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A Brief Discussion on Adolescent Anxiety and Depression

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Abstract: ***Adolescence is a critical developmental stage with high susceptibility to anxiety and depression. This review summarizes relevant findings covering epidemiology, pathogenesis, neurobiology, diagnosis and treatments. Global prevalence of adolescent emotional disorders has risen continuously and was further escalated by the COVID-19 pandemic, with females at higher risk. Pathogenesis results from combined genetic, epigenetic and toxic stress factors alongside brain network and gut-brain axis dysfunction. Differing from adults, affected adolescents mainly present with irritability, somatic discomfort and school refusal, prone to misdiagnosis. SSRIs dominated pharmacotherapy with fluoxetine prioritized, while CBT and IPT-A are effective non-drug interventions. Multilevel collaborative prevention systems are essential to optimize adolescent mental health management.***

Keywords: Adolescent anxiety and depression, Gender difference, Pathogenesis, Fluoxetine.

1. Introduction

Adolescence is the most beautiful stage in everyone's life and a key transitional stage for physical and mental development, and even neurodevelopment. It is characterized by significant physical, cognitive and psychosocial maturation. At the same time, it is also a period when individuals are highly susceptible to internalized mental illnesses. With social development, adolescent depression and anxiety are no longer regarded as a short-term developmental stage or typical adolescent anxiety, but as serious, disabling and often chronic diseases. These diseases have a very high risk of heterogeneous continuation, which means that untreated internalized disorders in adolescence often persist into adulthood, either maintaining their original diagnostic presentation or evolving into highly comorbid mental disorders or substance use disorders [1].

2. Epidemiology of Anxiety and Depression in Adolescents.

Over the past three decades, the global burden of mental health disorders among adolescents has reached a critical level, primarily due to the rising prevalence of anxiety and depression. A comprehensive systematic analysis of the 2021 Global Burden of Disease (GBD) study revealed that nearly 1.2 billion people worldwide suffer from mental disorders, an epidemiological reality that has now become a leading cause of disability globally [2]. By 2023, mental illness had caused approximately 171 million people to become disabled globally, surpassing cardiovascular disease, cancer, and musculoskeletal disorders in years of disability survival [2]. Crucially, the group with the largest increase in disability rates is adolescents and young adults aged 15 to 19, followed by adult women, who consistently show a higher susceptibility to internalization disorders [3]. In recent years, the prevalence of anxiety disorders among adolescents and young adults aged 10 to 24 has continued to rise. The prevalence of mood problems appears to vary depending on geographical and economic circumstances. In low- and middle-income countries, the prevalence of mood problems among adolescents is alarmingly high, with the prevalence of depression estimated at between 1% and 58%, and the prevalence of anxiety disorders estimated at between 1% and 30% [4]. Among children and adolescents worldwide, the prevalence of generalized anxiety symptoms was 18.2%, social phobia was 20.2%, specific phobia was 20.9%, and separation anxiety was 14.0%.

Furthermore, the study found that gender differences begin to emerge rapidly during adolescence. The prevalence of depressive symptoms generally shows a higher rate in women (approximately 17.5%) than in men (approximately 15.1%). This difference aligns with endocrine changes and complex sociocultural pressures, which have a particularly severe impact on adolescent girls.

The COVID-19 pandemic has altered existing patterns and acted as a catalyst for global psychosocial distress. The sudden disruption of educational environments, loss of key peer interactions, forced social isolation, and widespread anxiety about health and economic stability have severely damaged the mental health of young people worldwide [5]. A landmark meta-analysis combining 29 cross-sectional studies involving 80,879 adolescents worldwide showed that the prevalence of depression and anxiety had catastrophically doubled before the pandemic [5]. Researchers found that the combined prevalence of clinically elevated depression and anxiety was estimated at 25.2% (95% confidence interval, 21.2%–29.7%) and 20.5% (95% confidence interval, 17.2%–24.4%), respectively. However, modulatory analyses showed that clinically higher levels of depression and anxiety were more prevalent in studies collected later in the pandemic (b = 0.27; 95% CI, 0.10–0.44). The prevalence of elevated clinical symptoms of depression and anxiety was also higher in female patients (b = 0.04; 95% CI, 0.01–0.07), while only depressive symptoms were higher in older children. The analysis of moderating variables in this comprehensive epidemiological meta-analysis revealed key information about the timing and demographic dynamics of the pandemic's impact. The significantly higher prevalence of clinical symptom exacerbation in data collected later in the pandemic suggests a cumulative toxic effect from long-term

