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Effect of Exogenous Melatonin to treat on Anxiety Disorders in Girls During Puberty

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Abstract: ***Anxiety disorders are increasingly prevalent among adolescents, particularly among early to mid-pubertal girls, who face heightened biological and psychosocial vulnerability during pubertal transition. Almost one in three (31.9%) adolescents aged 13–18 suffer from anxiety disorders, which include generalised anxiety disorder, panic disorders, specific phobias, agoraphobia, obsessive-compulsive disorder, post-traumatic stress disorder, and separation anxiety disorder (Anxiety Disorders | Knowledge Action Portal on NCDs, 2025) Anxiety disorders not only hamper the daily schedule of the adolescent, but also undermine their academic performance, social interactions and relationship quality. Furthermore, it causes emotional distress as well as takes a toll on physical health, causing symptoms such as fatigue, fast heartbeat, trembling, headaches, sleep disturbances, and shortness of breath, among others. Melatonin, a neurohormone produced by the pineal gland, is widely recognised for its role in sleep regulation from an early stage; however, recent evidence suggests its potential anxiolytic effects. A study conducted in Iran in 2013 demonstrated that sublingual melatonin given before cataract surgery under topical anesthesia effectively reduced patient anxiety and improved operating conditions. A 3 mg dose of sublingual melatonin was given 60 minutes before surgery, which was effective for sedation, offering a timely onset and sustained peak levels during the procedure. This dose falls within the 0.3–10 mg range, known to produce similar hypnotic effects, supporting its suitability for premedication (Khezri & Merate, 2013). A second study conducted in China in 2024 proved that melatonin reduced depression like behaviour caused by chronic stress in rats. It was found that melatonin alleviated the CRS-induced hippocampal microglial pyroptosis and depression-like behaviour in rats by inhibiting the Cathepsin B/NLRP3 signalling pathway (Gao et al., 2024). However, the gender and age-specific efficacy of melatonin in treating anxiety remains underexplored, especially in adolescent girls undergoing puberty. A lack of targeted research and clinical guidelines for this subgroup limits the potential therapeutic use of melatonin in anxiety management. Given its accessibility and affordability, melatonin presents itself as a compelling alternative for the treatment of anxiety disorders, especially in low- and middle-income countries. The current systematic review aims to compile the findings from the plethora of available studies that report the exogenous usage of melatonin drugs to treat anxiety, as well as the pathways in which the drug could potentially help to counter anxiety. This can have significant implications for clinical practice and treatment, including the management of anxiety in adolescent girls.***

Keywords: anxiety disorders, melatonin, puberty, adolescent girls

1. Introduction

Anxiety disorders are a group of mental health disorders that can have a prominent impact on a patient's physical health, causing psychophysiological symptoms such as fatigue, fast heartbeat, trembling, headaches, sleep disturbances, and shortness of breath, among others. Anxiety disorders are the world's most common mental disorders, affecting 301 million people in 2019 (Anxiety Disorders | Knowledge Action Portal on NCDs, 2025). Normal anxiety, on the other hand, is an appropriate reaction to stress, which is considered healthy. In contrast, in anxiety disorders, the person tends to experience excessive fear or concern that is not in line with the actual threat level. In contrast to typical anxiety, which diminishes once the stressor is eliminated, anxiety disorders continue for six months or longer and hinder daily functioning (What Are Anxiety Disorders? 2025). A comparison of normal anxiety to that of anxiety disorders has been outlined in Table 1. Anxiety disorders usually do not have a singular cause but are the cumulative outcome of a variety of reasons. These factors can be genetic, environmental, and psychological. A review concluded that the most common reasons for anxiety are family history of Major Depressive Disorder, disturbed family environment, childhood sexual abuse, low self-esteem, and lower educational attainment as major contributing factors (Blanco et al., 2014). Anxiety disorders are a group of mental disorders characterized by significant and uncontrollable feelings of anxiety and fear such that a person's social, occupational, and personal functions are significantly impaired (Anxiety Disorders, 2025). That statement indicates that anxiety disorder is not merely a singular condition; rather, it comprises a collection of interconnected disorders. Each of these disorders includes experiences of anxiety and fear, but they may present differently and impact individuals in various ways. Some common anxiety disorders include Generalised Anxiety Disorder, Panic Disorder, Social Anxiety Disorder, specific Phobias, Agoraphobia, Separation Anxiety Disorder, Selective Mutism, Post-Traumatic Stress Disorder, and Obsessive-Compulsive Disorder. Adolescents represent a particularly vulnerable population when it comes to anxiety disorders. This crucial stage involves significant mental, emotional, and physical changes in life, making them more susceptible to anxiety. Approximately 31.9% of adolescents aged 13–18 suffer from anxiety disorders (Any Anxiety Disorder, 2017) . Most of the data on the prevalence of adolescent mental health disorders come from one large, nationally representative epidemiological study, the National Comorbidity Survey Replication Adolescent Supplement, which surveyed 10,148 adolescents between the ages of 13 to 17 years. The median age of onset of anxiety disorders was 6 years compared to 11 years for behaviour disorders, 13 years for mood disorders, and 15 years for substance use disorders. Rates of anxiety disorders showed a female predominance, with higher rates of treatment in females as well (Merikangas et al., 2009). This disparity highlights the importance of providing targeted mental health resources and support specifically for adolescent girls, who face unique social, hormonal, and developmental challenges that can increase anxiety. Addressing these needs at an early stage is essential to prevent the progression into chronic mental health disorders, thereby safeguarding adolescents' overall development and mitigating the adverse consequences they may already be experiencing.

