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The Review of Mechanisms and Intervention Methods for Comorbidity of ADHD and Anxiety

Yuhan Gong

Taylor's University, Subang Jaya,47500, Malaysia

Abstract. Attention Deficit Hyperactivity Disorder (ADHD) and anxiety disorders represent significant psychological conditions that frequently co-occur, presenting substantial challenges for clinical diagnosis and treatment. However, critical gaps persist in the clinical application of mechanistic understanding and intervention strategies for this comorbidity. This review systematically examines the potential mechanisms underlying ADHD-anxiety disorder comorbidity across four dimensions: neural circuitry, neurochemical dysregulation, hypothalamic-pituitary-adrenal (HPA) axis dysfunction, and genetic predisposition. It indicates that prefrontal-limbic system dysfunction, imbalances in key neurotransmitters, stress-related HPA axis dysregulation, and genetic variants such as ADORA2A and DRD2 may play pivotal roles in the comorbid mechanism. The review also evaluates the strengths and limitations of current interventions, including pharmacological treatment and cognitive behavioral therapy, outlines challenges in clinical practice, and suggests directions for future therapeutic approaches. Overall, this synthesis advances the clinical understanding of ADHD-anxiety comorbidity mechanisms and supports progress toward precision assessment and individualized intervention strategies.

Keywords: Attention Deficit Hyperactivity Disorder; Anxiety; Comorbidity; Mechanisms.

1. Introduction

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), the primary diagnostic features of Attention Deficit Hyperactivity Disorder (ADHD) include inattention, hyperactivity, and impulsivity. These behaviors may occur individually or in combination (American Psychiatric Association, 2000). Reimherr FW, et al. (2015) defined the two foundations of ADHD presentation: inattention presentation and emotional regulation disorder presentation. In 2017, Reimherr et al. operationally defined emotional regulation disorders using three domains of the Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS): temper, emotional instability, and emotional overreactivity. They concluded that emotional instability and emotional overreaction are more common in adult ADHD. In addition to the core symptoms of attention deficit and hyperactivity/impulsivity, ADHD patients often experience behavioral issues, learning difficulties, and emotional symptoms (Drechsler R, Brem S). For example, studies indicate that ADHD patients are more prone to traffic accidents, have higher unemployment rates, and face increased risks of divorce and relationship breakdowns. They encounter fewer opportunities for career advancement and experience prolonged feelings of failure and diminished self-esteem (Barkley R, Murphy K, 1996-9). These symptoms begin in childhood and persist into adulthood in most affected individuals (Guldberg-Kjaer, Sehlin, & Johansson, 2013; Primich & Iennaco, 2012).

Anxiety is characterized by excessive worry and uncertainty about future negative events, manifesting as a state of unease, tension, or concern related to uncertain events. Anxiety disorders are more severe and often accompanied by physiological symptoms such as sweating, rapid heartbeat, and dizziness (DSM-5). When these episodes occur frequently and interfere with social functioning, they develop into pathological anxiety (Mah et al., 2016). Clinically, if anxiety becomes frequent or prolonged, it may interfere with an individual's daily life and be classified as a pathological anxiety disorder. Functional neuroimaging studies indicate that anxiety disorders are characterized by hyperactivity in the amygdala and other limbic system regions, as well as reduced functionality in regulatory areas such as the prefrontal cortex and hippocampus, leading to impaired emotional regulation (Goldin et al., 2009; Nitschke et al., 2009). Additionally, chronic anxiety is associated with

brain structural deterioration, potentially increasing the risk of depression and Alzheimer's disease (Mah et al., 2016).

