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Review Article

Advancing role of melatonin in the treatment of neuropsychiatric disorders

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ABSTRACT

Melatonin is a pineal neurohormone whose secretion is influenced by circadian changes of 24 hour night and day cycle. Over the recent past, several studies have highlighted the ubiquitous influence of the circadian timing in almost all the physiologic functions. An altered/deficient sleep–wake cycle has been correlated with physiological imbalances which are linked to the development of various disorders, viz depression, anxiety, psychosis, attention deficits, sleep deprivation and others. Melatonin and its oxidation products, viz cyclic 3-hydroxymelatonin, N1-acetyl-N2-formyl-5-methoxykinuramine and N1-acetyl-5-methoxykinuramine possess excellent antioxidant properties. Melatonin's beneficial neuroprotective properties are mostly attributed to excellent free radical scavenging properties. A gathering body of evidence has shown that besides strong antioxidant activities, melatonin is a pleiotropic regulator molecule which orchestrates multiple functions through all the three melatonin receptors, i.e. MT_1, MT_2, and MT_3. For example, MT_2 receptor agonistic activity is attributed to neuroprotective, hypnotic and anxiolytic properties while MT_1 and MT_2 agonistic activity is associated with the clinical efficacy of agomelatine. The third melatonin receptor has been identified as quinone reductase (QR) 2, an enzyme involved in detoxification. MT_3 agonist has been linked to strong hypotensive effects in preclinical study.

In conclusion, the gathering body of evidence both from preclinical and clinical literatures suggests strong antioxidant activities and diverse pleiotropic mechanisms of melatonin for potential neuroprotective role in diverse neuropsychiatric disorders. However, there is still a lack of melatonergic ligands with high selectivity and specificity to precisely target any particular neuropsychiatric disorders for which limited therapeutic options are currently available clinically.

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1.   Introduction

Melatonin (N-acetyl-5-methoxytryptamine) is regarded as a human time-keeping machine and is also referred to as the hormone of darkness. It performs clock and calendar functions to make the human body adapt to diurnal variation which influences the 24-h rhythms in human physiology and behaviors. In 1958, Lerner and colleagues isolated and chemically characterized melatonin in the mammalian pinealocytes [1]. Lately, because of the involvement of melatonin in many physiological and behavioral functions such as sleep–wake cycle, hormonal secretion, thermoregulation, and other physiologic events, melatonin is now called pleiotropic neurohormone [2]. Melatonin has also been reported to regulate feeding behavior, energy metabolism, free radical scavenging, immunity, maintenance of vasculature, inflammation, cancer cell proliferation, reproduction, growth and development, and aging [3].

1.1.   Physiological response of melatonin and suprachiasmatic nucleus

Suprachiasmatic nucleus or nuclei (SCN), a tiny region located in the anterior part of the hypothalamus and situated directly above the optic chiasm, is called as master circadian-pacemaker or the central body clock of mammals responsible for controlling circadian rhythms. The activity of SCN is governed by the expression of clock genes. Signals from SCN travel along multiple-synaptic pathways, involving complex intrahypothalamic connection, to control circadian rhythm via the regulation of melatonin secretion [4]. Light activates photosensitive, melanopsin-containing, retinal ganglion cells, which are sensitive to short-wavelength visible light and communicate the information directly to SCN via the retinohypothalamic tract (RHT). Neuronal axons in RHT release the glutamate and pituitary adenylate cyclase activating polypeptide (PCACP), mediating clock gene expression in SCN. Inhibitory projections (γ-aminobutyric neurons) in SCN send a direct inhibitory projection to paraventricular nucleus (PVN) of the hypothalamus. Neuronal cells in PVN activate preganglionic neurons of intermediolateral cell column which control the sympathetic output to the pineal gland regulating the secretion of melatonin by the pineal gland [5–7]. Melatonin is primarily produced by the pineal gland from amino acid tryptophan. Small amounts of melatonin is also produced in gut, Harderian gland, bone marrow, epithelial hair follicles, skin, retina, salivary glands, platelets, lymphocytes and developing brain but the physiological significance of melatonin from these extrapineal sites, except retina, is still a matter of debate. Norepinephrine (NE) is the major neurotransmitter involved in the regulation of arylalkylamine N-acetyltransferase (AANAT), the rate limiting enzyme in melatonin synthesis. There are two pathways involved in the synthesis and release of melatonin which are stimulated by NE. The first is β_1-adrenergic/cyclic adenosine monophosphate (cAMP)/protein kinase A (PK_A) activation, and the second involves α_1-adrenergic/calcium [Ca^{2+}] pathways. Activation of β_1 receptors increases cAMP concentration, intracellularly, leading to the activation of cAMP-dependent PK_A. Both elevated cAMP levels and PK_A activation are critical for stimulation of AANAT. Secondly, the activation of α_1 recep-

