

**Comorbidity and Polypharmacy: A Systematic Literature Review of Pharmacological
Interventions for Pediatric ADHD and Associated Comorbidities**

Saachi Patel

A Dissertation Submitted to the Faculty of
The Chicago School of Professional Psychology
In Partial Fulfillment of the Requirements
For the Degree of Doctor of Clinical Psychology

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PREVIEW

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Abstract

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common childhood neurodevelopmental disorders that impacts 8.4% of children in the United States. ADHD is highly comorbid with other psychiatric disorders, especially anxiety, depression, and oppositional defiant disorder. Behaviors of ADHD combined with other psychiatric disorders can negatively impact social, academic, and occupational activities. The recommended line of treatment for ADHD is the use of psychostimulants; however, with the presence of comorbid disorders, there is little empirical evidence investigating the efficacy and safety of using multiple medications to treat ADHD and associated comorbidities. The clinical significance of psychotropic medication is becoming widely studied, polypharmacy is a common treatment option that may aim to treat psychiatric comorbidities associated with ADHD. This systematic literature review aimed to investigate the current literature and assess the effectiveness and safety of combination psychotropic medication use and the potential benefits and drawbacks it may impose on the pediatric population. There were mixed results regarding the efficacy of polypharmacy for symptoms of ADHD and associated comorbidities. Methylphenidate with selective serotonin reuptake inhibitors (SSRI) was the most common combination for ADHD and depression/anxiety symptoms. ADHD and symptoms of oppositional defiant disorder appeared to respond well with the use of methylphenidate and antipsychotics, however, adverse effects were significant. Adverse effects were observed in multiple studies, questioning whether children and adolescents will comply with polypharmacy treatment. Results from this comprehensive review revealed the complexities of polypharmacy practices and the limited nature of this research area.

Table of Contents

List of Figures	10
Chapter 1: Nature of the Study	11
Purpose of the Study	13
Conceptual Framework	14
Summary	14
Chapter 2: Review of Literature	15
Attention-Deficit/Hyperactive Disorder (ADHD)	15
ADHD Subtypes	15
Nature of Comorbid Diagnoses	17
Differential Diagnosis	17
ADHD and Comorbidities	18
ODD and ADHD	19
Depression and ADHD	20
Anxiety and ADHD	21
Neurochemistry of ADHD	23
Pharmacological Interventions for ADHD	24
Guidelines for ADHD Treatment	25
Guidelines to Treating Pediatric Comorbid Conditions	26
Psychostimulants	28
The Multimodal Treatment Study of Children with ADHD	28
Methylphenidate	30
Amphetamines	30

Pharmacodynamic/Pharmacokinetics of Stimulants	31
Side Effects, Effectiveness, Long Term Consequences of Stimulants	32
Nonstimulants	34
SNRIs	34
Alpha-2 Adrenergic Agonists	36
Antidepressants	37
SSRIs	37
Fluoxetine	38
Sertraline.....	39
Citalopram	39
Escitalopram	40
Antidepressants and Stimulant Treatment	40
SNRIs.....	41
NDRI.....	42
MAOI.....	43
Antipsychotics	44
Haloperidol (FGA)	44
Chlorpromazine (FGA)	45
Risperidone (SGA)	45
Olanzapine (SGA)	46
Aripiprazole (SGA)	46
Antipsychotics and Stimulants	47
Chapter 3: Methodology	49

Defining the Research Question	50
Eligibility Criteria for Studies.....	51
Inclusion Criteria	51
Exclusion Criteria.....	52
Key Words	52
Selection of Studies	53
Chapter 4: Results	55
Stimulant and SSRI/NDRI.....	68
Stimulant and SSRI.....	68
Stimulant and Atypical Antidepressant	70
SNRI and SSRI	71
Stimulant and SNRI	71
ADHD and Oppositional/Aggressive Behaviors	73
Stimulant and Alpha-2 Adrenergic Agonist.....	73
Stimulant and Second-Generation Antipsychotic	73
Stimulant and Alpha-2 Adrenergic Agonists	74
Stimulant and Atypical Antipsychotic.....	75
Stimulant and Anticonvulsant	76
Side Effects of Polypharmacy Treatment	87
Chapter 5: Discussion & Conclusion	93
Introduction.....	93
Interpretation of Findings	93
Adverse Effects	95