Research indicates that anxiety is one of the most common comorbid conditions associated with ADHD, with a comorbidity rate of approximately 25% to 50% among individuals with ADHD (Koyuncu et al., 2022). Comorbidity can influence the manifestation and prognosis of ADHD symptoms in complex ways (Halldorsdottir & Ollendick, 2014). According to Jacob et al. (2014), the overlap between ADHD and generalized anxiety disorder (GAD) has led to productive research on both conditions and their overlapping domains. In adults, GAD and ADHD frequently co-occur. Piñeiro-Dieguez (2016) found that 23% of adult outpatient ADHD patients had anxiety disorders. Conversely, the prevalence of ADHD among adult patients in anxiety disorder clinics was 28% (Van Ameringen M., et al., 2011). Reimherr et al. (2017) further confirmed the high degree of overlap between ADHD and anxiety. In their ADHD clinical trial, 30% of participants experienced high levels of comorbid anxiety. In their clinical trial, approximately 30% of participants experienced significant comorbid anxiety, and among 106 ADHD patients, 24% exhibited anxiety disorders. Additionally, research on ADHD and anxiety comorbidity indicates that adolescents with persistent ADHD symptoms have higher anxiety levels than those with subclinical ADHD (Cadman T, et al., 2016). Jensen et al. (2001) even suggested that ADHD with anxiety could constitute a distinct subtype of ADHD. Children with a dual diagnosis of ADHD and anxiety disorder exhibit more severe impairments than adolescents with either ADHD or anxiety disorder alone (Bowen, Chavira, Bailey, Stein, & Stein, 2008). Symptoms are also more severe and complex. For example, attention problems, school phobia, and impaired social skills (Mikami, Ransone, & Calhoun, 2011). These symptoms exacerbate the psychological burden and social dysfunction of patients.

1.1 Bidirectional influence

Currently, there are two main explanations for the comorbidity mechanism between ADHD and anxiety: the anxiety effects model and the ADHD effects model (Bubier & Drabick, 2009). The anxiety effects model posits that anxiety leads to excessive self-focus and high levels of behavioral inhibition, resulting in the overconsumption of attentional resources and thereby interfering with task performance and concentration (Bubier & Drabick, 2009). However, Shannon et al. (2021) conducted an in-depth exploration of this model and found that anxiety could not significantly predict subsequent ADHD symptoms at any time point; conversely, ADHD symptoms could significantly predict subsequent anxiety development. Additionally, studies by Baldwin & Dadds (2008) and Overgaard et al. (2014) also failed to find that anxiety symptoms predict ADHD, further weakening the explanatory power of this model. In contrast, Shannon et al. (2021) found that early ADHD symptoms in the preschool stage could predict anxiety symptoms at multiple subsequent time points. Pliszka (2019), when exploring the comorbidity between ADHD and social anxiety disorder (SAD), also noted that ADHD may be one of the risk factors for anxiety development.

From a treatment perspective, some studies suggest that the phenomenon of using psychostimulants to alleviate anxiety symptoms may stem from the hypothesis that anxiety is caused by “secondary anxiety” resulting from functional impairments triggered by ADHD; however, this explanation is not fully satisfactory (Jarrett et al., 2016). Early studies also suggested that anxiety may weaken the response of ADHD patients to stimulant treatment (Pliszka, 1989; Tannock, Ickowicz & Schachar, 1995). Additionally, attention deficits themselves may have an anxiogenic effect, meaning that ADHD patients may experience anxiety due to attention issues (Roth et al., 2004); conversely, anxiety may also exacerbate their attention deficits (Manassis, 2007). Further studies have explored the interactive relationship between the various components of ADHD and anxiety. For example, a longitudinal study by Michelini (2015) found that social anxiety was negatively correlated with hyperactivity/impulsivity symptoms. Koyuncu et al. (2022) noted that attention deficits in ADHD may exacerbate anxiety, which in turn further impairs attention, creating a vicious cycle. It is worth noting that attention deficit symptoms in ADHD are typically more persistent, while anxiety symptoms may become more prominent in adulthood. Finally, researchers also emphasized the role

of environmental factors. Baldwin & Dadds (2008) proposed that ADHD symptoms may trigger negative feedback in the environment, thereby inducing anxiety symptoms. One common form of negative feedback is negative parenting styles. Gallagher & Cartwright-Hatton (2008) found that harsh or overly reactive parenting styles are significantly associated with the occurrence of both ADHD and anxiety symptoms.