structural disruption. Furthermore, older adolescents and younger women consistently exhibited a higher symptom burden, confirming existing demographic vulnerabilities identified in pre-pandemic literature. The acute and sustained influx of psychopathology underscores the urgent need to rapidly expand evidence-based Western medicine interventions, as the demand for mental health care continues to exceed available clinical resources.

3. Etiology and Pathogenesis

The pathogenesis of adolescent anxiety and depression cannot be simply attributed to a single biological or environmental factor. Instead, a better understanding of it requires a highly integrated perspective on biopsychosocial and neurodevelopmental factors. The asynchronous development of the brain during adolescence creates a developmental "mismatch". The evolutionarily older limbic system structures are closely related to emotion processing, threat detection, and reward seeking, and they mature and reach functional maturity much earlier than the prefrontal cortex [6]. The prefrontal cortex is responsible for top-down executive control, cognitive flexibility, and inhibition of acute emotional responses. This point in neurodevelopment creates a highly vulnerable period, making the adolescent brain abnormally sensitive to external stressors and environmental stimuli.

3.1 Toxic Stress and the Qualities-Stress Model

The occurrence of these diseases can usually be explained by a aptitude-stress model, in which intrinsic genetic and neurobiological vulnerability (aptitude) interacts with adverse environmental exposure (stress). Prolonged exposure to severe adversity—known as "toxic stress"—without the supportive protection of caregivers can lead to severe disruption of the normal developmental trajectory. Toxic stress fundamentally alters physiological circuits and neuroendocrine regulation, particularly in relation to the hypothalamic-pituitary-adrenal (HPA) axis. Chronic activation of the HPA axis can lead to hypercortisolism, which in turn has neurotoxic effects on the developing hippocampus, impairing memory consolidation, cognitive flexibility, and mood regulation, thus laying the foundation for chronic depression and anxiety [7].

3.2 Genetic and Epigenetic Drivers

Genetic factors play an important role in the etiology of depression and anxiety, but their mechanism of action is not monogenic Mendelian inheritance, but a complex polygenic mechanism. Family history is one of the most powerful risk factors; longitudinal cohort studies have repeatedly shown that maternal depression significantly increases the risk of psychopathology in offspring [1]. Recent advances in molecular psychiatry have isolated some specific gene polymorphisms that interact with environmental stressors. For example, the oxytocin receptor (OXTR) rs2254298 polymorphism is closely associated with psychopathology in female adolescents. Studies have shown that adolescent girls carrying the AG genotype are significantly more depressed when faced with high family adversity, which clearly reveals the interaction between genes and environment. Similarly, the A allele of OXTR rs53576 is significantly associated with deep loneliness in adolescent girls, especially after negative social evaluation [8]. These genetic susceptibility modulates the neurochemical response of the brain to social stressors and lowers the threshold for the onset of clinical depression and anxiety.

4. Neurobiological Mechanisms and Network Hypothesis

Beyond macroscopic structural vulnerability, advanced neuroimaging techniques—particularly resting-state functional connectivity (RSFC) and task-based functional magnetic resonance imaging (fMRI)—have revealed specific microscopic neural circuit alterations that define the neurobiology of adolescent internalization disorders.