Table 1: Difference between Normal Anxiety and Anxiety Disorders

Feature	Normal Anxiety	Anxiety Disorder	
Trigger	Response to an immediate stress, stressor is over, and anxiety goes away	Anxiety is out of proportion, often with no particular reason for it	(Herndon, 2021)
Duration	Temporary; concerns go away over time without much or any intervention	Persistent, people with an anxiety disorder experience anxiety excessively or persistently for approximately 6 months, or even during shorter time periods in children	(American Psychiatric Association, 2013) (Akers, 2024)
Impact on Daily Life	Symptoms of normal anxiety do not negatively interfere with daily functioning.	Anxiety disorders interfere with daily activities and can impair a person's family, social and school or working life	(Marques, 2018)

2. Methodology

To gather relevant research on the relationship between melatonin and anxiety disorders in adolescents, a focused literature search using Google Scholar and PubMed was conducted. The goal was to find studies published between 2015 and 2025 that explore how melatonin, whether taken as a supplement or discussed in terms of its natural biological role, might affect anxiety levels in young people, particularly during puberty or in those experiencing trait anxiety. The study used Google Scholar first to get a broad overview of the topic and observed how it has been discussed across different fields like psychology, medicine, and neuroscience. Then, to dive deeper into medical and biological research, PubMed was used. Combination of keywords were utilized to shortlist all possible relevant papers: (a) Melatonin-related: "melatonin", "melatonin supplementation"; (b) Anxiety-related: "anxiety", "trait anxiety", "anxiety disorder"; (c) Adolescent-related: "teenagers", "young adults", "puberty", "adolescents". Moreover, during the search on PubMed, MeSH (Medical Subject Headings) terms were used to find studies that were more medically focused and precise with special emphasis on (a) research involving adolescent humans (typically aged 10–19) and (b) articles that clearly discussed melatonin's role in anxiety or emotional regulation during puberty. Papers in languages other than English were excluded from the study.

