International Journal of Biochemistry Research & Review

29(6): 52-60, 2020; Article no.IJBCRR.57506
ISSN: 2231-086X, NLM ID: 101654445

Serum Melatonin with Respect to Mental Health (Anxiety & Depression) Status of First Year M.B.B.S Students

Vinita H. Belsare[1*], Arun Tadas[1], Sanjay Agrawal[2] and Hrishikesh Belsare[3]

[1]Deptarment of biochemistry, Indira Gandhi Government Medical college, Nagpur.
[2]Department of Community Medicine, Indira Gandhi Government Medical college, Nagpur.
[3]Department of Pediatrician, Director Belsare children Hospital, Nagpur.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/IJBCRR/2020/v29i630198
Editor(s):
(1) Dr. K. V. Ramanath, Dayanand Sagar University (DSU), India.
Reviewers:
(1) Hanan Farouk Aly Abduallah, National Research Centre, Egypt.
(2) Andiara Souza, Universidade Federal de São Carlos/São Paulo, Brazil.
(3) Karolina Szewczyk-Golec, Nicolaus Copernicus University, Poland.
Complete Peer review History: http://www.sdiarticle4.com/review-history/57506

Original Research Article

Received 09 April 2020
Accepted 14 June 2020
Published 01 July 2020

ABSTRACT

Introduction: Melatonin is a pineal hormone secreted in circadian manner, with a peak during evening and night. Night-time light exposure is a powerful suppressor of nocturnal melatonin secretion. Dopamine and serotonin have complex relationship in melatonin synthesis and secretion. Reduced levels of melatonin have been associated with severe depression. Melatonin exhibits GABA-like effects may be responsible to reduce anxiety.
Objectives: To determine the Serum Melatonin levels with respect to bedtime and its correlation with the severity of anxiety and depression. Also, to find the difference in anxiety score, depression score and serum melatonin level with respect to gender.
Methods: A cross sectional study was done amongst first year medical students, and anxiety and depression score was calculated using Hamilton's anxiety and depression scale. Estimation of Serum Melatonin was done on the fasting morning blood samples.
Results and Conclusion: The present study shows that there is no significant difference in melatonin secretion in the students with late bedtime. With the increasing severity of the anxiety the serum melatonin was found to be lower, but the difference was not statistically significant. Similar

**Corresponding author: E-mail: vinitarjunamrut@gmail.com;*

results were observed with depression. The results shows non-significant higher anxiety and depression scores in females as compared to males. The study results also shows the significant high levels of melatonin in males as compared to females. Low melatonin levels in females may be attributed to high anxiety and depression in females.

Keywords: Melatonin; sleep; anxiety; depression.

1. INTRODUCTION

Melatonin, the pineal hormone, is a peptide hormone secreted by the pineal gland, its chemical name is N-acetylmethoxytrypamine. It is secreted in a circadian manner, with a peak during the evening and night. Melatonin receptors belong to the class of G-protein-coupled receptors named MT1 and MT2[1] and are primarily expressed in the Central nervous system (CNS); however, they are also widely distributed in other body tissues, together and separately. Within the CNS, the MT1 receptor is prominently expressed in the Suprachiasmatic Nucleus (SCN), the hippocampus, the retina, the caudate, putamen, the nucleus accumbens, the substantianigra and the ventrotegmental area [1,2]. Notably, most of these areas belong to the central dopaminergic pathways, suggesting a tight correlation between the melatonergic and monoaminergic systems, at least the dopaminergic one.

