Depression co-morbidity with ADHD

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Abstract
Background: ADHD symptoms typically arise during childhood, and often persist into adulthood, with childhood ADHD symptom severity significantly predicting persistence into adulthood. Moreover, ADHD is highly associated with comorbid conditions. Major depressive disorder (MDD) is one of the most common lifetime comorbidities associated with ADHD. MDD is a serious mood disorder that affects children's and adolescents' physical, emotional, and social-cognitive development. It is characterized by feelings of sadness and lack of interest or pleasure. ADHD and depression are individually associated with long-term negative outcomes, but their co-occurrence is associated with even greater levels of impairment and negative outcomes; this includes greater psychosocial difficulties and higher rates of hospitalization. It is important to not only understand the high occurrence of ADHD and depression together and how to differentiate between them, but also to examine the reasons for their coexistence. Multiple theories have emerged from this area of research. One set of theories suggests that ADHD and depressive disorders simultaneously arise due to the interplay of multiple "common causes," or shared etiological factors (genetic, neurobiological, and environmental). Other theories assert that depression arises because of the secondary impairments associated with childhood ADHD symptoms, including social and academic difficulties.

Keywords: Depression, co-morbidity, ADHD

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Introduction:
ADHD symptoms typically arise during childhood, and often persist into adulthood, with childhood ADHD symptom severity significantly predicting persistence into adulthood. Moreover, ADHD is highly associated with comorbid conditions, with the prevalence of co-occurring psychiatric disorders in children and adolescents ranging from about 40% to 80%. Major depressive disorder (MDD) is one of the most common lifetime comorbidities associated with ADHD (1)

Depression in children and adolescents:
MDD is a serious mood disorder that affects children's and adolescents' physical, emotional, and social-cognitive development. It is characterized by feelings of sadness and lack of interest or pleasure (2).

The main symptoms are depressed mood, irritability, feelings of worthlessness and guilt, problems with sleeping, weight loss, thoughts of death and suicide, or withdrawal from (social) activities. The symptoms can vary from mild to severe, and they must last at least 2 weeks for a diagnosis of depression. In addition, the DSM-5 contributed to better recognition and understanding of depression in childhood, adding two crucial distinctions between symptoms in children and adults. First, children may express irritability rather than sad or depressed mood. Second, weight loss may result in failure to reach appropriate weight milestones(2).
The presence of depression symptoms can occur even without a formal diagnosis of depression, and this is why antecedents of children's and adolescents' symptoms of depression are investigated in the general and clinical population as well as the possible developmental consequences of depression. (3)

Prevalence of depression among ADHD:
A large body of research, utilizing both cross-sectional and longitudinal study designs, as well as community and clinical samples, shows that depressive disorders occur at significantly higher rates in those with ADHD compared to those without. The association between the disorders has been documented in meta-analytic research as well. (4).

Rates of depression and ADHD co-occurrence seem to increase during the developmental period of adolescence and persist into adulthood. In community samples, the rate of MDD in youths with ADHD is 5.5 times higher than in youths without ADHD, with rates ranging from 12.5% to 50% across different studies, moreover comorbidity rates are even higher in clinical samples (5).

Impact of comorbidity between ADHD and Depression:
ADHD and depression are individually associated with long-term negative outcomes, but their co-occurrence is associated with even greater levels of impairment and negative outcomes; this includes greater psychosocial difficulties and higher rates of hospitalization, worse depression outcomes, including an earlier age of depression onset, a longer duration of illness, increased symptom severity, and **Differentiation between ADHD and MDD**

A) **Disparities in the Clinical Presentation of MDD and ADHD**

In terms of diagnosis, ADHD and MDD have some common symptoms such as problems with focus and restlessness. ADHD and MDD frequently occur together, making it challenging to diagnose accurately. Nevertheless, research indicates that even when individuals with ADHD and depression symptoms are considered, a separate diagnosis of ADHD can still be made. (4).
Individuals with ADHD display consistent difficulty regulating attention and focus (including hyper-focusing), engage in impulsive and hyperactive behaviors, and exhibit global deficits in executive functioning. These diagnostic hallmarks of ADHD do not overlap with current criteria for MDD. Further, though attention difficulties are seen in the diagnostic criteria of both ADHD and MDD, the attention deficits seen in ADHD are enduring and begin in childhood, whereas those seen in MDD are specific to the depressive episode and remit once the episode end. Additionally, irritability (i.e., an increased proneness to anger relative to peers at the same developmental level) should be considered when addressing ADHD and depression in children. (6)
Irritability is a core symptom of depression in children and is reported in one-third of children with depression, and though irritability is not a defining diagnostic feature of ADHD, it is present