Conventional Treatments for Anxiety Disorders

With anxiety affecting such a large population, especially girls, knowing how to control it is as important as diagnosing it, especially to ensure healthy emotional development during these critical years. Over the past few decades, several evidence-based approaches have emerged to manage anxiety. There is no single, universally effective method for managing anxiety; rather, treatment approaches are often tailored to the individual's specific symptoms, type of anxiety disorder, developmental stage, and personal preferences. The main strategies to treat anxiety disorders typically involve either psychotherapy or medication. It can also be taken as a combination of both. (Anxiety Disorders - Diagnosis and Treatment - Mayo Clinic, 2025) Psychotherapy or talk therapy is one of the most common techniques to cure anxiety disorders. This therapy involves talking to a licensed medical professional, who can be either a psychologist or a psychiatrist. The second method used to treat anxiety disorders is medication. They are usually referred to as antidepressants, but they work on the same neurotransmitters as melatonin. Popular medications for anxiety disorders include Sertraline (Zoloft), Escitalopram (Lexapro), Paroxetine (Paxil), Citalopram (Celexa), Fluoxetine (Prozac) and Fluvoxamine (Luvox) – the approximate cost for which, in Indian and USA markets have been summarized in Table 2 (Bhatt, 2024). While these treatment methods have proven effective for many individuals, it is important to acknowledge that both psychotherapy and medication come with their own sets of limitations and potential drawbacks. Research conducted on 5562 individuals concluded that many of them reported high rates of negative effects (though not always linked to treatment). This was especially true of those with the experiences of unpleasant memories (57.8%), unpleasant feelings (30.3%), and a lack of understanding of the treatment/therapist (19.3/18.4%). Indicators of malpractice were less common, with the exception that 16.8% felt violated by statements of their therapist (Strauss et al., 2021) Though therapists prescribe antidepressants, these come with their own side effects, such as nausea, headaches, dizziness, weight changes, and increased anxiety during early treatment. A peer-reviewed paper notes that all anti-anxiety drugs have the potential to impair higher brain functions, with oversedation being the most common adverse effect - a fact especially concerning in young children and the elderly. It also highlights that anti-anxiety medications are grossly overprescribed, raising further concerns about their suitability in vulnerable populations (Edwards, 1981). Hence, these types of drugs are particularly risky for adolescents, and other lines of treatment should be considered. Given the limitations and the potential side effects of psychotherapy and medications, melatonin is an emerging treatment option for anxiety, particularly in younger populations. As a naturally occurring hormone involved in sleep regulation, it is increasingly being explored for its anxiolytic effects and is being considered as a safer option with minimal side effects. Melatonin, a neurohormone produced by the pineal gland, is widely recognised for its role in sleep regulation from an early stage; however, recent evidence suggests its potential anxiolytic effects. A study conducted in Iran in 2013 demonstrated that sublingual melatonin given before cataract surgery under topical anaesthesia effectively reduced patient anxiety and improved operating conditions. A 3 mg dose of sublingual melatonin was given 60 minutes before surgery, which was effective for sedation, offering a timely onset and sustained peak levels during the procedure. This dose falls within the 0.3–10 mg range, known to produce similar hypnotic effects, supporting its suitability for premedication (Marzieh Beigom Khezri & Hamid Merate, 2013). A second study conducted in China in 2024 proved that melatonin reduced depression-like behaviour caused by chronic stress in rats. It was found that melatonin alleviated the CRS-induced hippocampal microglial pyroptosis and depression-like behaviour in rats by inhibiting the Cathepsin B/NLRP3 signalling pathway (Gao et al., 2024). Given melatonin's established role in regulating the sleep–wake cycle and circadian rhythms, these being processes that are frequently

disrupted in individuals with anxiety, it can be further explored as a therapeutic agent for anxiety relief. Sleep and circadian rhythm disruption (SCRD) is often seen in conditions like schizophrenia, bipolar disorder, and depression. Research suggests these disruptions aren't just caused by medication or daily routine changes—they likely stem from shared biological pathways. Some of the same genes that regulate our body clock have also been linked to mental illness, and vice versa. This is where melatonin could help as a medication. Since it already plays a vital role in regulating the circadian rhythm and the body's internal biological clock, it could be a promising medication for several mental health disorders (Jagannath et al., 2013).

Furthermore, it has already shown anxiolytic effects in clinical studies. In a study conducted in Denmark, researchers explored whether melatonin could help reduce anxiety in adults before and after surgery. They reviewed 12 clinical trials that included a total of 774 patients. These patients were given melatonin, usually 3 to 6 mg, shortly before their operations. The team then compared how anxious these patients felt with those who received either a placebo, a common sedative like midazolam, or another treatment. The results stated that "Melatonin may be equally as effective as standard treatment with midazolam in reducing preoperative anxiety (measured 50 to 100 minutes after administration)" (Madsen et al., 2020). According to Sleep and Sleep Disorders, the mechanisms by which melatonin induces sleep differ based on dosage. Another study conducted in 2010 explored whether Neu-P11, a synthetic melatonin receptor agonist, could produce antidepressant and anxiolytic effects in an established rodent model. It concluded that Neu-P11 showed consistent antidepressant and anxiolytic effects in rodents, which were better than those of natural melatonin (Tian et al., 2010)