Limitations	96
Conclusion	97
References	99
Appendix A	123

PREVIEW

List of Figures

Figure 1: <i>The Search Process Including Search Terminology and Databases.</i>	54
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PREVIEW

Chapter 1: Nature of the Study

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder that is characterized by The Diagnostic and Statistical Manual of Mental Disorders (*5th ed.; Text Revision* [DSM-5-TR]) as a persistent pattern of inattention and/or hyperactivity-impulsivity (American Psychiatric Association [APA], 2013). Behaviors of inattention, hyperactivity, and impulsivity are persistent for at least six months and are inconsistent with the developmental level of the individual. These behaviors negatively impact social, academic, and occupational activities (APA, 2013). ADHD is recognized as one of the most common causes of behavioral and learning difficulties in children (Wolraich et al., 2019). Common symptoms of ADHD in school-age children include poor concentration, poor organization, impulsivity, forgetfulness, restlessness, learning difficulties, low self-esteem, and defiant behavior (Barkley, 2014). ADHD is highly comorbid with other psychiatric disorders, most notably depression, anxiety, and oppositional defiant disorder (ODD). Thirty to 40% of individuals with ADHD also have ODD and 61% to 67% of individuals with ODD have ADHD (Ghosh et al., 2017). Roughly one-third of pediatric patients with ADHD meet the criteria for depression while one-fourth to one-half of patients with depression may meet the criteria for ADHD (Wolraich et al., 2019).

As the DSM and International Classification of Diseases (ICD-10) criteria have been revised multiple times, psychiatric comorbidities have become more prevalent when diagnosing (Pincus et al., 2004). The DSM is a categorical system that separates psychiatric symptoms and behaviors into distinctive diagnoses and has exclusionary criteria to eliminate multiple diagnoses. Nontraditional diagnosing encourages using multiple diagnoses of the DSM and ICD, where clinicians can capture all relevant clinical information. Even though diagnosing ‘maximal’ comorbidity is encouraged, this strategy may not reflect the most optimal conceptualization.

Feinstein (1970) first devised the term “comorbidity” to describe additional clinical entities that could exist during the course of a patient’s primary disorder. Because of the potential for excessive comorbidities, exclusionary criteria were added to later editions of the DSM to reduce the overall number of comorbidities (Pincus et al., 2004). Patients with comorbid psychiatric disorders are more likely to demonstrate higher rates of treatment dropout as well as poorer treatment adherence than patients without mental illnesses (DeMarce et al., 2008). With increasing mental health comorbidities, treatment planning and options may be limited and contradictory.

Because of the high prevalence of comorbidities with pediatric ADHD, the administration of multiple medications concurrently or *polypharmacy* is becoming increasingly prevalent for treatment. Pharmacological *monotherapy*, or the use of a single medication, has always been a common practice for ADHD; however, with the complexities of ADHD and associated comorbidities, polypharmacy practices have become popular. In addition to increased monotherapy prescription rates for ADHD alone, ADHD polypharmacy treatment has increased to a 20.5% rate between 2006 and 2015 (Girand et al., 2020). A variety of psychotropic medications have now become a popular option for the treatment and management of ADHD symptoms. Stimulants like methylphenidate are the longest used and most studied pharmacological intervention for ADHD as hundreds of studies have investigated their efficacy and safety (Storebø et al., 2018). Because of high comorbidity rates of ADHD and anxiety, depression and/or ODD, combined treatment of psychostimulants and antidepressants have become popular treatment options for pediatric ADHD patients with comorbid symptoms (Girand et al., 2020).