in approximately 25–45% of children with the disorder. Importantly, children with ADHD who also experience elevated irritability are at elevated risk of developing depression symptoms. Thus, it is important to consider irritability, as it may be an early marker of mood problems in children with ADHD. Despite the uniqueness of symptom expression across ADHD and MDD, both disorders do contribute to functional impairment in similar domains (e.g., sleep disturbances, higher rates of substance use, interpersonal relationship strain, and poorer academic performance **(7)**

B) **Differences in the causes and potential outcomes.**

As a neurodevelopmental disorder, ADHD is best understood as a highly heritable "brain-based" disorder that broadly impacts self-regulation and contributes to deficits in executive functioning. Neurobiological research has suggested that underactivity in areas of the frontal cortex that regulate various cognitive and emotional processes may explain why general executive functioning deficits are a hallmark of ADHD **(8).**

Research has identified prenatal risk factors (e.g., low birth weight, premature birth, lack of oxygen during birth), neuronal receptor density, and epigenetic etiological factors **(9).**

Symptoms of ADHD emerge in childhood or early adolescence. Generally, those with ADHD experience chronic and persistent impairment in attention and executive functioning that is independent of mood disturbances. Though symptoms of ADHD may worsen during periods of heightened anxiety or depression, these symptoms persist even in the absence of internalizing symptoms **(10).**

Research on MDD etiology remains complicated. Genetic factors, trauma exposure, substance use, female gender, and comorbid illnesses have all been linked to MDD. In contrast to ADHD diagnosis, there is no "age of onset" criterion for MDD; however, research suggests symptom onset typically occurs in adolescence or young adulthood. MDD among children is less common, but prevalence rates are around 2%. MDD is comprised of nine possible symptoms and, in turn, is highly heterogeneous among those who share this diagnosis. Symptom profiles can differ drastically from person to person because of which symptoms they endorse. MDD is also episodic in nature, meaning an individual may have episodes of depression that are followed by periods of euthymic mood and minimal functional impairment in various domains, including attention and executive functioning **(11).**

C) **Disparities in Cognitive Functions**

Diagnostic criteria for both MDD and ADHD suggest similar difficulties in various areas of cognitive performance (e.g., motivation, concentration); however, the function of these symptoms differs between disorders. As outlined by Criterion A.8 of MDD in the DSM-5-TR, for example, the diminished ability to concentrate endorsed by many depressed individuals may appear reflective of the diagnostic criteria for general inattention caused by ADHD (Criterion A.1). **(12)**

Causes for the concurrent occurrence of ADHD and depression:

It is important to not only understand the high occurrence of ADHD and depression together and how to differentiate between them, but also to examine the reasons for their coexistence. **(12)**

Multiple theories have emerged from this area of research. One set of theories suggests that ADHD and depressive disorders simultaneously arise due to the interplay of multiple "common causes," or shared etiological factors (genetic, neurobiological, and environmental). Other theories assert that depression arises because of the secondary impairments associated with childhood ADHD symptoms, including social and academic difficulties. **(12)**

A) Shared Etiology Theory

Genetic and environmental risk theories point to "common cause" endophenotypes that underlie both ADHD and depressive disorders. Research has illustrated the clear importance of genetic factors and neurobiological constructs (e.g., reward responsivity, emotion regulation) that relate to the etiology of both disorders. Environmental stressors (e.g., quality of parenting, family context, lack of access to care) may also serve to exacerbate the risk of comorbidity. **(12)**

The Neurobiology of Co-occurring ADHD and Depression

Evidence suggests that both disorders are heritable, with ADHD considered highly heritable, approximately 80% and depression considered moderately heritable approximately 40% . Several twin studies have found that up to 70% of the co-occurrence of ADHD and depression can be explained by shared genetic factors . Currently, no one gene is believed to significantly influence the development of either disorder alone or in tandem. Instead, scientists suspect it is the more minor influence of many genes that contributes to the development of ADHD and depression **(1).**

Shared Brain Structure

Aberrant activity in shared brain structures may help to explain ADHD and depression comorbidity. **Gardner et al. (14)** found that individuals with ADHD and depression comorbidity exhibited abnormal activity in the cerebellum and frontal brain regions. The cerebellum is involved in cognitive processing as well as behavioral and emotional control. Meanwhile, the frontal regions of the brain encompass the prefrontal cortex and limbic system structures (the hippocampus and amygdala, in particular), which have been implicated in executive dysfunction and affective dysregulation **(15)** across psychopathologies.