1.2 Current Research Status

Some adolescents do not respond to current standard treatments. Doss and Weisz (2006) and Kendall and Clarkin (1992) emphasize the importance of studying predictive and moderating factors influencing treatment outcomes. Comorbidity is one such factor (Halldorsdottir & Ollendick, 2014). Halldorsdottir and Ollendick (2014) reviewed 10 studies on the impact of ADHD and anxiety disorder (AD) comorbidity on treatment outcomes. Some studies found that ADHD comorbidity significantly reduces the therapeutic effect of CBT on anxiety disorders. For example, patients with obsessive-compulsive disorder (OCD) and ADHD had lower treatment response rates and remission rates after CBT (Storch et al., 2008). Additionally, Halldorsdottir and Ollendick (2014) noted in a study on specific phobia that ADHD symptoms were associated with poorer treatment outcomes. Halldorsdottir and Ollendick (2014) suggest this is because core ADHD symptoms, such as inattention and hyperactivity, significantly interfere with the CBT process, especially exposure exercises and cognitive restructuring that require sustained attention. Habituation requires individuals to repeatedly expose themselves to anxiety-provoking stimuli to reduce emotional responses. However, some studies have not found significant effects. Manassis et al. (2002) analyzed the treatment outcomes of children with various anxiety disorders (such as generalized anxiety, separation anxiety, social anxiety, phobias, etc.) and found that while some children exhibited high activity levels, these ADHD symptoms did not significantly predict treatment outcomes. Similarly, the study by Southam-Gerow, Kendall, and Weersing (2001) also noted that ADHD symptoms (including inattention and hyperactivity) did not significantly affect the overall effectiveness of anxiety treatment. Additionally, the method of assessing ADHD can influence research conclusions. If ADHD is diagnosed using a clinical structured interview (such as the ADIS-C/P), children with comorbid ADHD are more likely to experience poorer treatment outcomes (Halldorsdottir et al., 2014; Storch et al., 2008). However, some studies found poor outcomes, while others did not find significant associations (Halldorsdottir and Ollendick, 2014). Some adolescents do not respond to current standard treatments. In response to this situation, Doss and Weisz (2006) emphasize the need to study predictive and moderating factors of treatment outcomes. In summary, intervention methods for ADHD and anxiety comorbidity also require further discussion and synthesis.

1.3 The present study

The developmental mechanisms underlying ADHD and anxiety comorbidity remain poorly understood. Discussions of these mechanisms are particularly critical for intervention and treatment. This paper reviews multiple relevant studies and finds that current research primarily focuses on three interrelated core mechanisms: brain mechanisms, neurochemical mechanisms, and genetic susceptibility. Brain mechanism interactions demonstrate the multifaceted nature of comorbidity, particularly when anxiety intensifies, potentially leading to ADHD exhibiting the unique symptom of "anxious impulsivity" (Epstein et al., 1997). Neurophysiological studies emphasize the role of brain circuitry and neurochemical imbalances, providing more precise targets for clinical interventions such as targeted medication and behavioral interventions (Nigg et al., 2004). From the perspective of genetic susceptibility, research indicates that ADHD and anxiety exhibit independent transmission patterns within families, despite shared genetic risk factors (Biederman et al., 1991). Twin studies further support the high heritability of ADHD (Thapar et al., 2001). Furthermore, the clinical significance of studying these mechanisms lies in addressing the diagnostic and treatment challenges associated with comorbidity (De Los Reyes & Kazdin, 2005). Mechanistic analysis can advance precise subtyping or identify the Slow Cognitive Tempo (SCT) subtype (Carlson & Mann, 2002),

which may help explain the heterogeneous presentation of comorbid patients. This study, by integrating brain mechanisms, neurochemistry, and genetic perspectives, will lay the foundation for mechanistic subtype classification and individualized treatment, and provide additional guidance for clinical practice.