Table 2: Cost Comparison of Medication for treating Anxiety Disorders in USA & India

Treatment	Average Monthly Cost (USD) per unit	Average Monthly cost [INR] per unit	Dependency Risk	Prescription Required
Melatonin	$0.031 – $0.19 (Spring Valley, Walmart, USA; Walmart, n.d.) $0.09 (Basic Vitamins; Walmart, n.d.)	₹5 – ₹20 (avg) Up to ₹40–₹50 (premium)	Low	Often No
Benzodiazepines			High	Yes
Lorazepam	Lorazepam: $0.012–$0.464 per tablet (GoodRx, n.d.)	Lorazepam: ₹1.50–₹4.50 per tablet (1mg, n.d.)		
Clonazepam	Clonazepam: $0.397–$0.73 per tablet (Drugs.com, n.d.)	Clonazepam: ₹3–₹12 per tablet (1mg, n.d.)		
Estazolam	Estazolam: ≈$0.73 per tablet (Drugs.com, n.d.)	Estazolam: ₹5.86 per tablet (1mg, n.d.)		
SSRIs (e.g., Sertraline)	$20–$100+ (Drugs.com, n.d.)	₹6 – ₹20 (1mg, n.d.)	Moderate	Yes
Cognitive Behavioural Therapy (CBT)	Cost per session: $100 to $250 (out-of-pocket) (Psychological Healing, n.d.)	Cost per session: Rs.1500- Rs 3000 (London Speech and Psychotherapy, 2022)	None	Yes

Melatonin can be used as a more preferred form of medication over traditional anxiolytic treatments due to its several economic advantages, especially in developing and underdeveloped countries. In many countries, it is easily available as an over-the-counter medicine, which reduces prescription cost, has a low cost of production, fewer side effects, and, most importantly, is widely accessible; thus, it can be especially useful in populations where access to therapy is limited and can be used as an alternative to more expensive and less accessible anxiolytic and antidepressant medications.

Mechanism of Melatonin Action

Melatonin aids in reducing anxiety through several interconnected pathways, as summarized in Figure 1. It suppresses the overactivation of the sympathetic nervous system or the body's "fight or flight response" by lowering the body's stress markers, such as noradrenaline, high blood pressure, and faster heart rate, which are often key markers of stress. It is aided by enhanced GABAergic signalling and nitric oxide-mediated inhibition. Furthermore, melatonin suppresses the stress hormone or the hypothalamic–pituitary–adrenal (HPA) axis, reducing cortisol release, which helps to calm an overactive nervous system. It even interferes with the RAAS pathway by blocking hormones like angiotensin II and aldosterone, both of which are related to neuroinflammation and anxiety symptoms. Additionally, since melatonin is a potent antioxidant, it protects the brain by neutralising harmful reactive oxygen and nitrogen species, while also enhancing the activity of protective enzymes like superoxide dismutase and catalase. Thereby, it protects the neurons from oxidative stress, a contributor often overlooked in anxiety pathology.