The hypothalamic SCN and the hippocampus are two major sites of melatonin action in the CNS. The SCN activity is inhibited by melatonin via MT1 receptors [3], mostly during the daytime, when the SCN neuronal activity is higher. The main role of the pineal gland is to produce melatonin in response to the absence of light stimuli, which may, in turn, activate a glutamate-mediated response from retinal receptors to SCN gamma aminobutyric acid (GABA)ergic neurons, thereby generating an environment-to-endocrine input translation that is at the basis of circadian rhythms in humans [4]. Located in the middle of the brain, although externally to the blood- brain barrier, the pineal gland represents a powerful triage organ, where neurotransmission signals from the SCN are converted to endocrine secretion, which, in turn, may regulate other monoaminergic neurotransmitter systems, such as dopamine, norepinephrine and serotonin. Melatonin secretion is obviously tightly dependent on the availability of serotonin in pinealocytes. Since serotonin is the precursor of melatonin, this neurotransmitter is, indeed, the principal actor of the light/dark circadian regulation of melatonin secretion [5]. Dopamine, indeed, is present in sympathetic nerves projecting to the pineal gland, not only as a precursor of norepinephrine, but also as a neurotransmitter, which has been demonstrated to have a crucial role in melatonin secretion control. Therefore, dopamine seems to exert a complex modulatory control on melatonin synthesis, highly dependent on light/dark cycles. Recent evidence demonstrated an entangled mechanism by which dopamine may regulate norepinephrine-dependent melatonin secretion. The complex relationships between the endogenous circadian pacemaker and the development of depressive symptoms are far from being elucidated [6]. The worsening of diurnal mood variation (DMV) with the early morning is a classic symptom of the melancholic features of major depressive disorder (MDD) and is one of the time-linked symptoms that has promoted speculation about the role of the circadian system in its pathogenesis [7]. MDD seems to be related to a disruption in the central circadian clock function and not to an alteration in a specific rhythm [6].

In addition, the type of rhythm abnormality seems to be highly variable in depressed patients, including phase advance or phase delay of rhythms and increase or decrease in the rhythm amplitude [7]. There is substantial evidence that circadian rhythms are more attenuated in MDD than euthymic states, with decreased circadian amplitudes in core body temperature, motor activity, thyroid-stimulating hormone, norepinephrine (NE) and cortisol, as was found in several studies [9]. These decreased amplitudes might result from the weakened output of the endogenous oscillator and are one of the most relevant chronobiological abnormalities in depression that may be corrected by antidepressant drugs [8,9].

In the current literature, anxiety among medical students is less studied than depression. A 2014 systematic review of the prevalence of anxiety among medical students outside of North America found a large range of prevalence between 7.7% and 65.5% across 11 studies 10 Anxiety symptoms are common in patients with

MDD. Several studies reported that the GAB Aergic mechanism is involved in the hypnotic action of melatonin [10,11]. Melatonin increases concentration of GABA in the hypothalamus [12], augments GABA turnover in several brain regions, increases GABA-induced chloride influx in the hypothalamus [13], potentiates $GABA_A$ receptor mediated current [14] and causes an enhancement of [3H] GABA binding [15]. Electrophysiological experiments in anaesthetized animals show that melatonin exhibits GABA-like effects [16]. The amygdala is a key circuit for processing neuronal inputs from other parts of the brain, initiating output signals to responding nuclei and generating various physiological responses related to anxiety [17,18] Some trial studies evaluating agomelatine treatment efficacy in depressed patients reported Hamilton Anxiety (HAMA) scale scores. Agomelatine (among a series of synthetic naphthalene melatonin analogs) was superior in reducing HAMA scores compared to sertraline [19].

Physiologically, light exposure is the most effective environmental cue for melatonin secretion in humans. Several studies have reported a positive association between daytime light exposure and nocturnal melatonin levels [20,21]. Night-time light exposure is a powerful suppressor of nocturnal melatonin secretion through the activation of the suprachiasmatic nucleus of the hypothalamus, which contains the master biological clock [22]. Based on the literature, we hypothesized a negative relationship between melatonin level and dimensional measures of anxiety and depressive symptoms. Also increased prevalence of anxiety and depression is seen in females as compared to males. Literature studies have shown increased melatonin levels in females than in males [23,24,25]. Though other studies of melatonin in adolescents did not find significant sex differences [26,27] .

1.1 Objectives

The objective of the study was

1) To see the late-night sleep effect on Serum Melatonin levels
2) To investigate the correlation between Serum Melatonin levels and the severity of anxiety and depression symptoms.
3) To find the difference in Serum Melatonin level with respect to gender.

2. METHODS

This is a cross sectional study done on first year M.B.B.S students of both sexes in the age group 17-23 yrs. from urban and rural backgrounds of Government Medical College, during April – May 2017. The study was approved by Institutional Ethical committee. We planned for purposive sampling, so our sample size was 100. 3 students were absent (47 boys and 50 girls). They were informed about the purpose of the study and asked to participate in the study. An informed written consent was taken from all the volunteers medical students prior to the start of study.