tors leads to increases in the intracellular calcium concentration ($[Ca^{2+}]_i$) by the release of calcium ions from intracellular stores followed by Ca^{2+} influx into the pinealocytes [8]. Amino acid tryptophan, the precursor for melatonin synthesis, is actively up taken into the pinealocytes, hydroxylated and decarboxylated to serotonin. During the day, serotonin in pinealocytes is stored, and remains unavailable to enzymes (monoamine oxidase and melatonin-forming enzymes) which would otherwise act on it. With the onset of darkness, postganglionic sympathetic outflow to the pineal increases which causes the release of NE and the subsequent activation of adrenergic receptors on pinealocytes causes stored serotonin to become accessible for intracellular metabolism. Melatonin is produced by the metabolism of serotonin into in two steps which are catalyzed by AANAT or serotonin N-acetyltransferase (SNAT) and hydroxyindole-O-methyltransferase (HIOMT) or acetylserotonin N-methyltransferase (ASMT). N-acetylation of serotonin by AANAT produces N-acetylserotonin (NAS) and O-methylation of NAS by HIOMT, eventually, produces melatonin (Fig. 1) [8,9].

1.1.1.   Melatonin receptors

Melatonin mediates physiological effects via MT_1 and MT_2 melatonin receptors which are specific G-protein coupled receptors. MT_1 receptor is reported as sensitive to the pertussis toxin while MT_2 melatonin receptor is reported as sensitive to the cholera toxin. MT_1 and MT_2 receptors are expressed in the central nervous system (CNS), including, hippocampus, ventral tegmental areas, and SCN. Additionally, MT_1 receptor also expresses in retina, ovary, testis, mammary gland, coronary arteries, gall bladder, aorta, liver, kidney, skin and the cardiovascular system and MT_2 melatonin receptor in retina and human pituitary gland [8,10]. Melatonin mediated intracellular signaling involves modification of the activities of adenylyl cyclase (AC), phospholipase C (PLC), guanylylcyclase (GC), cyclic guanosine monophosphate (cGMP) as well as calcium and potassium channels [8,10,11]. Physiological responses associated with MT_1 receptor activation include the modulation of neuronal firing, arterial vasoconstriction, cell-proliferation in cancer cells, reproductive and metabolic functions [10], and MT_2 receptor associated physiological responses include the phase shift circadian rhythms of neuronal firing in the SCN, inhibition of dopamine release in retina and leukocyte rolling in arterial beds, induction of vasodilatation, and enhancement of immune responses [11]. Two additional proteins were also reported as melatonin receptors or melatonin receptor modulators. A third melatonin receptor, MT_3, was also identified which binds to quinone reductase 2 (QR2). GPR50 is another melatonin-related protein having 45% similarity to human MT_1 and MT_2 receptors. GPR50 does not directly bind to melatonin but it influences the binding of melatonin to MT_1 receptor [12]. A deletion of GPR50 has been genetically linked to psychiatric disorders such as bipolar disorder and major depression [13].