The use of medication in pediatric psychology has steadily increased over the years and has become more accepted in treating several psychiatric disorders like ADHD, depression, anxiety disorders, obsessive-compulsive disorders, and psychoses (Rapoport, 2013). Before this current trend of increased pharmacological use in pediatric psychiatry, there was (and remains) an increasing concern of the long-term adverse effects of medication. Over the past decade, a significant number of pediatric randomized control trials (RCT) have been conducted to demonstrate the efficacy of psychostimulants, antidepressants, and antipsychotics. Although these RCTs have established a clinical efficacy of these drugs (when tested against a placebo), a variety of methodological problems, like short duration studies, cross-over methodologies, washout periods, insufficient sample sizes, and minimal replication in naturalistic replications, cast some doubt on their effectiveness or “real-world” impact. With increased developments and research into pediatric psychiatry, there is growing concern that children are being overprescribed and overmedicated, especially in the United States. Despite pharmacotherapy being the first line of treatment for ADHD, studies have demonstrated that prescription rates for ADHD medications have drastically increased in the past 20 years which may be due to an increase in patients being diagnosed with ADHD (Renoux et al., 2016). Children and adolescents are considered a vulnerable population and may be at a higher risk of being affected by suboptimal psychiatric practices, especially patients with multiple existing comorbidities. Although there have been considerable developments in pediatric psychiatry, there is further investigation that needs to be made in order to fully understand the adverse and long-term effects, especially with prescription rates increasing drastically.

Purpose of the Study

This study utilized a systematic literature review that assessed existing literature on pharmacological interventions for ADHD and comorbid anxiety, depression, and ODD symptoms. Due to the increasing polypharmacy treatment of these disorders, critical analysis should be conducted to review the safety and efficacy of using multiple psychotropic medications concurrently. Furthermore, as polypharmacy is becoming increasingly popular for children and adolescents, there must be further investigation regarding the effects this has on the developing brain and central nervous system.

Conceptual Framework

According to Khan et al. (2003), a systematic literature review should contain four key characteristics: a clearly outline research question, the inclusion of pertinent studies, and evaluation of study quality, and an overall summarization of the findings based on a clearly outlined methodology. To achieve these characteristics, Khan et al. (2003) created five steps: identifying the review question, determining the relevance of studies, assessing for quality of studies, summarizing findings, and interpreting the information presented. This systematic literature review will adhere to these five steps to ensure that characteristics of such a review are met.

Summary

ADHD is a highly comorbid disorder that affects a large part of the pediatric population. As the clinical significance of psychotropic medication is becoming widely studied, polypharmacy is a common treatment option that may aim to treat psychiatric comorbidities associated with ADHD. This study aims to investigate current literature and assess the effectiveness and safety of combination psychotropic medication use and the potential benefits and drawbacks it may impose on the pediatric population.

Chapter 2: Review of Literature

Attention-Deficit/Hyperactive Disorder (ADHD)

ADHD is one of the most common childhood neurodevelopmental disorders and affects 7.2% of children around the world (American Academy of Pediatrics [AAP], 2019). Within the United States, ADHD is thought to affect around 8.4% of children ages 2 to 17, representing roughly 5.4 million children (AAP, 2019). ADHD emerges in early childhood and usually continues into adulthood.

ADHD Subtypes

Attention deficit hyperactivity disorder currently includes a list of 18 behavioral symptoms that are divided into two sets (inattention and hyperactivity-impulsivity) with nine symptoms each (APA, 2013). According to the DSM-5-TR, there are three subtypes of ADHD: combined presentation (ADHD-COMB), predominantly inattentive presentation (ADHD-IA), and predominantly hyperactive-impulsive presentation (ADHD-HI) (APA, 2013).