4.1 Default Pattern Network (DMN) and Depressive Rumination

The default mode network (DMN) consists of a series of anatomically distinct but functionally interconnected brain regions, including the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), and inferior parietal lobe. The DMN is highly active during passive rest, spontaneous cognition, and self-referential thinking [9]. In the context of major depressive disorder in adolescents, the default mode network (DMN) exhibits pathological hyperconnectivity and hyperactivity. Excessive functional connectivity between the mPFC and the anterior cingulate cortex (ACC) is strongly positively correlated with depressive rumination (repetitive, passive, and inescapable focus on distressing symptoms and negative self-evaluation). These self-referential networks exhibit abnormal hyperactivation when depressed adolescents process negative social feedback or criticism, suggesting an underlying neurocognitive vulnerability that makes them prone to internalizing negative information. Conversely, resting-state functional connectivity disorder between the amygdala and orbitofrontal cortex (OFC) and parahippocampal gyrus is associated with disruptive behavioral manifestations that often accompany adolescent depression and tend to mask underlying adolescent depression [10].

4.2 Marginal-prefrontal Loop and Salience Network

Models of adolescent depression and anxiety are highly dependent on limbic system circuits. The amygdala, as the brain's primary threat detection center, shows significant overactivation in both facial expression recognition tasks and negative emotion processing in anxious and depressed adolescents. In healthy neurodevelopment, the prefrontal cortex plays an inhibitory, top-down regulatory role over the amygdala, thereby promoting fear extinction and emotional calm. However, in anxious adolescents, these prefrontal control systems are underdeveloped and show significant underactivation, particularly in the medial prefrontal cortex, during fear extinction recall [11]. Furthermore, the salience network (SN) – composed of the dorsal anterior cingulate cortex and the anterior insula, which together coordinate the brain's response to emotionally significant stimuli – shows abnormal connectivity. Effective resting-state connectivity between the amygdala and the default mode network (DMN)

is disrupted, and the amygdala shows significant underconnection within the salience network [12]. This network failure prevents the adolescent brain from properly encoding precise information and filtering out irrelevant threatening stimuli, resulting in chronic, pervasive hyperarousal and specific fear responses characteristic of adolescent anxiety disorders.

4.3 Reward Circuit and Pleasure Deficiency

While the limbic system is overactive in processing negative stimuli, the reward circuitry in the brains of adolescents with depression is pathologically underactive. The reward system —connecting the prefrontal cortex, striatum (particularly the nucleus accumbens), and ventral tegmental dopamine neurons — is crucial for motivation, pleasure, and goal-oriented behavior. Neuroimaging studies show reduced striatal activation in depressed adolescents during reward-processing tasks. This sluggish neural response is directly related to the clinical symptom of severe anhedonia, preventing adolescents from experiencing pleasure from previously enjoyable activities.

4.4 Neurochemical Basis and the Gut-Brain Axis

The pathogenesis is also related to microscopic neurochemical dysregulation. Major depressive disorder in adolescents is associated with excessive glutamatergic neurotransmission, leading to enhanced intracortical facilitation [13]. Brain-derived neurotrophic factor (BDNF) is a protein that is crucial for synaptic plasticity, neuronal survival and neurogenesis and is closely related to a variety of diseases. Decreased BDNF levels in the prefrontal cortex and hippocampus impair the adolescent brain's ability to structurally adapt to stress, thereby promoting the formation of depressive symptoms [6].

The study highlights the profound influence of the gut-brain axis on the pathophysiology of depression. The gut microbiota plays a key role in regulating tryptophan metabolism. Under physiological conditions, tryptophan is a precursor to serotonin, a neurotransmitter closely related to mood regulation. However, under chronic stress or systemic inflammation—a condition common in individuals with high anxiety or depression—tryptophan metabolism deviates from the serotonin synthesis pathway and is instead metabolized via the kynurenine pathway. This metabolic shift leads to increased production of neurotoxic quinolinic acid. Quinolinic acid is a potent agonist of NMDA receptors that drives neurotoxic excitation, exacerbates neuroinflammation, and significantly contributes to the structural and functional deficits observed in the brains of adolescents with depression [8].

5. Clinical Manifestations and Diagnostic Complexity

While the diagnostic criteria for major depressive disorder and various anxiety disorders listed in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) are generally applicable across all age groups, the phenotypic presentation of these disorders in adolescents differs significantly from that in typical adults. This discrepancy often leads to diagnostic masking or the misinterpretation of severe psychopathology as normal adolescent rebellion.