1.1.2.   Melatonin metabolism

Metabolism of melatonin (Fig. 2) primarily takes place in hepatic cells with the aid of cytochrome P450, family 1, subfamily A, polypeptide 1 (CYP1A1) and cytochrome P450, family 1, subfamily B, polypeptide 1 (CYP1B1). However, it was reported that CYP1A2 and, to some extent, CYP2C19, are primarily respon-
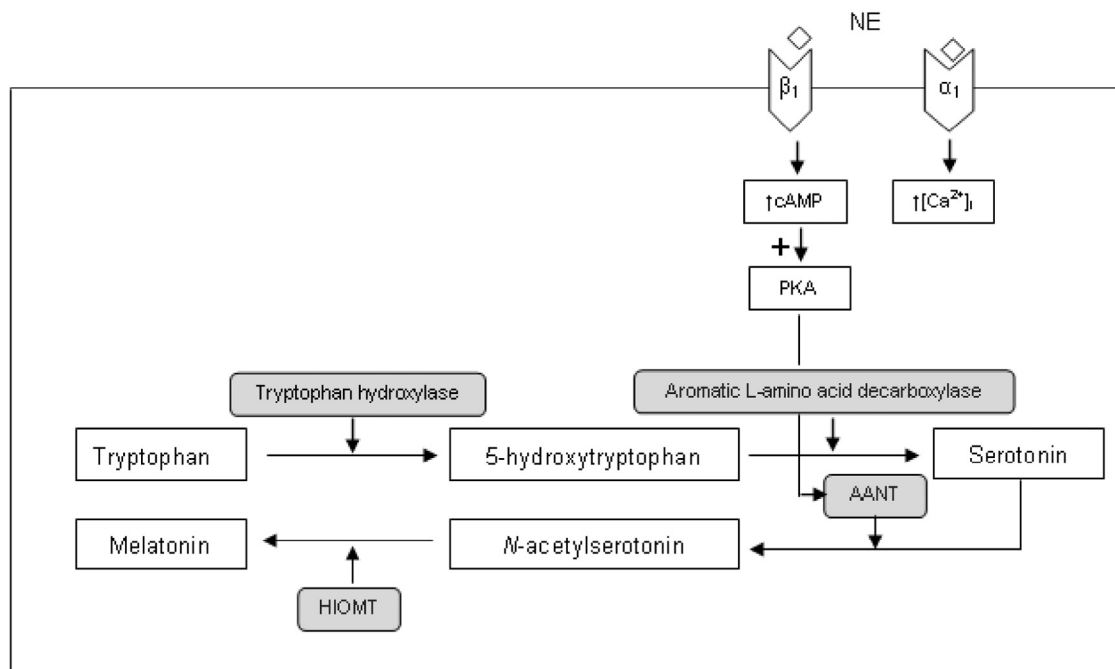
Fig. 1 – Diagrammatic depiction of melatonin synthesis and regulation. AANT: arylalkylamine N-acetyltransferase; cAMP: cyclic adenosine monophosphate; HIOMT: hydroxyindole-O-methyltransferase; PKA: protein kinase A.

sible for the plasma clearance of melatonin by the hepatic cells. In humans, melatonin is principally metabolized to 6-hydroxymelatonin, which is further conjugated with sulfate and excreted in urine [14].) In addition, extrahepatic metabolism of melatonin into 6-hydroxymelatonin occurs by CYP1B1 which has a prominent extrahepatic distribution and does not show significant expression in hepatic cells.