Children with ADHD, predominantly inattentive presentation (ADHD-PI) present with significant problems with inattention and the absence of impulsivity and hyperactivity. Barkley (2014) found that children with ADHD-IA have significant deficits with memory retrieval and perceptual-motor speed. These children are often described as cognitively “sluggish” and socially withdrawn (when compared with ADHD-COMB children) (Hodgens et al., 2000; McBurnett et al., 2001).

The ADHD, predominantly hyperactive-impulsive presentation (ADHD-HI) was first introduced in the DSM-IV (APA, 1994). Field trials for the DSM-IV found that a small percentage of children with ADHD-HI had significantly hyperactive-impulsive behaviors and the absence of inattentive symptoms (Lahey et al., 1994). Many of these children in the study were

either in preschool or early elementary, indicating that this subtype may be a precursor of ADHD-COMB. A study by Lahey et al. (2005) has confirmed this hypothesis and found that across an 8-year assessment, nearly all children in the ADHD-HI group shifted to the ADHD-COMB.

With regards to developmental functioning, pediatric ADHD can impact adaptive functioning, motor coordination, language ability, learning difficulties, and self-perception (Barkley, 2014). Adaptive skills include self-help skills, independence, self-knowledge, social and communication skills, and motor skills (Barkley, 2014). Children with ADHD generally have poorer adaptive functioning than typically developing children (Barkley, 2014). These adaptive functioning deficits are usually common in daily living in social communication areas; a child with ADHD typically has difficulties organizing information and utilizing effective communication skills (Barkley, 2014).

In terms of motor coordination, many children with ADHD exhibit difficulties with strength, adjusting speed, visual-motor coordination, and manual dexterity (Barkley, 2014). Children with ADHD inattentive or ADHD combined subtypes are most likely to display significant motor coordination difficulties when compared with children with ADHD hyperactive-impulsive subtype. Children with ADHD experienced difficulties with receptive, expressive, and pragmatic language skills (Staikova et al., 2013). These linguistic deficits may interfere with comprehending instructions, initiating, maintaining, and ending a conversation (Staikova et al., 2013). Because of these language deficits, children with ADHD are likely to experience social difficulties and overall social functioning. These children are also highly likely to experience learning disabilities and academic achievement than neurotypical developing children (Sexton et al., 2012). In a review of 17 studies that assessed for comorbidity in ADHD

and learning disabilities (LDs), researchers concluded that the comorbidity between ADHD and LDs rate is as high as 45% (DuPaul et al., 2013). According to Barkley (2014), children with ADHD who do not meet the criteria for a learning disorder exhibit some degree of learning difficulty. Coexisting learning problems typically include lower academic achievement, grade retention, higher high school dropout rates, use of special education programs/services, and lower higher education rates. Lastly, children with ADHD are more likely to display lower self-esteem due to the challenges they experience in everyday activities (Edbom et al., 2006).

Nature of Comorbid Diagnoses

With each edition development of the DSM, psychiatric disorders provoked some controversy in the field of psychiatry. A range of issues were raised such as pros and cons of defining disorders rather than categorizing them, influence of pharmaceutical industries on developing new categories, and transforming normal emotional experiences into disorders (van Loo & Romeijn, 2015). These issues led to the phenomenon of comorbidity, or the presence of two or more mental disorders in an individual (van Loo & Romeijn, 2015). Comorbidity among psychiatric illnesses is an important area of study due to its high prevalence and influence on disease severity. Researchers from a constructivist perspective argue that comorbidity is a product of our current diagnostic system while those arguing from a realist standpoint believe that comorbidity, by identifying commonalities of different disorders, indicates a genuine nature of psychiatric diseases. Comorbidities are thought to be a pertinent part of understanding ADHD, as a significant number of children and adolescents with an ADHD diagnosis have a comorbid disorder.

Differential Diagnosis

Differential diagnosis is the process of distinguishing between two or more conditions that share similar symptoms (Wolraich et al., 2019). In the context of ADHD, differential diagnosis is important because many of the symptoms of ADHD, such as inattention, hyperactivity, and impulsivity, can also be caused by other medical or psychiatric conditions. Ruling out other potential causes of symptoms can lead to a more accurate diagnosis of ADHD and appropriate treatment options.