5.1 Major Depressive Disorder in Adolescents

The diagnosis rate of major depressive disorder in children has been low, and it is estimated that 50% of adolescents do not receive a formal diagnosis or appropriate intervention before adulthood. If left untreated, major depressive disorder in adolescents usually resolves within 7 to 9 months; however, the relapse rate is unusually high, with about 70% of affected adolescents experiencing a severe depressive episode again within five years [14]. Clinically, adolescents with MDD are significantly less likely to exhibit classic depressive vegetative symptoms common in adults, such as severe somnolence, generalized psychomotor retardation, or severe lack of energy. Instead, adolescent depression is typically characterized by extreme, atypical changes in weight and appetite, severe mood swings, and most critically, severe and uncontrollable irritability. In adolescents, irritability may completely replace sadness or depression as the primary, pathological clinical marker of a depressive episode. In addition, while adolescents exhibit fewer psychotic delusions compared to adults with major depressive disorder, they have a very high tendency toward impulsive self-harm and suicidal ideation [15]. Nearly 30% of adolescents with major depressive disorder reported experiencing active suicidal ideation in the past year, and more than 10% reported attempting suicide, which calls for active and sustained clinical vigilance from primary care and psychiatrists.

5.2 Adolescent Anxiety Disorder

Anxiety disorders in this group manifest as excessive and uncontrollable worry, which seriously affects academic performance, peer relationships and family interactions. Different anxiety phenotypes often appear sequentially during development; separation anxiety disorder (SAD) usually appears before specific phobias, and as adolescents' social circles expand and become more complex, social phobia (SoP) and generalized anxiety disorder (GAD) will subsequently appear [16].

The clinical manifestations of anxiety disorders in adolescents are primarily somatic. Affected adolescents rarely possess the emotional sensitivity required to express abstract fear concepts; instead, they often seek primary care physicians for a range of unexplained physical discomforts. These discomforts include severe migraines, chronic abdominal pain, functional gastrointestinal discomfort, and severe, difficult-to-treat sleep disorders.

A serious and increasingly common behavioral manifestation of adolescent anxiety disorder is school refusal. This is not simply skipping school; rather, it is caused by extreme panic, separation anxiety, or severe social anxiety that prevents them from attending school normally, or even renders them incapable of attending school. School refusal is a clinical emergency because the resulting academic isolation can rapidly exacerbate accompanying depressive symptoms and isolate adolescents from important peer support networks.

5.3 Diagnostic Assessment Framework

Accurate diagnosis requires the use of validated screening tools appropriate for adolescent development. The Patient Health Questionnaire-9 (PHQ-9) for adolescents has been widely used in primary care settings for rapid assessment of the severity of depressive symptoms and screening for suicidal ideation [17]. For comprehensive assessment, the Child Depression Rating Scale-Revised (CDRS-R) is the gold standard tool for clinicians [18]. For anxiety, the Revised Child Anxiety and Depression Scale (RCADS) allows for self-reported and parent-reported measurements of specific anxiety and depressive symptom dimensions, thus helping to triangulate adolescent dysfunction [19].

6. Drug Treatment Strategies

In Western medicine, the primary drug treatment for anxiety and depression in adolescents is selective serotonin reuptake inhibitors (SSRIs), followed by serotonin and norepinephrine reuptake inhibitors (SNRIs). For this highly sensitive population, drug treatment requires a delicate balance between clinical efficacy and the risk of rare but serious adverse psychiatric events. Due to the unique metabolic, hepatic, and neurodevelopmental characteristics of adolescents, drugs that are effective in adults may not be effective in children.

Summary of clinical medication guidelines: Among selective serotonin reuptake inhibitors (SSRIs), fluoxetine is the first-line treatment for major depressive disorder (MDD), with a minimum age of 8 years and older. It is also the first-line treatment for obsessive-compulsive disorder (OCD), with a minimum age of 7 years and older. Escitalopram, another drug for treating MDD, is suitable for patients aged 12 years and older. Sertraline can be started for OCD patients aged 6 years and older.