The common metabolic pathways of melatonin [I] involve firstly, 6-hydroxylation to 6-hydroxymelatonin [II], which is sulfated to 6-sulfatoxymelatonin [V], and secondly, by O-demethylation to NAS [III], which is further conjugated to its sulfate [VI] and its glucuronide [VII] and excreted in urine. A minor pathway involves deacetylation to 5-methoxytryptamine [IV], which can be further metabolized to a range of minor metabolites, including pinoline, bufotenine, N,N-dimethyltryptamine, and serotonin, which acts as precursor to melatonin production [I] in the serotonin–melatonin cycle [14]. Other important metabolites resulting from melatonin oxidation include cyclic 3-hydroxymelatonin, N1-acetyl-N2-formyl-5-methoxykinuramine (AFMK) and N1-acetyl-
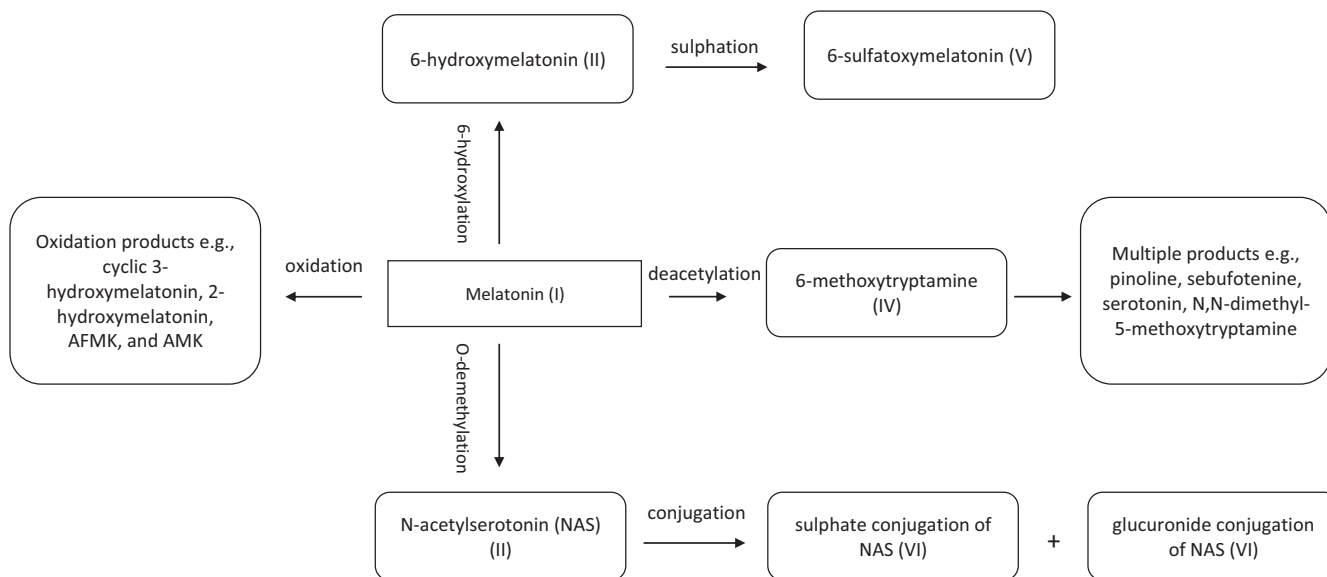

Fig. 2 – Diagrammatic illustration of the common metabolic pathways of melatonin and its oxidative products. AFMK: N1-acetyl-N2-formyl-5-methoxykinuramine; AMK: N1-acetyl-5-methoxykinuramine.

5-methoxykinuramine (AMK). AFMK is formed by pyrrole-ring cleavage, by myeloperoxidase, indoleamine 2,3-dioxygenase and various non-enzymatic oxidants [14].

2. Melatonin in various neuropsychiatric disorders

Melatonin received wide attention as it has been observed that patients suffering from neuropsychiatric disorders usually have abnormal melatonin secretion and many neuropsychiatric disorders including anxiety, depression, insomnia, narcolepsy, epilepsy, schizophrenia, Parkinson's disease (PD), and Alzheimer's disease (AD) have a disturbed circadian rhythm [15–17]. A recent review on melatonin use has indicated MT_2 melatonin receptor's involvement in the pathophysiology of sleep disorders, anxiety, depression, AD and pain, and has also reported that selective MT_2 receptor agonists have hypnotic and anxiolytic properties [18], and selective MT_2 receptor agonists are being discovered for possible treatment of mental disorders for which limited drug therapies are currently available [18]. Melatonin potential to treat several neuropsychiatric diseases could be due to its pleiotropic biological effect, some of which are mediated via activation of MT receptors and others are due to strong antioxidant activities which protect nuclear and mitochondrial DNA from reactive oxidative species. AFMK and AMK are melatonin by-products having excellent radical scavenging activity [19]. AMK has been reported to scavenge reactive oxygen and nitrogen species, and is a mitochondrial modulator, downregulator of cyclooxygenase-2, inhibitor of cyclooxygenase, neuronal and inducible NO synthases, and is a better hydroxyl radicals scavenger than melatonin [20]. Diverse therapeutic role of melatonin has been attributed to its ability to induce apoptosis and arrest cell cycle, antimetastatic and antiangiogenic, anti-inflammatory, and antioxidant effects. Also, melatonin has been reported to detoxify xenobiotic and endobiotic compounds via the up-regulation of Nrf2 (a protein which controls the expression of antioxidant proteins) and recently reported as an inhibitor of proteasome. The involvement in sleep initiation, vasomotor control, adrenal function, antiexcitatory actions, immunomodulation including anti-inflammatory properties, antioxidant actions, and energy metabolism influencing mitochondrial electron flux and mitochondrial biogenesis contribute to the neuroprotection by melatonin [21].