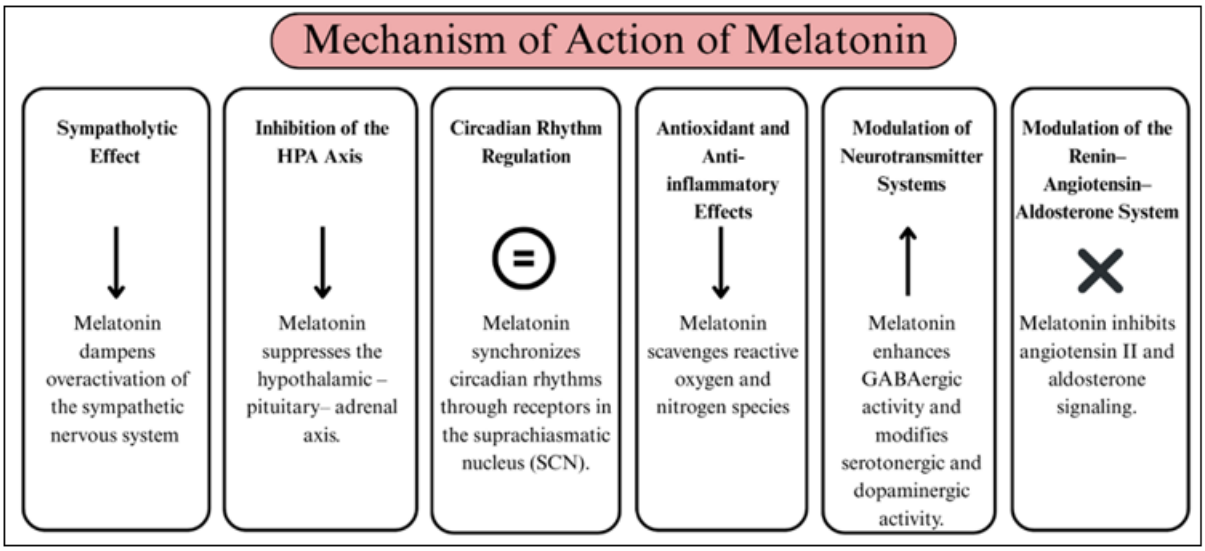

Figure 1: Melatonin reducing Anxiety via different physiological pathways

Melatonin reportedly also influences several major neurotransmitter systems involved in emotional regulation. It enhances GABAergic activity, which strengthens inhibitory signals in the brain and promotes a calming effect. It also modulates serotonin receptors, particularly 5-HT1A and 5-HT2C, helping to stabilise mood and emotional responses.

Furthermore, melatonin reduces excessive dopaminergic activity, which has been associated with heightened anxiety. Melatonin's primary functions, which are to regulate the sleep-wake cycle, also help to reduce anxiety by improving sleep quality and mood stability, since a disturbed sleep-wake cycle worsens anxiety. It synchronises the body's internal clock through its action on the suprachiasmatic nucleus. This neuroprotective effect of melatonin helps restore the balance between excitatory and inhibitory signals in brain areas involved in emotion, such as the amygdala. Interestingly, melatonin doesn't rely only on specific receptors to work; it also acts independently to neutralise harmful reactive molecules directly. Research also highlights the importance of timing: melatonin is most effective when it's present during or shortly after the brain is exposed to excitatory stress, like overstimulation by glutamate receptor agonists. (Southgate et al., 2008)

Anxiety in the Indian Context

To address the lack of national data on adolescent anxiety in India, researchers conducted a systematic review and meta-analysis of 13 Indian studies focused on this age group. The findings revealed that studies with a higher risk of bias reported an average anxiety prevalence of 41%, while more reliable, low-bias studies still showed a considerable prevalence of 29%. Importantly, statistical testing indicated no signs of publication bias, suggesting that the results are robust and not distorted by selective reporting. These findings point to a substantial and under-recognised mental health burden among Indian adolescents, with nearly one in three potentially experiencing an anxiety disorder. There is an urgent need for early intervention strategies, school-based mental health programs, and culturally appropriate support systems to address the growing psychological challenges faced by India's youth. (Pal et al., 2022)

The 2015 study by Singh et al., published in the Indian Journal of Psychiatry, examined anxiety, stress, depression, and psychosocial functioning among 1,812 Indian adolescents aged 12 to 19 years. Using validated tools such as the DASS-21 and the Strengths and Difficulties Questionnaire (SDQ) in both English and Hindi, the researchers confirmed that these scales were effective in assessing mental health in this population. The study found that older adolescents experienced significantly higher levels of psychological difficulties, including anxiety and stress, compared to younger peers. School dropouts were particularly vulnerable, showing elevated levels of anxiety, depression, and stress. Gender differences were also observed, with girls reporting higher anxiety and stress, as well as greater prosocial behaviour. Additionally, rural and urban adolescents showed differing psychosocial profiles. Importantly, negative family relationships and low self-concept were strongly linked to higher emotional distress. Overall, the study underscores the complex interplay of age, gender, education, and family environment in shaping the mental health of Indian adolescents, highlighting the need for early, targeted interventions. (Singh et al., 2015)

