org/ezproxyr.med.und.edu/10.1089/104454603322163844>

Hegerl, U., Himmerich, H., Engmann, B., & Henseh, T. (2010). Mania and attention-deficit/hyperactivity disorder: common symptomatology, common pathophysiology and common treatment? *Current opinion in psychiatry*, 23(1), 1-7. <https://doi.org/ezproxyr.med.und.edu/10.1097/YCO.0b013e318328331f694>

Kowatch, R. A., Sethuraman, G., Hume, J. H., Kromelis, M., & Weinberg, W. A. (2003). Combination pharmacotherapy in children and adolescents with bipolar disorder. *Biological psychiatry*, 53(11), 978-984. [https://doi.org/ezproxyr.med.und.edu/10.1016/s0006-3223\(03\)00677-2](https://doi.org/ezproxyr.med.und.edu/10.1016/s0006-3223(03)00677-2)

Marangoni, C., De Chiara, L., & Faedda, G. L. (2015). Bipolar disorder and ADHD: comorbidity and diagnostic distinctions. *Current psychiatry reports*, 17(8), 604. <https://doi.org/ezproxyr.med.und.edu/10.1007/s11920-015-0604-y>

Masi, G., Perugi, G., Toni, C., Millepiedi, S., Mucci, M., Bertini, N., & Pfanner, C. (2006). Attention-deficit hyperactivity disorder - bipolar comorbidity in children and adolescents. *Bipolar disorders*, 8(4), 373-381. <https://doi.org/ezproxyr.med.und.edu/10.1111/j.1399-5618.2006.00342.x>

McIntyre, R. S., Alsuwaidan, M., Soczynska, J. K., Szpindel, I., Bilkey, T. S., Almagor, D., Woldeyohannes, H. O., Powell, A. M., Cha, D. S., Gallagher, 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>

Rucklidge, J. J. (2006). Impact of ADHD on the neurocognitive functioning of adolescents with bipolar disorder. *Biological psychiatry*, 60(9), 921-928. <https://doi.org/ezproxyr.med.und.edu/10.1016/j.biopsych.2006.03.067>

Scheffer, R. E., Kowatch, R. A., Carmody, T., & Rush, A. J. (2005). Randomized, placebo-controlled trial of mixed amphetamine salts for symptoms of comorbid ADHD in pediatric bipolar disorder after mood stabilization with divalproex sodium. *The American journal of psychiatry*, 162(1), 58-64. <https://doi.org/ezproxyr.med.und.edu/10.1176/appi.ajp.162.1.58>

State, R. C., Frye, M. A., Altshuler, L. L., Strober, M., DeAntonio, M., Hwang, S., & Mintz, J. (2004). Chart review of the impact of attention-deficit/hyperactivity disorder comorbidity on response to lithium or divalproex sodium in adolescent mania. *The Journal of clinical psychiatry*, 65(8), 1057-1063. <https://doi.org/ezproxyr.med.und.edu/10.4088/jcp.v65n0805>

Tramontina, S., Zeni, C. P., Ketzner, C. R., Pheula, G. F., Narvaez, J., & Rohde, L. A. (2009). Aripiprazole in children and adolescents with bipolar disorder comorbid attention-deficit/hyperactivity disorder: a pilot randomized clinical trial. *The Journal of clinical psychiatry*, 70(5), 756-764. <https://doi.org/ezproxyr.med.und.edu/10.4088/JCP.08m04726>

## Acknowledgements

I would like to express my deepest gratitude to my husband Bodee for his unwavering support and encouragement throughout my graduate studies and this scholarly project. I want to thank my family and friends for their continual support and kindness that has helped me through this program. In addition, a deep thanks goes out to my fellow peers Robert White, PA-S, Allison Stoeffler, PA-S, and Rachel Kisse, PA-S, for their advice and encouragement on my scholarly project and for their friendships throughout the Physician Assistant Program. I would also like to thank Dr. Marilyn Klug for her advice and expertise in statistics. A big thanks goes to my brother Mark Van Slyke who helped provide academic guidance while developing this project. An additional thanks goes to Megan Denis, MLIS at the University of North Dakota's Library Resources for taking the time to share her expertise and helping to refine the research of this literature review.