2.1. Anxiety and panic disorder

Several studies have reported a promising therapeutic role of melatonin in anxiety and panic disorders [22–26]. A recent study has shown that melatonin could increase the beneficial effect of buspirone against several parameters of anxiety including the immobilization of stress-induced anxiety-like behavioral and oxidative damage in mice [22]. Melatonin administration during the night-time chronically ameliorated the stress-induced behavioral disturbances, particularly the cognitive dysfunctions and depressive phenotypes in mice [23]. Treatment with melatonin and agomelatine alone was ineffective as anxiolytic agent but when combined the efficacy of anxiolytic

drugs was potentiated [24]. The beneficial effect of melatonin premedication in surgery to reduce anxiety and fear of surgery has been reported in clinical studies [25–27]. In patients undergoing cataract surgery, premedication with sublingual melatonin reduced the anxiety scores and provided excellent operating conditions for doctors [25]. Preoperative use of melatonin was reported to possess similar efficacy to benzodiazepines in reducing preoperative anxiety with minimal action on psychomotor performance and sleep–wake cycle. Thus, melatonin could serve as an alternative to benzodiazepines in the remediation of preoperative anxiety with no significant adverse effects in short-term use [26,27]. Another recent study has indicated that premedication with oral or sublingual melatonin could be equally effective in reducing preoperative anxiety in adults similar to the standard treatment with midazolam [26]. Moreover, melatonin was also reported to have an opioid sparing effect and also reduced intraocular pressure. Hence, melatonin could also be used to prevent postoperative delirium [27]. A review of the published data has reported the clinical efficacy of agomelatine in generalized anxiety disorder. However, trials evaluating agomelatine efficacy in generalized anxiety disorder are currently few and require several randomized, placebo-controlled studies on larger samples and in the treatment of other anxiety disorders, such as panic disorder, social anxiety disorder, obsessive–compulsive disorder and post-traumatic stress disorder to solicit therapeutic benefit of melatonin in generalized anxiety disorder [28]. Recently, Patel and Kurdi [29], in a clinical study, compared the effects of oral melatonin and oral midazolam in preoperative anxiety, cognitive, and psychomotor functions. Melatonin given orally at 0.4 mg/kg showed comparable anxiolytic activity to that of oral midazolam without the impairment of general cognitive and psychomotor functions as observed with the treatment of midazolam [29].

2.2. Migraine

Migraine is primarily a headache disorder which is characterized by recurrent episodes of headache associated with gastrointestinal, neurologic, and autonomic symptoms. Some evidence is present to show that the melatonergic system could possibly play an important role in the pathogenesis of migraine. Previously, in 2011, Tabeeva et al. [30] reported that agomelatine could possibly be used as a preventive treatment for migraine. Agomelatine has been reported as a novel treatment option for migraine prophylaxis due to its specific mechanism of action and similarity to melatonin. In 2013, Guglielmo et al. [31] reported two cases of patients with migraine being successfully treated with agomelatine; one patient presented with comorbid depression, whereas the other had no comorbidities. Recently, Plasencia-García et al. [32] presented a case series of 6 female patients who visited outpatient clinics for Recurrent Major Depressive Disorder [American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders IV Text Revision (DSM-IV-TR)] and all had moderate depressive episode [mean Montgomery–Asberg Depression Rating Scale (MADRS) score of 26.66 ± 3.72] at the time of assessment. All patients were suffering from migraine since 20 years with nearly 4 attacks per month (based on the diagnostic criteria of the International Headache Society, 2004), and