2. Comorbidity Mechanisms

2.1 Comorbidity mechanism Brain mechanism

Multiple studies have shown that attention-deficit/hyperactivity disorder (ADHD) exhibits significant structural and functional abnormalities at the neural mechanism level, particularly in the prefrontal cortex (PFC). The PFC is closely associated with executive function and attention control and is one of the most affected regions in ADHD patients (Prevatt et al., 2015). Structural studies have shown that the volume of the prefrontal cortex in ADHD patients is significantly smaller than that in healthy controls (Castellanos et al., 2002), and there is a delay in developmental progression, with the peak of gray matter maturation in the prefrontal cortex occurring approximately three years later than in healthy children (Shaw et al., 2006). In terms of functional connectivity, the prefrontal-striatal loop, which includes the prefrontal cortex, striatum, and anterior cingulate cortex, exhibits impaired function, with significantly reduced activation during executive control and behavioral inhibition (Bush et al., 2008; Silk et al., 2009). These neural mechanism abnormalities result in ADHD individuals exhibiting impaired working memory, difficulty in response inhibition, deficits in cognitive flexibility and planning ability (Sergeant et al., 2003), as well as abnormalities in attention regulation, such as deficits in alertness, directed attention, and sustained attention (Sergeant et al., 2003). In addition to the PFC, ADHD is also associated with changes in the volume of multiple brain regions, such as the basal ganglia, the cerebellum,and the corpus callosum (Krain & Castellanos, 2006). Anxiety-related studies have shown that chronic stress can lead to hippocampal atrophy and reduced neurogenesis, thereby impairing episodic memory and threat detection abilities (Krugersn et al., 2010). Its reduced volume is associated with fear generalization in PTSD patients, and excessive secretion of glucocorticoids also damages hippocampal neurons and reduces brain-derived neurotrophic factor (BDNF) (Kitayama et al., 2005; Schoenfeld et al., 2017). Shi et al. (2023) further distinguished the functions of the dorsal hippocampus (dHPC) and ventral hippocampus (vHPC), with the former primarily regulating spatial memory and the latter being key to anxiety regulation. Hippocampal atrophy induced by chronic stress is closely associated with impaired neuroplasticity. Disrupted connectivity with the orbitofrontal cortex (OFC) may impair reward processing, decision-making, and behavioral inhibition (Bechara et al., 2004), thereby explaining the impulsive behavior and delay aversion characteristics observed in ADHD patients. ADHD patients often exhibit delayed cortisol circadian rhythm phase (Baird et al., 2011), and individuals with inattentive type ADHD show reduced reactivity to acute stress responses (Corominas-Roso et al., 2015). In contrast, the hyperactive-impulsive subtype is associated with higher baseline cortisol levels and enhanced stress responsiveness, particularly in male children (Hatzinger et al., 2007, forming a “stress-anxiety” positive feedback mechanism. Inflammatory factors can disrupt HPA axis function, and HPA dysfunction in turn inhibits its anti-inflammatory effects, creating a vicious cycle (Bellavance & Rivest, 2014).

In spatial working memory tasks, the following findings were observed: First, cerebellar activity was negatively correlated with ADHD severity, and individuals with high anxiety levels exhibited reduced filtering capacity for irrelevant stimuli, leading to increased interference (Baier et al., 2014); Second, under high working memory load, the interaction between anxiety and ADHD leads to reduced activity in the bilateral striatum and thalamus, impairing task performance. In this pathway, the nucleus accumbens integrates inputs from the prefrontal cortex, amygdala, and hippocampus to regulate information entering the thalamus (Levy, 2004). Together, these factors weaken cognitive resource integration capacity, forming a vicious cycle of executive dysfunction and anxiety interference.