Adolescents comprise about 21% of India's population. This community-based cross-sectional study surveyed 300 adolescents aged 10–19 years in an urban area of Delhi to estimate the prevalence and types of anxiety disorders using the SCARED tool, which consists of 41 questions, and a score >21 indicates the presence of an anxiety disorder. The findings revealed that 35.3% of adolescents had an anxiety disorder, with social anxiety (14%) being the most common, followed by separation anxiety (13.7%), generalised anxiety (12.3%), panic disorder (11.7%), and significant school avoidance (9.3%). Anxiety was more prevalent among females and older adolescents (15–19 years). The study also found that adolescents from nuclear families, those reporting adverse life events, and those with a family history of substance use were more likely to show signs of anxiety. Notably, 7.7% of the adolescents reported their own history of substance use, and nearly one-fourth were dissatisfied with their body image, particularly older males. (None Febida BPK et al., 2025)

Thus, the findings highlight that India is no exception to the growing global concern around adolescent mental health

since anxiety disorders are affecting a significant portion of the country's youth.

Impact of Incorporation of Melatonin in Treating Anxiety Disorders

The potential role of exogenous melatonin in alleviating anxiety is increasingly being explored at the intersection of sleep medicine and psychiatry, as evidenced by the summary of studies demonstrated in Table 3. While traditionally categorised as a circadian rhythm regulator, emerging findings suggest melatonin may exert indirect anxiolytic effects by stabilising biological rhythms and modulating stress-related neuroendocrine systems (Leone et al., 2023; Hussein et al., 2024). Rather than functioning as a classical anxiolytic, melatonin appears to operate more subtly, mitigating vulnerability to anxiety through improved sleep and physiological regulation.

Circadian misalignment and insomnia are consistently linked with heightened emotional reactivity and poorer stress regulation. Interventions that restore consolidated sleep appear to strengthen amygdala–prefrontal connectivity and normalise activity within the hypothalamic–pituitary–adrenal (HPA) axis (Wei et al., 2020; Barlow et al., 2021). Efficacy of Melatonin for Sleep Disturbance in Children with Persistent Post-Concussion Symptoms: Secondary Analysis of a Randomized Controlled Trial. Journal of Neurotrauma, 38(8), 950–959. https://doi.org/10.1089/neu.2020.7154

Preclinical evidence adds further plausibility, with murine studies demonstrating melatonin's role in dampening cortisol feedback and oxidative stress responses under conditions of chronic stress (Adejoke Yetunde Onaolapo et al., 2016). Nevertheless, the limitations are notable. In acute procedural anxiety, melatonin has repeatedly been shown to be less effective than benzodiazepines, likely reflecting its slower onset of action and weaker direct influence on GABAergic transmission (Bolt et al., 2023; Mellor et al., 2022). Its role, therefore, seems less aligned with crisis intervention and more attuned to longer-term adjunctive use, where improving sleep–wake regulation may secondarily reduce chronic anxiety symptoms. The appeal of melatonin also lies in its safety profile. It has been widely prescribed in paediatric populations, often ahead of robust longitudinal data (Paton et al., 2024); Händel et al. (2023), While most trials report reassuring short-term tolerability, concerns persist regarding puberty, hormonal regulation, and long-term neurodevelopment (Moon & Lee, 2022). Without systematic follow-up, clinical enthusiasm risks outpacing the evidence base.

Taken together, melatonin's therapeutic potential should be understood as supportive rather than curative. It's most likely utility resides in chronic contexts—such as insomnia-related anxiety or trauma-associated circadian disruption—where stabilisation of arousal systems can create conditions more conducive to recovery (Rolling et al., 2025)). Rather than supplanting psychotherapies or first-line pharmacotherapies, melatonin might serve as a physiological scaffold upon which other interventions can build. Future progress depends on trials that move beyond sleep endpoints to directly measure anxiety trajectories, incorporating validated scales and long-term monitoring of developmental and endocrine outcomes. Until such evidence is available, melatonin should be positioned as an adjunctive option: safer than traditional sedatives, biologically plausible, but most effective when integrated into a broader therapeutic strategy.