Shared Endophenotypes

Endophenotypes are the neurological traits that interact to determine a final, observable feature or behavior, a phenotype, which may or may not be abnormal. Specific endophenotypes that ADHD and MDD may share are reward responsiveness **(4).**, emotional processing/regulation, and executive functioning **(16).**

Low reward responsivity has been identified in depression as impacting the severity of anhedonic symptoms and in ADHD as a desire for increased stimulation to overcome a naturally low set point and feel pleasure. In both disorders, reward responsivity can prevent individuals from anticipating expected rewards, accurately ascertaining the amount of effort required to attain a reward and engaging in goal-directed behaviors to attain a reward. In one study, reward responsiveness was shown to mediate the relationship between ADHD and depression **(4).**

An additional construct that might serve as a shared endophenotype for ADHD and MDD is emotion dysregulation. Emotion dysregulation can be conceptualized as an emotional expression that is excessive relative to social norms, rapidly occurring, and poorly controlled, and as a maladaptive allocation of attention to emotional stimuli **(17).**

Research suggests that emotion dysregulation is a shared etiological risk factor for ADHD and depression **(4).** Emotion dysregulation may also act in tandem with reward responsiveness. Children with ADHD and a low hedonic tone may experience increased sensitivity to rewards and, thus, suffer from heightened frustration when the reward is withheld **(17).**

Being unable to experience pleasure begets irritability, which is a symptom of both depression and ADHD **(17).**

Functional magnetic resonance imaging (fMRI) studies have uncovered limbic system abnormalities (principally in the amygdala, thalamus, and hippocampus) that contribute to an over-perception of negative stimuli in ADHD. Researchers have theorized that poor frustration tolerance combined with an over-perception of negative stimuli not only exacerbates emotional dysfunction in individuals with this comorbidity but is also predictive of future depressive episodes. A third potential endophenotype for ADHD and MDD is executive dysfunction. Executive function is defined as the self-regulatory neurocognitive processes that operate over time to help people achieve their goals. These processes are largely located in the prefrontal cortex of the brain and have been implicated in comorbid ADHD and depression **(18)**
Impulsivity, poor inhibitory control, impaired reasoning ability, cognitive inflexibility, poor working memory, and difficulty task switching are all associated with a hypo functioning dopamine system. In ADHD, these mechanisms are apparent in an individual's behavior and intrinsic to the disorder's criteria. In depression, the same impulsive tendency may manifest as suicidal ideation and irritability, or impulsive behaviors may result in consequences that maintain or worsen the depressed mood **(19).**

B) Social and Environmental Factors

The influence of neurobiological and genetic factors should not be understood in isolation, but rather, within a social and environmental context. Multiple factors related to familial and peer relationships, as well as academic functioning, may exacerbate existing genetic and neurobiological risks and/or may be salient contributors in themselves to the development of comorbid depressive disorders amongst individuals with ADHD. **(12)**

C) Family Factors:

The inattentive, hyperactive, and impulsive behaviors and associated impairments that characterize childhood ADHD may provoke negative and inconsistent parenting styles and contribute to communication difficulties within families **(12)** Specific parenting factors, including inconsistent management of children's disruptive behaviors, parent-child relationship difficulties, and low parental support, have all been found to be important and significant mediators in the relationship between ADHD symptoms and depression. Two longitudinal studies have emphasized the significance of the quality of the parent-child relationship in the co-occurrence of ADHD and depression. One study discovered that a positive parent-child reationship can have a protective effect, **(18)** while the other study found that worsening relationship quality with mothers during adolescence may mediate the link between ADHD symptoms and depression, particularly in adolescent boys. **(4).**

D) Demoralization Theory:

In the school context, compared to their peers, children with ADHD may experience academic and peer difficulties simultaneously. In turn, both academic and social impairments in childhood predict depression symptoms. The dual-failure model, or "demoralization theory" **(12),** suggests that over time these compounding peer and classroom-related difficulties will be internalized by youth with ADHD as failures, contributing to a negative self-concept and leading to depression symptoms. The demoralization theory of ADHD and depression comorbidity aligns with childhood depression competency models, which explain how children's self-concept can be shaped and strengthened by external influences, such as negative feedback or attributions of blame

from others (e.g., parents, teachers) in response to their academic and social challenges. The self-perceptions formed in early childhood can serve as the basis for cognitive distortions and the emergence of depression symptoms during later childhood and adolescence. This theory is substantiated by the typical timing of symptom onset: ADHD symptoms typically manifest in early childhood, while depressive disorders typically emerge in late adolescence **(20).**

Protective Factors against depression:

Cognitive Thinking Styles:

Many children with ADHD form judgments regarding their abilities in an overly optimistic manner, a phenomenon labeled "positive illusory bias". However, there is less evidence for positive illusory bias in children who experience co-occurring depression symptoms. Research shows that decreases in positive illusory bias over time are associated with an increase in depression symptoms **(21).**

The initial evidence suggests children who maintain high self-esteem despite ADHD-related impairment may be protected. On the other hand, the positive illusory bias may also set children up for further failure and demoralization by preventing them from recognizing their difficulties and changing behavior in response to negative feedback. More research is needed to test the function of the positive illusory bias and to understand its adaptive and/or maladaptive consequences. **(12)**

Treatment Access

In addition to individual cognitive factors, treatment for ADHD symptoms in childhood may also be protective in the ADHD-depression trajectory. One study found that the more years of treatment for ADHD (of any modality), the lower the likely hood of having co-occurring depression **(21).**

A second study found that the association between childhood ADHD and depression was no longer significant when accounting for the persistence of ADHD symptoms **(4).,** further supporting the potential protective effect of early treatment for ADHD and managing its symptoms **(4).**

Assessment

One of the most important factors in differentiating ADHD from a myriad of other disorders (including MDD) is establishing a clear timeline of symptom onset and affiliated impairment. Current diagnostic criteria for ADHD (per the DSM-5-TR) require symptom presence before the age of 12. While this criterion has been contested in recent literature, there is still minimal evidence to suggest high prevalence rates of "late-onset" ADHD in older adolescents and emerging adults **(22).**

Challenges in diagnosing depression in ADHD patients:

In youths with ADHD a diagnosis of depression is further complicated by multiple symptoms that overlap between the two disorders or with other childhood psychiatric disorders **(20).** Medications used to treat ADHD may cause side effects like insomnia or decreased appetite that mimic vegetative symptoms of depression **(20).** Previous study reported that symptoms that best differentiate ADHD youths with and without co-morbid MDD are social withdrawal, anhedonia,

depressive cognitions, suicidal thoughts, and psychomotor retardation, whereas irritability, concentration problems, and most other vegetative symptoms do not **(20).**

Not surprisingly, total scores on even well-validated depressive measures are less accurate when screening for MDD among children with ADHD **(20)**

Both parents and children may offer valid but discrepant information about children's depressive symptoms. Parents are typically more accurate regarding the temporal course of depressive symptoms, and, along with teachers, are better reporters regarding symptoms of ADHD, irritability, and externalizing disorders, whereas youths tend to be better reporters of depressive cognitions, suicidal thoughts, and anxiety symptoms, especially as they get older **(20).**

Youths with ADHD may overestimate their social and other competencies **(21),** and symptoms of distractibility, carelessness, and impulsivity may make them less accurate in reporting depressive symptoms. On the other hand, parents of ADHD youths may confuse symptoms of depression with symptoms of other co-morbidity **(20),** and may be biased by their own mental health problems in reporting their child's symptoms **(23)**

Treatment

I) Pharmacological treatments

Two dominant (yet not conflicting) theories exist concerning medication treatment for individuals with ADHD and concurrent depression. The first suggestion is that treating ADHD alone may have downstream effects on depression. In a longitudinal study of individuals with ADHD, both ADHD medication use (i.e., history of any ADHD medication use) and the duration of ADHD medication use were associated with lower rates of medical visits related to depression symptoms **(16).**