2.1 Data Collection

A brief questionnaire was asked to all the participants regarding demographic components and bedtime i.e. timing to go to sleep. Morning fasting blood samples were taken around 9 A.M under all aseptic precautions. Serum samples were stored at -70 degrees within 2 hrs of collection and processed within 7 days. Serum melatonin was estimated by ELISA METHOD (Elabscience).This ELISA kit uses Competitive-ELISA as the method. The micro ELISA plate provided in this kit has been pre-coated with Human MT. During the reaction, Human MT in the sample or standard competes with a fixed amount of Human MT on the solid phase supporter for sites on the Biotinylated Detection Ab specific to Human MT. Excess conjugate and unbound sample or standard are washed from the plate, and Avidin conjugated to Horseradish Peroxidase (HRP) is added to each microplate well and incubated. Then the Substrate Reagent is added to each well. The enzyme-substrate reaction is terminated by adding Stop Solution and the color change can be measured spectrophotometrically at a wavelength of 450 nm ± 2 nm. The concentration of Human MT in samples can be calculated by comparing the OD of the samples with the standard curve. The concentration of Serum Melatonin was expressed in pg/mL. The blood value range from several pg/mL during the day to more than 50 pg/mL at its night time peak.

Hamilton's anxiety scale was applied to the study group. Anxiety scale consists of 14 items, each defined by a series of symptoms, and measures both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety). Each item is scored on a scale of 0 (not present) to 4

(severe), with a total score range of 0–56, where <17 indicates mild severity, 18–24 mild to moderate severity and 25–30 moderate to severe [28].

Hamilton's depression scale was applied to the study group. This version contains 17 items ($HDRS_{17}$) pertaining to symptoms of depression experienced. Method for scoring varies by version. For the $HDRS_{17}$, a score of 0–7 is generally accepted to be within the normal range (or in clinical remission), while a score of 20 or higher (indicating at least moderate severity) [29].

2.2 Statistical Analysis

Results of this study were analysed with statistical software as SPSS 21 version. Mean value with S.D, Median with range was taken. Non-parametric Kruskal- Wallis test, Mann Whitney test was used on median value for analysis and as a test of significance. p value of 0.05 was considered statistically significant.

3. RESULTS

Table 1 shows the distribution of students with respect to their bed time. There is almost no difference to the melatonin level in the students with respect to bedtime. The p value was found to be 0.384 which is not significant.

Table 2 shows the serum melatonin level in first year medical students according to their HMA scale grading. 12 students were normal, 77 students with mild anxiety and 8 with moderate to severe anxiety. Serum melatonin was found to be lower with the increasing anxiety grade. The p value was 0.389 which was not significant.

Table 3 shows the serum melatonin level in first year medical students according to their HMD scale grading. 76 students were normal, 13 students with mild anxiety and 8 with moderate to severe depression. Serum melatonin was found to be lower with the increasing depression grade. The p value was 0.367 which was not significant.

Table 4 shows anxiety and depression score with respect to gender. The results shows higher anxiety score in females as compared to males. The p value was found to be 0.07 which was not significant. The depression score was also higher in females as compared to males. The p value was 0.073 which not significant.

Table 5 shows the level of serum melatonin in male was higher than in female gender. The p value was found to be 0.041 which was statistically significant.

Table 1. Correlation of the bed time with serum melatonin levels

Bed time	No.	Melatonin level		p value
		Mean +_S.D	Median (range)	
11 PM	17	30.51+_13.73	29.68 (7.66,54.20)	0.384
11 PM- 12 AM	33	30.97+_13.52	31.87 (5.45,72.41)	
12 AM- 1 AM	32	30.69+_26.99	26.42 (4.39,128.20)	
1AM – 2 PM	15	30.79+_10.21	32.45 (12.98,48.44)	

Table 2. Correlation of serum melatonin level and anxiety level in the study group

Anxiety level	No.	Melatonin level	
		Mean +_S.D	Median (range)
Normal	12	34.10+_17.61	32.45 (4.67, 72.41)
Mild	77	31.16+_19.16	29.68 (4.39,128.2)
Moderate to severe	8	21.9+_10.75	15.57 (7.04,35.85)
p value =0.329			

Table 3. Correlation of serum melatonin level and depression level in the study group

Depression level	No	Melatonin level	
		Mean +_S.D	Median (range)
Normal	76	31.69+_16.83	31.39 (4.39,128.20)
Mild	13	30.78+_29.12	21.6 (12.45,125)
Moderate to severe	8	21.89+_10.62	18.53(7.04,35.85)
p value =0.367			