For many adolescent girls, anxiety translates as sleep disturbances, restlessness, or difficulty concentrating, symptoms that can negatively impact academic performance, social confidence, and self-esteem. Conventional treatments such as SSRIs or benzodiazepines are effective in many cases, but they come with side effects that may be especially concerning for young populations, including oversedation, dependency risks, or cognitive impairment. Cognitive-behavioural therapy (CBT), though effective, remains expensive and inaccessible for many adolescents in low- and middle-income countries such as India. Melatonin counters all these challenges since it is affordable, widely available, and associated with relatively few side effects. The mechanisms by which melatonin may reduce anxiety are biologically compelling. Its ability to dampen overactivation of the HPA axis, reduce cortisol release, and enhance GABAergic signalling suggests that melatonin targets pathways central to both stress and emotional regulation. Its antioxidant and neuroprotective properties add a layer of benefit, particularly in protecting the adolescent brain during a critical stage of development. Yet, while adult studies and animal models provide encouraging insights, the absence of robust, large-scale clinical trials specifically focusing on adolescent girls is a glaring limitation. The hormonal fluctuations of puberty, particularly shifts in oestrogen and progesterone, may interact with melatonin in ways that are not particularly understood. Adolescent girls also face unique sociocultural stressors during adolescence, including pressures related to body image, academic achievement, and social expectations, all of which can amplify anxiety. Without direct studies in this population, any conclusions about melatonin's efficacy remain tentative. Another dimension worth considering is accessibility. In India and other low- to middle-income settings, where up to one-third of adolescents may experience anxiety symptoms, melatonin could represent a scalable intervention. Unlike psychotherapy, which requires trained professionals, or SSRIs, which require prescriptions and monitoring, melatonin is inexpensive, over the counter in many countries, and culturally more acceptable as a natural option. However, this very accessibility raises concerns about unsupervised use, inappropriate dosing, and the potential masking of deeper psychological issues that still require therapy or family-level intervention.

Table 3: Summary of studies that explored Melatonin as a possible alternative to conventional treatments for Anxiety Disorders

Study (Year)	Design	Population	Sample Size	Main Findings	Treatment Method	Gaps/ Limitations
Leone et al. (2023)	Retrospective cohort	Adolescents (6–18y), 87%	n=25,575	Emergency visits for self-harm decreased by ~54% within 12 months of melatonin initiation, particularly in girls. The	Prescription-grade melatonin, titrated to sleep	Lack of randomization; no standardized dosing