a pain intensity of over 9 as per Visual Analogue Scale (VAS). All patients were receiving amitriptyline, beta-blockers and topiramate as prophylactic treatment for headaches, which was stopped due to lack of response or adverse effects. Initially agomelatine was administered at a dose of 25 mg for depressive episode which was increased to 50 mg/24 hours in 4 patients due to lack of remission after 8 weeks of treatment. Remission in depressive episode (MADRS 1.16 ± 1.16) with considerable reduction in frequency of migraine attack (from 4 to <1 attacks/month) and intensity of the attacks (from 9 to 2) was noted after 4 months. The patients reported a considerable reduction in frequency of attacks from the first month of treatment. Guglielmo et al. attributed the improvement to treatment with agomelatine in all these cases since the patients were non-responders to past treatment with other antidepressants for migraine episodes despite remission of the symptoms of depression. Hence, it may be assumed that efficacy of agomelatine could be related to the synergic action between melatonin agonism and 5-HT$_{2C}$ antagonism. However, further studies are needed to clarify the precise pathophysiological and neurochemical mechanisms involved in the specific antimigraine response [31].

2.3.   Epilepsy

Treatment of epilepsy continues to pose a challenge in spite of the availability of advanced medications because firstly, a significant proportion of patients show drug resistance [33], and secondly, poor adherence and drug interactions associated with multi-drug prescription and the fear of worsening seizures by some of the prescribed medications lead to an incomplete cure from epilepsy. An increasing body of literature reports that melatonin might possibly play an important role in the treatment of pharmacoresistant and other refractory types of epilepsy [34,35]. Melatonin has been reported to easily cross the blood–brain barrier and modulate electrical activities of neurons by reducing glutamatergic and enhancing γ-aminobutyric (GABA) neurotransmission. In animal studies, melatonin administration was reported to inhibit audiogenic and electrical seizures, as well as reduce pentylenetetrazole-induced convulsions including convulsion produced by pilocarpine, L-cysteine and kainate [34]. The by-products of melatonin, kynurenic acid, have been reported to have endogenous anticonvulsant and also free radical scavenging and antioxidant activities. In a study on the effect of a high concentration of melatonin on PC12 cells investigated norepinephrine release and melatonin's role on excitatory postsynaptic potential in rat hippocampal slices reported inhibitory effect of melatonin on neurotransmitter release which is possibly by blocking voltage-sensitive Ca^{2+} channels. In pilocarpine-induced epilepsy model, melatonin administration chronically reduced a number of spontaneous seizures and cell damage in animals having status epilepticus [35]. In one of the studies, Moeizi et al. [36] explored the interaction of melatonin and agmatine (a biogenic amine with anticonvulsant properties) on seizure susceptibility in pentylenetetrazole-induced clonic seizure model in mouse and also studied melatonin receptors involvement using luzindole, a MT$_{1/2}$ receptor antagonist, and prazosin, a MT$_3$ receptor antagonist. Luzindole (2.5 mg/kg) significantly prevented the anticonvulsant effect of melatonin (40 and 80 mg/kg) but not prazosin

(0.5 mg/kg), indicating that MT$_{1/2}$ receptor could be involved in the anticonvulsant effect of melatonin. The anticonvulsant efficacy of melatonin, both effective dose (80 mg/kg) and non-effective dose (20 mg/kg), was significantly enhanced by the concurrent administration of agmatine (5 mg/kg). This suggested an additive effect of melatonin in decreasing pentylenetetrazole-induced seizure threshold in mice [36]. A study investigated the effect of melatonin treatment (10 mg/kg/day, diluted in drinking water, 8 weeks) during epileptogenesis and on the consequences of a kainate induced status epilepticus in murine models [37]. The findings of the study suggested that melatonin delayed the appearance of spontaneous recurrent seizures and decreased their frequency only during the treatment period. In epileptic rats, melatonin treatment showed positive effect on the behavioral alterations associated with hyperactivity, depression-like behavior during the light phase, and deficits in hippocampus-dependent working memory. Further, the treatment of melatonin reduced the neuronal damage in CA1 region of hippocampus and piriform cortex, and improved hippocampal serotonin level in epileptic rats. However, long-term treatment of melatonin following status epilepticus could not prevent the development of epileptogenesis but was able to reduce some of the deleterious effects which occurred during the chronic epileptic state [25,37]. Also, in a similar study involving kainate model of temporal lobe epilepsy, treatment of melatonin during the epileptogenesis prevented harmful effects of status epilepticus in spontaneously hypertensive rats. Also, melatonin treatment was able to reduce the neuronal onslaught, specifically in CA1 region of hippocampus and piriform cortex and decreased hippocampal serotonin levels both in the control and spontaneously hypertensive epileptic rats. Melatonin treatment chronically post status epilepticus significantly improved seizure activities and neuronal loss but epilepsy-induced behavioral abnormalities were unaltered in spontaneously hypertensive rats [38].