ADHD and Comorbidities

For individuals diagnosed with ADHD, co-occurrent mental, neurodevelopmental, medical, and physical conditions are not uncommon. Because the core symptoms of ADHD may be masked by comorbidities, the diagnostic processes can be challenging as symptoms may not be easily detected or distinguished from other disorders. While there is much research investigating ADHD and its comorbidities as products, there are very few studies that have investigated the effects of comorbidities on the functioning of children and adolescents with ADHD. Increasing evidence that suggests that ADHD is a heterogeneous disorder that has several patterns of comorbidity (Seymour & Miller, 2017). Around 60-70% of children with ADHD have at least one other psychiatric disorder, and close to half have two other disorders (Barkley et al., 2008). According to the DSM-5-TR (2013), a quarter of children or adolescents with ADHD have a co-occurrence of conduct disorder. A lesser percentage of children and adolescents who meet criteria for ADHD also meet criteria for disruptive mood dysregulation disorder (APA, 2013). Other disorders that may be comorbid with ADHD include obsessive compulsive disorder, tic disorders, and autism spectrum disorder (APA, 2013). Of the most common comorbid psychiatric disorders that are co-occurrent with pediatric ADHD, major

depressive disorder (MDD), ODD, and anxiety disorder are the most prevalent (BurgiĆ Radmanović & Burgić, 2020).

ODD and ADHD

ODD is a childhood psychological disorder that is characterized by ongoing patterns of defiance, hostile behaviors, and lack of cooperation (APA, 2013). Oppositional defiance can be a normal part of development but becomes problematic when it is frequent, consistent, and disruptive to functioning. The DSM-5-TR differentiates that resistance to conforming to others' demands are different in both disorders: in ODD, this behavior is demonstrated by "negativity, hostility, and defiance" (APA, 2013, p. 63), whereas in ADHD, resistance is usually an aversion from mentally challenging tasks due to decrease in maintaining mental efforts, forgetfulness, and impulsivity (APA, 2013). Although this core symptom of resistance is different in both disorders, ADHD youth are likely to develop a comorbid diagnosis of ODD. It is reported that 89.7% of children diagnosed with ADHD also meet criteria for ODD (Mulraney et al., 2016). A large sample study conducted by Kim et al. (2010) investigated the common behavioral features of 2,673 children and adolescents with both ODD and ADHD diagnoses and found the following commonalities: decreased levels of persistence and self-directedness, increased symptoms of anxiety, depression, and aggressive behaviors.

Individuals with ADHD are likely to exhibit oppositional behaviors similar to those of ODD. Even though behavioral disruption is common between ODD and ADHD, hyperactivity and inattention from ADHD are different than argumentative symptoms and irritability from ODD (Ghosh et al., 2017). The co-occurrence between ODD and ADHD can be differentiated by clinical presentations as well as differential antecedents and functional consequences (Ghosh et al., 2017). To better understand the comorbidity between ODD and ADHD, the correlated-risk

factor model and the developmental precursor model were created. Developed by Rhee and colleagues (2008), the correlated-risk factor model suggests that comorbidity between ODD and ADHD may be due to correlated or shared risk factors (Rhee et al., 2008). Studies have supported this model suggesting that comorbidity is due to shared genetic factors or environmental factors. The developmental precursor model suggests that ADHD symptoms lead to the development of ODD (Barkley, 2006). Children with ADHD are more likely to develop oppositional behaviors through peer influences as well as be rejected by their peers (Hoza et al., 2005). Early ODD symptoms may also predict the persistence of ADHD and increase risks for conduct disorder, MDD, and anxiety.