Table 4. Anxiety and depression score with respect to gender

Variables	Males		Females		p value
	Mean +_S.D	Median(range) 2:49	Mean +_S.D	Median (range) 50:98	
Anxiety score	4.59+_4.9	3(0,21)	6.66+_6.31	4.5 (0,26)	0.07
Depression score	3.53+_5.3	2(0,24)	4.93+_5.43	3.5(0,26)	0.073

Table 5. Serum melatonin levels with respect to gender

Gender	No.	Serum melatonin		p value
		Mean +_S.D	Median(range)	
Male	49	32.66+_18.27	32.99 (4.47,128.21)	0.041*
Female	48	28.82+_18.75	25.59 (4.39,125)	

4. DISCUSSION

Melatonin secretion in humans exhibits diurnal variation: levels are lowest during the day, and peak overnight during sleep [30]. Melatonin release from the pineal gland may also be suppressed by exogenous factors, particularly natural and artificial light [31]. In studies of adults, significant inverse associations between exposure to light at night – often resulting from nightshift work – and melatonin levels have been documented [32]. However, the relationships between similar exposures and melatonin levels in younger populations have not been widely studied. The results of the present study shows that there is no significant difference in melatonin secretion in the students with late bedtime. Similar type of result was that, the night-time behaviours of adolescents, did not impact urinary melatonin levels [33].

The medical students experience a much higher prevalence of anxiety compared to the general population. This study depicted that, as the severity of anxiety increased, the levels of melatonin tended to be lower as compared to the students with normal to mild anxiety, but the difference was not found to be statistically significant. Studies have demonstrated that melatonin alleviated lipopolysaccharide-induced anxiety which suggested that melatonin may be used as adjuvant anti-anxiety treatment [34]. In addition, Bustamante and Lira used melatonin to reduce anxiety scores of patients [35].

Major depression often accompanies panic disorder and other anxiety disorders. While depression and anxiety have distinct clinical features, there is some overlap of symptoms. For example, in both depression and anxiety, irritability, decreased concentration and impaired sleep are common. There are various factors associated with the increase of medical students' depression and anxiety. In the present scenario, medical students are subjected to academic stress which lead to late night studies. Moreover these students are addicted to smart phone and late night use of smart phone. All these factors may cumulatively lead to disturbance in circadian rhythm affecting the Melatonin levels and also to increase in the prevalence of anxiety and depression. We found the level of melatonin was lower in moderate to severe depression as compared to normal to mild depression, but the difference was not statistically significant. As Melatonin biosynthesis and secretion are mainly regulated by norepinephrine; the level of Melatonin reflects the norepinephrine activity in brain. Melatonin secretion is an index of norepinephrine activity in depressed patients [36]. Earlier studies have found a correlation between melatonin levels and depression severity in patients [37,38,39]. However, both phase advance of melatonin secretion [40] and no significant phase shift of melatonin in depressed patients compared to controls [41,42] has been reported.Various publications have found no significant relationship between levels of melatonin and indices of depression severity [37,42,43,44].

Depression is more than twice as prevalent in young women than men. Our observation was high anxiety and depression score in females as compared to males. Similar finding has been reported by previous studies [45,46,47]. It could be because of differences in brain chemistry and hormone fluctuations. Hormonal differences are usually cited as the major explanation. Compared to men, women experience much more fluctuation in hormone levels that are associated with symptoms of depression. Estrogen and progesterone have been shown to affect neurotransmitter, neuroendocrine, and

circadian systems that have been implicated in mood disorders [48]. We also found high levels of Melatonin in males as compared to females. The difference was statistically significant. Previous studies have shown high levels of Melatonin in females as compared to males [49,50]. However, the clock time of peak Melatonin levels may differ between males and females because of differences in in-bed time. The low levels of melatonin attributed to females may be due to high prevalence of anxiety and depression in females. There are some limitations of our study, like small sample size with a limited range of depression severity, and confounding factors are not always accounted in the analysis (antidepressant medication, BMI, beta blockers, and season influenced melatonin secretion). We should identify epidemiological and social factors associated with anxiety in medical students in order to identify at-risk students and provide timely assistance and intervention. Also to investigate the circadian disturbance, circadian amplitude disturbance and phase shift effect of melatonin secretion due to anxiety and depression morning, evening and midnight (multiple) sample should be taken.