2.2 Neurochemical Mechanisms

Dopamine system dysfunction is a core feature of ADHD, particularly in relation to the nucleus accumbens and the limbic-prefrontal dopamine pathways, which regulate reward processing and behavioral inhibition (Nigg, 2006). Abnormalities in the mesolimbic dopamine pathway underlie the core symptoms of ADHD: DA neurons projecting from the ventral tegmental area (VTA) to the nucleus accumbens (NAcc) exhibit dysregulation in both tonic and phasic release dynamics (Grace, 2001; Sagvolden et al., 2005). Reduced tonic DA levels lead to impaired regulation of phasic DA release, weakening the delay-of-reinforcement gradient, and manifesting as impulsivity, delay aversion, and reward processing deficits (Sagvolden et al., 2005), forming the typical "fearless" behavioral pattern of ADHD. Additionally, studies have found that when ADHD co-occurs with anxiety, dopaminergic dysfunction may exacerbate emotional responses by weakening prefrontal cortex regulation of the amygdala, leading to worsening anxiety symptoms (Barkley & Fischer, 2010).

Deficiencies in the serotonin (5-HT) system are directly associated with anxiety pathology, particularly its role in regulating emotional responses in the amygdala-prefrontal cortex circuit (León-Barriera et al., 2023). Studies have found that patients with ADHD comorbid with anxiety exhibit a significant treatment response to the combination of selective serotonin reuptake inhibitors (SSRIs) and dopaminergic medications: in adult patients unresponsive to antidepressants, adding amphetamine not only improves ADHD symptoms but also significantly reduces anxiety scores (Gabriel, 2010). This suggests that the synergistic interaction between the dopamine (DA) and serotonin (5-HT) systems may stabilize mood by regulating the prefrontal-limbic circuit. Additionally, methylphenidate (MPH) has been reported to alleviate both ADHD and anxiety symptoms simultaneously (Snircova et al., 2016). Genetic studies further support the molecular basis of neurotransmitter system interactions, particularly the polymorphisms of the dopamine transporter gene (DAT1) and the serotonin transporter gene (5-HTTLPR), which may increase the risk of ADHD and anxiety comorbidity (Pliszka, 2009). Therefore, the comorbidity of ADHD and anxiety involves the combined dysfunction of the dopamine reward pathway, the norepinephrine alertness system, and the serotonin mood regulation network.

2.3 Genetic Mechanisms

Based on neurobiological and genetic evidence, the high comorbidity rate (approximately 30–40%) between ADHD and anxiety disorders has a significant genetic susceptibility basis. Twin studies indicate that the heritability of ADHD is as high as 70–80%, while that of anxiety disorders is approximately 30–50%. When co-occurring, the genetic correlation between the two is significant ($r = 0.40–0.70$), suggesting shared genetic risk factors (Thapar et al., 2001; Graetz et al., 2001). Molecular genetic studies further reveal that gene interactions between the adenosine and dopamine systems are the core mechanism: ADORA2A gene main effect: The rs2298383-TT genotype significantly increases the risk of anxiety in ADHD patients. Functional annotation confirms its location in the promoter region, where it influences receptor expression by regulating histone modifications and transcription factor binding (Fraporti et al., 2019). Additionally, there is an ADORA2A-DRD2 gene interaction: the T/C haplotype of ADORA2A interacts with the A/T haplotype of DRD2 to double the risk of anxiety, with 40% of the combined effect attributable to gene interaction. The biological basis for this interaction stems from the physical interaction of the A2A-D2 heterodimer: DRD2 variants alter signal transduction by regulating the ratio of D2 receptor subtypes (D2L/D2S) (Zhang et al., 2007), while ADORA2A variants may weaken adenosine's inhibitory regulation of dopamine signaling, collectively disrupting synaptic gating mechanisms in the mesolimbic system (Fraporti et al., 2019). Levy's (2004) neural circuit model provides a framework for explaining this genetic susceptibility: the prefrontal cortex (PFC)-hippocampus-nucleus accumbens pathway finely regulates fear signals input to the amygdala through synaptic gating. Genetic variants associated with ADHD may disrupt this mechanism through the following pathways: First, dopaminergic imbalance: abnormal midbrain-limbic system tonic/phasic dopamine (DA) relationships (Figure 1), leading to a steeper reinforcement gradient (Sagvolden et al., 2005),

manifested as delayed aversion and impulsivity; Second, synaptic gating dysfunction: reduced inhibitory function in the prefrontal cortex (PFC) and weakened hippocampal background regulation lead to excessive activation of the nucleus accumbens by amygdala fear input, resulting in an anxiety phenotype (Levy, 2004).