Depression and ADHD

Roughly one-third of pediatric patients with ADHD meet criteria for depression while one-fourth to one-half of patients with depression may meet criteria for ADHD (Rychik et al., 2020). The onset of ADHD is earlier than depression, typically before the age of 12 (Rychik et al., 2020). Children and adolescents with ADHD are 5.5 times more likely to develop MDD than those without ADHD (Daviss, 2008). According to Meinzer et al. (2016), there may be a longitudinal link between MDD and ADHD as childhood ADHD can predict increased levels of depressive symptoms throughout emerging adulthood. Furthermore, treatment of persistent ADHD symptoms may decrease development of depressive symptoms (Meinzer & Chronis-Tuscano, 2017).

The link between ADHD and symptoms of MDD are still unclear, but previous research has demonstrated that emotional regulation difficulties that are associated with ADHD symptoms may lead to increased depressive symptoms (Seymour et al., 2014). The ‘dual failure model’ explains that ADHD symptoms (stress generation, creation of stressful events due to behavior)

can lead to performance deficits which may contribute to depressive symptoms (Humphreys et al., 2013). According to Humphreys et al. (2013), poor school performance and peer issues can mediate the link between ADHD and depressive symptoms of MDD. These depressive symptoms may remain comorbid into her to adulthood, especially during college years where along with increased academic pressure, there is increased independence and responsibility (Rychik et al., 2020). Because the symptoms of MDD are broad, it is important to understand what specific depressive symptoms are the most associated with pediatric ADHD. A study by Daviss et al. (2008), investigated frequently overlapping symptoms between ADHD and MDD and examined which depressive symptoms best discriminated MDD among children and adolescents with ADHD. Findings from this study found social withdrawal, anhedonia, depressive cognitions, suicidal thoughts, and psychomotor retardation as significant symptoms when trying to identify MDD in ADHD youths (Daviss et al., 2008). In a clinical setting, recognizing how specific depressive symptoms of MDD comorbid with ADHD are different from an MDD diagnosis alone may be helpful for treatment planning. A study by Fraser and colleagues (2018) found that ADHD youth are more likely to underreport severity of their depressive symptoms. In this study, the most common symptoms of MDD included irritability, restlessness, concentration difficulties, and feeling “miserable/unhappy” (Fraser et al., 2018). Fraser et al. (2018) and Daviss et al. (2008) reported different MDD symptoms and behaviors in ADHD youth which may suggest that the presentation of MDD is vast and can vary within the pediatric population.

Anxiety and ADHD

The comorbidity of ADHD and anxiety is common with an estimated 25% of children and adolescents displaying symptoms of both disorders (Jarrett & Ollendick, 2008). Anxiety

disorders are common differential diagnostic considerations as attention problems can be related to cognitive and emotional reasons. Studies have revealed significant overlaps in the diagnostic criteria of ADHD and generalized anxiety disorder (GAD) such as fidgeting and restlessness and anxious impulsivities. The DSM-5-TR rules out anxiety disorders within the ADHD criteria, citing that ADHD and anxiety disorder share symptoms of inattention because of the individual's "attraction to external stimuli, new activities, or preoccupation with enjoyable activities" (APA, 2013, p. 64). This is different from inattention "due to worry and rumination" often displayed in anxiety disorders (APA, 2013, p. 64). Several studies have investigated the significance of anxiety symptoms in the pediatric ADHD population. A six-year follow-up study by Cadman et al. (2016) found that ADHD teenagers had increased anxious symptoms when entering emerging adulthood. The relationship between ADHD and anxiety is considered to be a significant one, so much so that some researchers have suggested creating a new distinct subtype of ADHD with anxious features (Reimherr et al., 2017). A review of existing literature by Reimherr and colleagues (2017) regarding commonalities in anxiety disorders and ADHD revealed significant overlaps in the diagnostic criteria of ADHD and GAD such as fidgeting and restlessness and anxious impulsivities. Poor concentration is another common symptom in both disorders where distractibility in a child with ADHD and anxiety is likely due to worries and fears as well as stimuli distractions (Reimherr et al., 2017).