5. CONCLUSIONS

1. The night time behaviour of the first year medical students may not have significant impact on secretion of Serum Melatonin levels.
2. Anxiety and depression are common mental health problems that come across the medical students, and the confounding factors responsible for it need to be taken care of.
3. Severity of the anxiety and depression alleviate the secretion of Melatonin.
4. Prevalence of Anxiety and depression is more in females than in males, which may be responsible for significantly lower levels of Melatonin in females as compared to males.

CONSENT AND ETHICAL APPROVAL

As per international standard or university standard guideline participant consent and ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Dubocovich ML, Markowska M. Functional MT1 and MT2 melatonin receptors in mammals. Endocrine. 2005;27:101–110. [PubMed] [Google Scholar]
2. Wu YH, Zhou JN, Balesar R, Unmehopa U, Bao A, Jockers R, van Heerikhuize J, Swaab DF. Distribution of MT1 melatonin receptor immunoreactivity in the human hypothalamus and pituitary gland: Colocalization of MT1 with vasopressin, oxytocin, and corticotropin-releasing hormone. J. Comp. Neurol. 2006;499:897–910. [PubMed] [Google Scholar]
3. Liu C, Weaver DR, Jin X, Shearman LP, Pieschl RL, Gribkoff VK, Reppert SM. Molecular dissection of two distinct actions of melatonin on the suprachiasmatic circadian clock. Neuron. 1997;19:91–102. [PubMed] [Google Scholar]
4. Reiter RJ. Pineal melatonin: Cell biology of its synthesis and of its physiological interactions. Endocr. Rev. 1991;12:151–180. [PubMed] [Google Scholar]
5. Jiang ZG, Teshima K, Yang Y, Yoshioka T, Allen CN. Pre- and postsynaptic actions of serotonin on rat suprachiasmatic nucleus neurons. Brain Res. 2000;866:247–256. [PubMed] [Google Scholar]
6. Courtet P, Olié E. Circadian dimension and severity of depression. Eur. Neuropsychopharmacol. 2012;22:S476–S481. [PubMed] [Google Scholar]
7. Wirz-Justice A. Diurnal variation of depressive symptoms. Dialogues Clin. Neurosci. 2008;10:337–343. [PMC free article] [PubMed] [Google Scholar]
8. Dallaspezia S, Benedetti F. Chronobiological therapy for mood disorders. Expert Rev. Neurother. 2011;11: 961–970. [PubMed] [Google Scholar]
9. Coogan AN, Thome J. Chronotherapeutics and psychiatry: Setting the clock to relieve the symptoms. World J. Biol. Psychiatr. 2011;12:40–43. [PubMed] [Google Scholar]
10. Tan DX, Manchester LC, Hardeland R, Lopez-Burillo S, Mayo JC, Sainz RM, Reiter RJ. Melatonin: A hormone, a tissue

factor, an autocoid, a paracoid, and an antioxidant vitamin. J Pineal Res. 2003; 34:75–78.
[PubMed] [Google Scholar]