6.1 Efficacy and Network Meta-analysis

The Lancet in 2016 by Cipriani et al. fundamentally and permanently altered the clinical landscape of antidepressant efficacy in adolescents. This comprehensive methodological meta-analysis identified 34 eligible clinical trials and compiled rigorous data from 14 different antidepressant treatments from 5,260 children and adolescents [20]. Cipriani's meta-analysis results were thought-provoking and prompted a paradigm shift in pediatric psychopharmacology, challenging decades of indiscriminate use practices. The analysis showed that only fluoxetine was statistically significantly superior to placebo in the acute treatment of major depressive disorder. The standardized mean difference (SMD) for fluoxetine was -0.51 (95% confidence interval [CrI]: -0.99 to -0.03). In stark contrast, other widely used medications, including citalopram, paroxetine, and tricyclic antidepressants, failed to demonstrate a statistically significant advantage over placebo in the primary efficacy endpoint of adolescent depression.

In addition, the tolerability of various antidepressants varied greatly. Fluoxetine was significantly better tolerable than duloxetine (odds ratio = 0.31, 95% confidence interval: 0.13 to 0.95) and imipramine (odds ratio = 0.23, 95% confidence interval: 0.04 to 0.78). Conversely, patients receiving venlafaxine, imipramine, and duloxetine had a much higher rate of discontinuation due to serious adverse events compared to patients receiving placebo. Crucially, the meta-analysis confirmed a very worrying safety signal for venlafaxine, indicating that venlafaxine was associated with an excessively high risk of inducing suicidal behavior or ideation compared to placebo and ten other active interventions [21]. The final, definitive interpretation of the Cipriani study suggests that fluoxetine is clearly the best, and arguably the only empirically supported, drug option when considering the delicate risk-benefit ratio of acute treatment for childhood MDD.

For anxiety disorders, medication is generally more effective and predictable than for depression. Selective serotonin reuptake inhibitors (SSRIs) are widely considered to be the first-line treatment for childhood anxiety disorders, with higher efficacy and lower discontinuation rates compared to selective serotonin and norepinephrine reuptake inhibitors (SNRIs). However, clinicians must be vigilant because SSRIs are more likely to produce transient behavioral activation — characterized by impulsivity, agitation, and insomnia—in children and adolescents with anxiety disorders compared to SNRIs [16].

Selective serotonin reuptake inhibitors (SSRIs) typically alleviate neuro-vegetative symptoms of depression, such as psychomotor retardation, severe fatigue, and lack of energy, several weeks before they adequately improve mood or eliminate core cognitive despair. This time lag creates an extremely dangerous clinical window during which previously lethargic and sluggish adolescents suddenly gain the physical and executive functions necessary to cope with persistent potential suicidal ideation [22]. Therefore, clinical protocols require extreme caution. The U.S. Food and Drug Administration (FDA) requires that anyone considering the use of antidepressants in children or adolescents must carefully weigh the increased risk of suicidal tendencies against the serious, life-threatening clinical risks of untreated depression. Patients starting medication must be closely monitored by clinicians and caregivers—usually by weekly appointments during the first month of treatment—to monitor for clinical deterioration, sudden suicidal tendencies, severe agitation, or loss of control of abnormal behavior. Retrospective public health analyses have indicated that the initial implementation of "black box warnings" had a chilling effect on prescribing behavior. Worryingly, the sudden decline in SSRI use is contradicted by a temporary surge in adolescent suicide deaths and psychotropic drug poisoning incidents [23]. This epidemiological chain reaction highlights an important clinical reality: while drug-induced suicide risk is real and needs to be monitored, untreated adolescents with major depressive disorder have the highest overall mortality risk.

7. Non-pharmacological Treatment Strategies

Given the limited effectiveness of medication in treating depression, evidence-based psychotherapy is widely recommended as a basic first-line treatment for mild to moderate adolescent anxiety and depression [8].