Hence, one suggestion is to initially address ADHD using either stimulant medication or non-stimulant medication sanctioned for ADHD. Following the monitoring of both ADHD and depression symptoms, if the medication for ADHD symptoms is well tolerated and successfully manages ADHD symptoms, but depression symptoms persist, the recommendation is to introduce an antidepressant medication alongside the ADHD medication **(12).** The concurrent use of ADHD and antidepressant medications is considered safe and efficacious **(24)**

On the other hand, the alternative recommendations propose that the more severe condition should be addressed initially. If depression is notably severe, especially if there are safety apprehensions related to suicidal tendencies, it is advised to first manage the symptoms of depression pharmacologically. Subsequently, as the symptoms become more controllable, the introduction of ADHD medication is considered appropriate **(25).**

II) Psychosocial Treatments

- **Cognitive Behavior Therapy (CBT)**

Though several psychosocial interventions have been studied as potentially beneficial for those with ADHD and comorbid depression symptoms **(20),** cognitive-behavioral therapy (CBT) is perhaps the most widely researched. **(12)**

Given the high prevalence of depression symptoms among those with ADHD, researchers have tended to examine depressive symptoms changes within trials of ADHD-focused CBT programs alone or in conjunction with ADHD medication Regarding the Treatment for Adolescents with Depression Study (TADS), it was observed that Cognitive Behavioral Therapy (CBT), even without antidepressant medication, could be beneficial for adolescents with ADHD and

depression. This implies that in situations where it is advisable to address ADHD symptoms before introducing depression medication, CBT may help alleviate depression symptoms. **(26).**

CBT as a treatment strategy for addressing ADHD may also have the added benefit of serving as a preventive measure against depression and enhancing the resilience to cope with feelings of low mood, particularly considering that depression usually manifests at a later stage in life compared to ADHD. CBT to teach coping skills to individuals with ADHD may reduce those cognitive mechanisms that mediate the relationship between ADHD and depression. Namely, dysfunctional attitudes, ruminative thinking, and cognitive and behavioral avoidance are noted as particularly salient mediators of this relationship and are constructs directly addressed in CBT treatment **(27).** Participating in these value-driven activities helps increase the frequency and quality of rewarding experiences for youth, reinforces behaviors that buffer against depression, and promotes sustained investment in utilizing executive skills. Pilot studies of the BEAM program have been conducted both in a research clinic **(4).** and within a high school, where it was delivered by school mental health providers **(4).** Results of these studies suggest that BEAM was feasible to implement, was well-received by parents and youth, and resulted in changes in depression symptoms and target mechanisms **(4).**

Academic performance -Focused Interventions:

As mentioned earlier, the Demoralization Theory suggests that the academic and social challenges linked to ADHD can result in feelings of failure and low self-efficacy, potentially leading to demoralization. Consequently, addressing academic difficulties may have a positive impact on depression. It was found that a rigorous intervention targeting academic skills was linked to notable reductions in depression symptoms among adolescents with ADHD. **(27)**

The SUCCEEDS program, which stands for "Students Understanding College Choices: Encouraging and Executing Decisions for Success," combines academic coaching with strategies like those utilized in BEAM. SUCCEEDS addresses common cognitive and behavioral barriers to effective decision-making and functioning in college and provides these students with skills around planning, decision-making, and reducing behavioral avoidance **(4).**

Parental Interventions

Studies have indicated that parental support and behavior management can act as mediators in the link between ADHD and depression. Therefore, intervening in these areas may have an impact on reducing depression symptoms in children with ADHD. **(28).**

Parent training interventions have been extensively researched in younger children and have shown significant empirical evidence in addressing symptoms of ADHD. Additionally, the quality of the parent-child relationship and parenting practices have been found to be predictive of depression symptoms in children, particularly when parents themselves experience symptoms of depression. Thus, addressing parenting practices may be a buffer against youth depression, namely among youth whose caregivers are experiencing more stress **(29)**

Parental depression symptoms are a strong predictor of children developing depression themselves, which is concerning given that approximately half of parents of children with ADHD experience depression **(4).** The integrated parenting intervention for ADHD (IPI-A) **(30)** is one such approach that provides a group-based parenting intervention for caregivers of youth with ADHD; it teaches both child behavior management skills and provides CBT to parents to address their own depression symptoms. Results found that parents' depression was reduced, and children experienced better behavioral and functional outcomes in those who were enrolled in the IPI-A.

Thus, reducing maternal depression in the context of behavioral parenting interventions could mitigate the risk of depression in youth with ADHD.

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