11. Buscemi N, Vandermeer B, Hooton N, Pandya R, Tjosvold L, Hartling L, Baker G, Klassen TP, Vohra S. The efficacy and safety of exogenous melatonin for primary sleep disorders. A meta-analysis. J Gen Intern Med. 2005;20:1151–1158.
[PMC free article] [PubMed] [Google Scholar]
12. Xu F, Li JC, Ma KC, Wang M. Effects of melatonin on hypothalamic gamma-aminobutyric acid, aspartic acid, glutamic acid, beta-endorphin and serotonin levels in male mice. Biol Signals. 1995;4:225–231.
[PubMed] [Google Scholar]
13. Rosenstein RE, Cardinali DP. Melatonin increases *In vivo* GABA accumulation in rat hypothalamus, cerebellum, cerebral cortex and pineal gland. Brain Res. 1986; 398:403–406.
[PubMed] [Google Scholar]
14. Wu FS, Yang YC, Tsai JJ. Melatonin potentiates the GABA(A) receptor-mediated current in cultured chick spinal cord neurons. NeurosciLett. 1999;260: 177–180.
[PubMed] [Google Scholar]
15. Coloma FM, Niles LP. Melatonin enhancement of [3H] -gamma-aminobutyric acid and [3H] muscimol binding in rat brain. Biochem Pharmacol. 1988;37:1271–1274.
PubMed] [Google Scholar]
16. Stankov B, Biella G, Panara C, Lucini V, Capsoni S, Fauteck J, Cozzi B, Fraschini F. Melatonin signal transduction and mechanism of action in the central nervous system: Using the rabbit cortex as a model. Endocrinol. 1992;130:2152–2159.
[PubMed] [Google Scholar]
17. Gross C, Hen R. The developmental origins of anxiety. Nat Rev Neurosci. 2004; 5:545–552.
[PubMed] [Google Scholar]
18. Greenberg PE, Sisitsky T, Kessler RC, Finkelstein SN, Berndt ER, Davidson JR, Ballenger JC, Fyer AJ. The economic burden of anxiety disorders in the 1990s. J Clin Psychiatry. 1999;60:427–435.
[PubMed] [Google Scholar]
19. Hope V, Hendersony M. Medical student depression, anxiety and distress outside North America: A systematic review. Med. Educ. 2014;48:963–979.
DOI:10.1111/medu.12512.
[PubMed] [CrossRef] [Google Scholar]
20. Little A. Treatment-resistant depression. Am. Fam. Physician. 2009;80:167–172.
[PubMed] [Google Scholar]
21. Mishima K, Okawa M, Shimizu T, Hishikawa Y. Diminished melatonin secretion in the elderly caused by insufficient environmental illumination. J ClinEndocrinolMetab. 2001;86:129–34.
[PubMed] [Google Scholar]
22. Obayashi K, Saeki K, Iwamoto J, Okamoto N, Tomioka K, Nezu S, et al. . Positive effect of daylight exposure on nocturnal urinary melatonin excretion in the elderly: a cross-sectional analysis of the HEIJO-KYO study. J Clin Endocrinol Metab. 2012;97: 4166–73.
DOI:10.1210/jc.2012-1873
[PubMed] [CrossRef] [Google Scholar].
23. Schernhammer ES, Kroenke CH, Dowsett M, Folkerd E, Hankinson SE. Urinary 6-sulfatoxymelatonin levels and their correlations with lifestyle factors and steroid hormone levels. J Pineal Res. 2006;40:116–24.
[PubMed: 16441548]
24. Crowley SJ, Acebo C, Carskadon MA. Human puberty: Salivary melatonin profiles in constant conditions. Developmental Psychobiology. 2012;54:468–473.
[PubMed: 21953482]
25. Caleb Hersh, Julia Sisti, Vincent Richiutti, Eva Schernhammer. The Effects Of Sleep And Light At Night On Melatonin In Adolescents Hormones (Athens). 2015; 14(3):399–409.
DOI:10.14310/horm.2002.1564
26. Cavallo A, Dolan LM. 6-Hydroxymelatonin sulfate excretion in human puberty. J Pineal Res. 1996;21:225–230.
[PubMed: 8989721]
27. Salti R, Galluzzi F, Bindi G, Perfetto F, Tarquini R, Halberg F, et al. Nocturnal melatonin patterns in children. J Clin Endocrinol Metab. 2000;85:2137–2144.
[PubMed: 10852442]
28. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol. 1959; 32:50–55.

29. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960;23: 56–62 .
30. Zeitzer JM, Dijk DJ, Kronauer R, Brown E, Czeisler C. Sensitivity of the human circadian pacemaker to nocturnal light: Melatonin phase resetting and suppression. J Physiol. 2000;526:695–702. DOI:10.1111/j.1469-7793.2000.00695.x [PMC free article] [PubMed] [CrossRef] [Google Scholar]
31. Gooley JJ, Chamberlain K, Smith KA, Khalsa SB, Rajaratnam SM, Van Reen E, et al. Exposure to room light before bedtime suppresses melatonin onset and shortens melatonin duration in humans. J Clin Endocrinol Metab. 2011;96:E463–472. [PubMed: 21193540]
32. Schernhammer ES, Kroenke CH, Dowsett M, Folkerd E, Hankinson SE. Urinary 6-sulfatoxymelaton in levels and their correlations with lifestyle factors and steroid hormone levels. J Pineal Res. 2006;40:116–24. [PubMed: 16441548].
33. Caleb Hersh, Julia Sisti, Vincent Richiutti, and Eva Schernhammer The Effects of sleep and light at nighton melatoninin adolescents. Hormones (Athens). 2015; 14(3):399–409. DOI:10.14310/horm.2002.1564
34. Aziriova S, Bednarova RK, Krajcirovicova K, Hrenak J, Rajkovicova R, et al. Doxorubicin-induced behavioral disturbances in rats: Protective effect of melatonin and captopril. Pharmacol Biochem Behav. 2014;124:284-289.
35. Bustamante-Garcia R, Lira-Rocha AS, Espejo-Gonzalez O, Gómez-Martínez AE, Picazo O. Anxiolytic-like effects of a new 1-N substituted analog of melatonin in pinealectomized rats. Prog Neuropsycho-pharmacol Biol Psychiatry. 2014;51:133-139.
36. Huang YL, Liang XB, Qian LQ, Cai C, Guo J, et al. Effects of Kaixin Powder on melatonin receptor expression and I-Mel binding affinity in a rat model of depression. Chin J Integr Med. 2015;21: 507-515.
37. Souetre E, Salvati E, Belugou JL, Pringuey D, Candito M, Krebs B, et al. Circadian rhythms in depression and recovery: Evidence for blunted amplitude as the main chronobiological abnormality. Psychiatry Res. 1989;28(3):263–78. Epub 1989/06/01 [PubMed] [Google Scholar].
38. Emens J, Lewy A, Kinzie JM, Arntz D, Rough J. Circadian misalignment in major depressive disorder. Psychiatry Res. 2009; 168(3):259–61. DOI:10.1016/j.psychres.2009.04.009 [PubMed] [CrossRef] [Google Scholar].
39. Hasler BP, Buysse DJ, Kupfer DJ, Germain A. Phase relationships between core body temperature, melatonin, and sleep are associated with depression severity: Further evidence for circadian misalignment in non-seasonal depression. Psychiatry Research. 2010;178(1):205–7. DOI:10.1016/j.psychres.2010.04.027 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
40. Voderholzer U, Laakmann G, Becker U, Haag C, Baghai T, Riemann D, et al. Circadian profiles of melatonin in melancholic depressed patients and healthy subjects in relation to cortisol secretion and sleep. Psychiatry Research. 1997;71(3):151–61. [PubMed] [Google Scholar]
41. Claustrat B, Chazot G, Brun J, Jordan D, Sassolas G. A chronobiological study of melatonin and cortisol secretion in depressed subjects: Plasma melatonin, a biochemical marker in major depression. Biol Psychiatry. 1984;19(8):1215–28. Epub 1984/08/01 [PubMed] [Google Scholar].
42. Rubin RT, Heist EK, McGeoy SS, Hanada K, Lesser IM. Neuroendocrine aspects of primary endogenous depression. XI. Serum melatonin measures in patients and matched control subjects. Archives of general psychiatry. 1992;49(7):558–67. . [PubMed] [Google Scholar].
43. Szymanska A, Rabe-Jablonska J, Karasek M. Diurnal profile of melatonin concentrations in patients with major depression: relationship to the clinical manifestation and antidepressant treatment. Neuro Endocrinology Letters. 2001;22(3):192–8. [PubMed] [Google Scholar]
44. Brown RP, Kocsis JH, Caroff S, Amsterdam J, Winokur A, Stokes P, et al. Depressed mood and reality disturbance correlate with decreased nocturnal melatonin in depressed patients. Acta Psychiatr Scand. 1987;76(3):272–5. [PubMed] [Google Scholar]

45. Fatemeh Bahrami, PhD, Naser Yousefi, PhD. Females are more anxious than males: A Metacognitive PerspectiveIran J Psychiatry Behav Sci. Autumn-Winter. 2011;5(2):83–90.
46. Wells A, Carter K. Preliminary tests of a cognitive model of generalized anxiety disorder. Behav Res Ther. 1999;37:585–94.
[PubMed] [Google Scholar]
47. Paul J. Rosch. Why do women suffer more from depression and stress? The American Institute of stress. January 2nd; 2014.
48. Kendra Cherry. The role of neurotransmitters, Brain Health. December 07; 2019.
49. Pippa J. Gunn, Benita Middleton, Sarah K. Davies, Victoria L. Revell, Debra J. Skene. Sex differences in the circadian profiles of melatonin and cortisol in plasma and urine matrices under constant routine conditions Chronobiol Int. 2016;33(1):39–50.
50. Paul R. Why is depression more prevalent in women? Albert, J Psychiatry Neurosci. 2015;40(4):219–221.
DOI: 10.1503/jpn.150205

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/57506