While the exact cause of ADHD is not known, this disorder has a complex etiology with many underlying factors including genetics, environmental, and behavioral factors. Genetic factors appear to play a significant role in the development of ADHD as studies have shown that ADHD runs in families, with children who have a parent or sibling with the disorder being more likely to develop it themselves (Faraone & Larsson, 2019). Epigenetic changes, or changes in

gene expression, are also important for the understanding of ADHD. Specifically, studies have found differences in DNA methylation, a common epigenetic modification, in individuals with ADHD compared to those without the disorder (Mirkovic et al., 2020).

Research into the neurochemistry and neurobiology of ADHD has shown alterations in brain structure and function, particularly in regions of the brain that are important for attention, motivation, and impulse control (Curatolo et al., 2010). Structural imaging has found differences in the volume and activity of the prefrontal cortex, striatum, and cerebellum in individuals with ADHD compared to those without ADHD (Curatolo et al., 2010). The understanding of the neurochemistry of ADHD is also necessary in order to treat specific neurochemical imbalances associated with ADHD and formulate effective treatment and interventions.

Neurochemistry of ADHD

As psychotropic medications are a primary intervention in the treatment of ADHD, an understanding of neurochemistry of ADHD and associated comorbidities is essential. Anderson (2019) defines *neurochemistry* as “the study of chemicals and their reactions in the nervous system... endogenous chemicals (especially neurotransmitters) and nongenetic molecular aspects of the nervous system, the pathogenesis of neuropsychiatric disorders, and the identification of disease biomarkers” (pp. 3132-3133). Studying neurotransmitters (NTs) and their selective actions contribute to our understanding of brain chemistry, brain receptors and transporters, and overall brain function across several psychiatric disorders. According to Ingersoll and Rak (2016), NTs must (1) be synthesized in the presynaptic neuron, (2) release from the presynaptic terminal, (3) cause some kind of inhibitory or excitatory signal, and (4) have a mechanism that removes it from the site of action. Although scientists have identified more than 60 distinct types of NTs in the human brain, research about how NTs are affected by psychotropic medication is

limited. The most common NTs targeted by psychotropic medication are glutamate (Glu), Gamma-aminobutyric acid (GABA), acetylcholine (Ach), dopamine (DA), norepinephrine (NE), and Epinephrine (Epi).

In ADHD, DA and NE are thought to be the NTs that are primarily affected. DA regulates pleasure/reward centers as well as motor behaviors, and underlying DA pathways are present in the frontal cortex, nucleus accumbens, and ventral tegmental (Blum et al., 2008). DA is also involved in the regulation of attention, which is compromised in ADHD (Blum et al., 2008). Lower DA production can impact one's ability to filter out non-salient aspects of their environment as they become conscious of every sound, object, and sensation. Imaging studies have identified that DA D2 receptors and DA transporters are higher in ADHD patients (Nikolaus et al., 2007). NE is found in both the central and peripheral nervous systems and is responsible, in part, for governing heart rate and blood pressure (Ingersoll & Rak, 2016). Derived from tyrosine, NE cell bodies are located in the locus coeruleus in the brain stem and are involved in a number of responses like feelings of reward, mood, and memory (Ingersoll & Rak, 2016). ADHD symptoms may be associated with abnormalities in NE functioning leading to altered levels of NE (McEvoy et al., 2002). Depleted levels of NE can affect working memory and attention regulation while excess levels produce PFC impairment (Arnsten, 2000).

Pharmacological Interventions for ADHD

Treating symptoms of ADHD and its common comorbidities with medication has increased over the years and has become the first line treatment for symptom relief. Despite this increase in prescribing practices, there remains ongoing concern about the over prescription, overuse, and long-term effects of such pharmacological interventions. RCTs continue to prove efficacy in treating symptoms of pediatric disorders like ADHD, however, most of these studies