Melatonin reduced some of the changes which occurred during the chronic epileptic state. Another study reported potentiation of phenobarbital efficacy by melatonin administration [39]. The probable mechanisms for antiepileptic efficacy of melatonin, as reported from animal studies, are inhibition of neurotransmitter release (possibly by blocking voltage-sensitive Ca^{2+} channels) and perhaps mediation via nitric oxide/L-arginine pathway [35,40]. Thus, melatonin could exert neuroprotective effects by attenuating status epilepticus-induced post-lesion and decrease the number of seizures [41]. In clinical studies, complete disappearance of seizures, reduced seizure latency [42], improvement in seizures severity [43], and control of convulsive episodes have been reported with melatonin therapy [44]. In 2012, a pilot study by Goldberg et al. [45] reported melatonin therapy to be safe and effective in decreasing daytime seizure frequency in patients with intractable epilepsy. The adjunct use of melatonin in the seizure management has been suggested. A clinical study has reported low serum concentration of melatonin in children with epilepsy or complex febrile seizure and the treatment of exogenous melatonin improved febrile seizure and epilepsy in children [46]; however a recent study has indicated against melatonin use in children who are suffering from convulsive disorders [47]. Based on literature from both animal and clinical studies, it may be concluded that melatonin has anticonvulsant effi-

cacy; however, at the moment there is no clear-cut evidence to justify its any imminent use in epilepsy.

2.4.   Depression and mood disorders

Disturbed sleep and circadian rhythms is a prominent feature of depression and altered melatonin secretion has been observed in major depression [48]. In shift workers, an abnormal melatonin secretion has been reported to cause several psychiatric diseases including depression. A preclinical study has reported reduction in the immobility time (an indicator of antidepressant activity) with the treatment of melatonin and NAS in the mouse tail suspension test [49]. It was reported that QR2/MT_3 agonist, 5-methoxycarbonylamino-N-acetyltryptamine, decreased, while the QR_2/MT_3 antagonist, prazosin, increased the duration of immobility in the tail suspension test in a dose-dependent manner. The modulation of QR2/MT_3 receptor has been correlated with the antidepressant effects of melatonin. Thus, novel antidepressant agents may be developed via MT_3 receptor agonistic approach [49].

One of the studies had evaluated the possible beneficial action of chronic night-time melatonin treatment against chronic mild stress (CMS) induced behavioral impairments. In this study, it was noted that stress exposed mice had reduced weight gain, hedonic deficit, cognitive deficits and decreased mobility in the behavioral despair test. These mice also displayed less anxiety. Administration of melatonin night-time, chronically, had considerably improved the stress-induced behavioral disturbances, viz. the cognitive dysfunction and depressive phenotypes. In conclusion, findings suggested that there was a mitigating role of melatonin against CMS-induced behavioral changes, including the cognitive dysfunctions, thus reaffirming its potential role as an antidepressant [23]. In 2011, Quera-Salva et al. [50] reported that antidepressant agents with intrinsic chronobiotic properties could offer a novel approach to the treatment of depression. A clinical study involving 14 depressed patients (5: major depression and 9: bipolar disorder) and 14 matched controls have shown increased MT_1 receptors in the SCN. The study suggests that increased MT_1 receptor expression may be involved in the circadian disorders and could contribute to the efficacy of melatonin or its agonists in the depression [51]. Seasonal affective disorders and mood disturbances which result from circadian malfunction could be treated by chronobiotic drugs, chronotherapy or bright light therapy, and melatonin and its agonists possess chronobiotic effects which could reset the circadian system [50,52]. A recent systematic review and meta-analysis did not find clear evidence of a therapeutic or prophylactic effect of melatonin against depression or depressive symptoms [26]. However, a randomized, double-blind, placebo-controlled trial investigating the effect of a 6 mg/day dose of melatonin given for three months post-surgery to patients with breast cancer having symptoms of depression, anxiety, sleep disorder, cognitive dysfunction and fatigue has shown reduced depressive symptoms, and increased sleep efficiency perioperatively and total sleep time postoperatively [48]. Agomelatine has been developed as a novel and clinically effective antidepressant drug with melatonergic (MT_1/MT_2) agonist and 5-HT_{2C} receptor antagonist properties and has been approved for the treatment of major depressive disorder in adults by the European Medi-