7.1 Cognitive Behavioral Therapy (CBT)

Cognitive behavioral therapy (CBT) is currently the most rigorously validated and empirically supported psychotherapy approach for internalization problems and mood disorders. CBT was originally proposed by Aaron Beck for the treatment of adult depression, and its theoretical application has been systematically adapted and extended to the fields of childhood anxiety and mood disorders [8]. Cognitive behavioral therapy (CBT) operates based on the neurocognitive premise that psychopathology is maintained by maladaptive schemas, cognitive distortions (such as catastrophic thinking and black-and-white reasoning), and severe behavioral avoidance.

For adolescent depression, extensive meta-analyses (covering more than 4,300 participants) have confirmed that cognitive behavioral therapy (CBT) can significantly reduce depressive symptoms. When early preventative measures are taken for high-risk adolescents, CBT can reduce the risk of subsequent depression by an astonishing 63%. Crucially, CBT has been shown to rapidly reduce suicidal ideation in adolescents with depression, providing a non-pharmacological mechanism to ensure patient safety [8].

For anxiety disorders, standardized CBT interventions, in sequence, focus on psychoeducation, physical management, cognitive restructuring, and exposure therapy. Adolescents are taught to recognize the physiological signs of panic and to use techniques such as diaphragmatic breathing and progressive muscle relaxation to reduce autonomic arousal.

Exposure therapy in cognitive behavioral therapy (CBT) is crucial and has a neurobiological basis. It directly targets the dysfunctional prefrontal-amygdala circuit. CBT activates the medial prefrontal cortex by forcing adolescents to be exposed to fear stimuli in a progressive, systematic and repetitive manner without taking avoidance actions. This sustained cortical activation ultimately helps with fear extinction learning, inhibits the overactive amygdala, and effectively remodels the neural pathways that maintain anxiety disorders [11].

7.2 Interpersonal Psychotherapy for Adolescents (IPT-A)

Interpersonal Psychotherapy for Adolescents (IPT-A) is another well-established, time-limited, and structured intervention that has shown significant efficacy in treating childhood depression. The theoretical framework of IPT-A is that, regardless of the biological, genetic, or neurochemical origin of a depressive episode, its occurrence, maintenance, and eventual resolution are inextricably linked to the adolescent's interpersonal relationships and social crises.

This therapy systematically targets four specific areas of interpersonal relationship problems:

1) Grief and loss: Dealing with the emotions of losing a loved one or the breakdown of an important relationship.

2) Interpersonal role conflict: dealing with serious, long-term conflicts with parents, peers, or authority figures.

3) Role transition: coping with the immense stress of life changes, such as transferring to a new school, parental divorce, or puberty physical changes.

4) Interpersonal communication deficits: Addressing long-term social isolation and developing the basic social skills needed to build and maintain peer networks.

Clinical trials have clearly demonstrated that a 12-week course of IPT-A can significantly reduce depressive symptoms, as measured by objective tools such as the Hamilton Depression Rating Scale, and is superior to supportive counseling or "standard treatment" in school clinics [14].

8. Conclusion

Adolescent anxiety and depression are not merely psychological pains of puberty, but a systemic pathological disaster caused by the combined effects of neurodevelopmental delay, polygenic epigenetic expression, systemic microecological remission, and the stress of a toxic environment during childhood. The 2024 Lancet Psychiatry Committee on Mental Health issued the most serious warning: Over the past 20 years, the mental health of emerging-onset adults worldwide has suffered from irrational and persistent distress, and mental illness has become the single largest threat to promoting a healthy generation, well-being, and productivity [24].

Therefore, future social governance and medical practice urgently require a radical transformation of public mental health management policies: not only abandoning the inefficient clinical model of intervening only in the terminal stages of psychological illnesses, but also establishing a multi-tiered, collaborative prevention system encompassing school education, primary healthcare, and specialized psychiatry. Furthermore, it necessitates increased resource allocation and financial support for adolescent-specific mental health treatment institutions, and lowering the barriers to accessing evidence-based psychological interventions and safe medication prescriptions. Only through systematic, interdisciplinary, and cross-sectoral collaboration can we build an unbreakable psychological resilience barrier for the next generation of adolescents amidst the multifaceted and multimodal pressures they face.

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