		psychiatric disorders		decline was not offset by an increase in accidental injuries. No increase in unintentional injuries, suggesting emotional benefits beyond just sedation. Hypothesized to enhance prefrontal cortex control over limbic system reactivity (reducing impulsive self-harm).	latency issues, with an average treatment duration of 6.4 months.	protocol; unclear applicability to OTC melatonin.
Hussein et al. (2024)	Double-blind RCT	Children (4–14y) undergoing cardiac catheterization, no psychiatric comorbidities	n=80	Significantly reduced anxiety and distress during medical procedures compared to placebo. Kids were calmer, but the effects were short-term (only tested for procedures). Acute GABA-A receptor modulation (similar to benzodiazepines but non-addictive). Cortisol suppression during stress was observed in the subset bloodwork.	Single dose (0.5 mg/kg, max 20 mg) administered 30 minutes pre-procedure.	Only tests acute procedural anxiety; no data on chronic anxiety disorders.
(Wei et al., 2020)	Pooled 7 RCTs	Children (mean 9–10y) with primary/secondary insomnia	n=387	37-minute faster sleep onset, 23-minute longer sleep duration with few adverse events. Sleep improved, but anxiety wasn't directly measured. Largest effects in ASD/ADHD subgroups (delayed sleep phase common). Sleep extension (23 min) correlated with next-day behaviour scores (r = 0.42	0.1–0.3 mg/kg (capped at ~5 mg) given 30–60 minutes before bedtime for 2–8 weeks.	Limited adolescent data (>12y); no anxiety-specific measures; short-term safety only.
(Bolt et al., 2023)	Non-inferiority RCT (stopped early)	Children (5–14y) with preoperative anxiety	n=110	Melatonin is inferior to midazolam for anxiety reduction (13-point difference on mYPAS scale). Confirms melatonin isn't a benzodiazepine alternative for acute anxiety. Onset too slow (peak plasma: 60 min vs. midazolam's 20 min).	Single dose (0.5 mg/kg, max 20 mg) pre-surgery.	Underpowered due to early termination; only applicable to acute settings.
(Mellor et al., 2022)	Cochrane review (12 RCTs)	Paediatric surgical patients (3–14y)	Variable (40–110/study)	Inconsistent anxiolytic effects; evidence quality low-to-moderate. Melatonin improved parental separation anxiety more consistently than child anxiety.	0.25–0.5 mg/kg given 30–60 minutes pre-surgery.	Heterogeneous dosing; poor blinding in some trials.
(Adejoke Yetunde Onaolapo et al., 2016)	Animal experiment	Adolescent mice (~4–5 weeks)	~60 total	Reduced anxiety-like behaviors and corticosterone levels. It reversed stress-induced dendritic atrophy in the prefrontal cortex (histology data	Daily oral melatonin (5–15 mg/kg) for 21 days. BDNF Rescue: Melatonin restored prefrontal BDNF levels to 85% of non-stressed controls (ELISA data).	High doses not comparable to human use; animal model limitations.
(Barlow et al., 2021)	Triple-arm RCT	Adolescents (8–18y) post-concussion	n=72	Improved sleep duration (~55 minutes) and mood (anxiety was not the primary endpoint). Reduced depressive symptoms and improved sleep continuity suggest potential cross-benefits.	Sublingual melatonin (3 mg/10 mg) nightly for 28 days.	Targeted sleep, not general anxiety symptoms. b) Short treatment period limits generalizability to chronic issues. c) No anxiety-specific scales or biological stress markers included.
(Nasini et al., 2023)	Acute behavioral/ EEG	Adolescent vs. adult mice	~40–50	Age-dependent effects: sociability (adolescents) vs. sedation (adults).	Single IP dose (20 mg/kg).	Not a clinically relevant administration route.
(Rolling et al., 2025)	Planned RCT	Youth (2–17y) with PTSD	~120 (planned)	Protocol targets PTSD-related insomnia/anxiety (results pending).	Extended-release melatonin nightly for 28 days. Circadian Biomarkers: Tracking dim-light melatonin onset (DLMO) pre/post-	Study ongoing; no published results.

					treatment. Measuring nocturnal HRV as a PTSD hyperarousal biomarker Using prolonged release to mimic the endogenous melatonin curve (avoiding 1.5h post-dose cortisol dip).	
Händel et al. (2023)	Systematic review and GRADE assessment	Children and adolescents with sleep problems, including neurodevelopmental disorders	≈1,350 across RCTs	Melatonin showed no serious adverse effects. Long-term use appeared safe, with uncertain effects on puberty.	Oral melatonin Duration: weeks to several years in long-term cohorts.	Heterogeneous dosing, focus on special populations, and limited long-term (>5 years) data.
(Paton et al., 2024)	Retrospective audit	Youth (≤18y), 74% neurodivergent	n=4,151	Poor monitoring: only 36% had efficacy reviews post-prescription.	Mostly immediate-release melatonin.	Lack of structured follow-up.
(Moon & Lee, 2022)	Systematic review	Pediatric insomnia/ADHD/ASD	Hundreds –1,000+	Mild side effects; no endogenous suppression.	2–10 mg nightly.	Puberty and growth impacts are unstudied.

3. Conclusion

Melatonin has the potential to become a valuable, low-risk adjunctive treatment for anxiety in adolescent girls during puberty. It offers biological plausibility, economic feasibility, and practical accessibility. However, without rigorous, targeted research, its promise remains theoretical. Future clinical trials should prioritise adolescent girls as a study group, investigate optimal dosing and timing during puberty, and examine long-term effects on both mental health and development. This review explored whether exogenous melatonin could play a meaningful role in reducing anxiety among adolescent girls during puberty, a period marked by both biological changes and intense psychosocial pressures. The evidence gathered suggests that melatonin may indeed hold promise, but it also reveals significant gaps that highlight the urgent need for age- and gender-specific research.

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