The genetic-neural circuit model for ADHD-anxiety comorbidity posits that genetic variation, particularly ADORA2A/DRD2 risk alleles, reduces the stability of A2A-D2 heterodimers, weakening adenosine's antagonistic effect on dopamine signaling. This receptor dysregulation leads to abnormal DA signaling and impaired PFC-hippocampal synaptic gating function, ultimately causing disinhibition of amygdala fear responses. This circuit disruption manifests behaviorally as the paradoxical coexistence of impulsivity and anxiety (Levy, 2004). Thus, the core genetic susceptibility involves ADORA2A-DRD2 interactions disrupting mesolimbic synaptic gating, mediating the "impulsivity-anxiety" phenotype. Future research should validate this model by integrating genotyping with neuroimaging to guide mechanism-targeted interventions.

3. Intervention Methods

In the treatment of ADHD, stimulants and non-stimulants can effectively improve attention deficit and hyperactivity symptoms in comorbid patients (Reimherr et al., 2017). Clinical evidence indicates that even with the FDA warning about stimulants exacerbating anxiety, patients with ADHD and comorbid anxiety respond to methylphenidate extended-release or atomoxetine similarly to patients with ADHD alone, without increasing the risk of dropout (Reimherr et al., 2017). Tomecortine may serve as an alternative option due to its lower risk of anxiety exacerbation (Clemow et al., 2017), while SSRI/SNRI combination with stimulants may enhance efficacy in treatment-resistant cases (Gabriel, 2010). At the psychological intervention level, ADHD symptoms may interfere with habituation mechanisms—the core process of symptom reduction achieved through sustained exposure to anxiety-provoking stimuli—and affect the efficacy of cognitive-behavioral therapy; inattention may hinder exposure implementation (Jarrett & Ollendick, 2008). The MTA study showed that comorbid children responded better to behavioral therapy than to medication alone (March et al., 2000). In the adult domain, CBT anxiety modules are recommended as adjunctive therapy to medication (Schatz & Rostain, 2006). Current limitations focus on three areas: first, the improvement of anxiety by medication lacks specificity, possibly due to the placebo effect or secondary benefits from ADHD remission (Reimherr et al., 2017); Second, the heterogeneity of comorbid subtypes has not been incorporated into treatment decisions, and different ADHD subtypes may differentially impact treatment efficacy (Frederick et al., 2017); third, differences in diagnostic tools and family factors may limit intervention effectiveness (Jarrett & Ollendick, 2008).

4. Summary and Outlook

This paper explores the neurobiological mechanisms, genetic susceptibility, and treatment strategies for the comorbidity of ADHD and anxiety disorders, revealing their high co-occurrence linked to brain dysregulation, neurotransmitter dysfunction, and genetic factors. ADHD symptoms typically precede and predict anxiety development, with comorbidity exacerbating severity, reducing treatment efficacy, and limiting current anxiety improvement. Addressing challenges in diagnosis and treatment necessitates mechanism-specific approaches for precision subtyping and individualized interventions. Critical unresolved issues include defining shared pathophysiology, identifying early biomarkers via neuroimaging, and designing personalized plans. Future research should prioritize elucidating gene-environment interactions using advanced genomics/epigenetics, and developing refined, multidisciplinary treatment strategies that combine optimized pharmacotherapy with personalized CBT and leverage emerging technologies like VR and AI-assisted therapy to enhance efficacy for this complex comorbidity.

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