cines Agency. The efficacy of agomelatine remains questionable despite evidence showing superiority of over placebo and selected antidepressant agents because it remains to be established that the magnitude of effect size is clinically significant and sample characteristics are relevant to the general patient population with major depressive disorder [53]. A synergistic interaction between melatonergic and serotonergic receptors in the agomelatine effects in restoring circadian rhythms and relieving depressive symptoms has been reported by several studies. Agomelatine does not have an affinity for histaminergic, adrenergic or dopaminergic receptors, suggesting that it may be free of side effects displayed by traditional antidepressant agents [54,55]. In a comprehensive meta-analysis by Taylor et al. [56], agomelatine has been reported as moderately more effective than placebo. The effect size for agomelatine compared with placebo was found to be similar to that of other marketed antidepressants, and showed similar efficacy to standard antidepressant in comparator controlled trials. Agomelatine has been reported a justifiable treatment option in patients who are unable to tolerate adverse effects of standard antidepressants or in whom standard drugs are contraindicated. Agomelatine's demonstrable acute efficacy is intriguing given its unique pharmacological mode of action and good tolerability. Thus, further researches are warranted to discover newer compounds possessing melatonergic activity and to confirm the efficacy of agomelatine in depression [56]. Anhedonia is known as a condition in which the capacity to experience pleasure is totally or partially lost. Currently, there is no definitive specific pharmacological approach to the treatment of anhedonia in depression. The efficacy of agomelatine on the dimension of anhedonia may be of particular importance in the treatment of major depressive disorder (MDD) with anhedonic features. A clinical study which included depression parameters, e.g. depressive (Hamilton Depression Scale; HAM-D) and anxious (Hamilton Anxiety Scale; HAM-A) symptoms, anhedonia (Snaith Hamilton Rating Scale; SHAPS), and sleep quality (Leeds Sleep Evaluation Questionnaire; LSEQ) showed significant improvements at all visits on the HAM-D, HAM-A, SHAPS, and LSEQ with the treatment of agomelatine. The study reported significantly greater efficacy on anhedonia and similar antidepressant efficacy to the serotonin-norepinephrine reuptake inhibitor, venlafaxine, in patients with MDD in an 8-week treatment period. Preliminary findings have described the efficacy of agomelatine in the treatment of anhedonia to be novel among antidepressant agents which are currently available [57,58]. Another clinical study involving 28 depressed patients with bipolar disorder reported agomelatine, 25 mg/day, to be an effective and well-tolerated adjunct to valproate/lithium for acute depression in BD-II [59].

In a review in 2013, De Berardis et al. [60] also highlighted the efficacy of agomelatine MDD and anhedonia. They reported appreciable reduction in SHAPS scores compared to venlafaxine in anhedonia and similar efficacy to sertraline and superior efficacy to venlafaxine and escitalopram in MDD treatment with agomelatine. Agomelatine also fared well in side effect and safety and acceptability profiles compared to current medications. Agomelatine does not cause loss of libido compared to venlafaxine and has better sexual acceptability than paroxetine in healthy male volunteers. Further, fewer discontinuation rates were reported for agomelatine for any cause

than venlafaxine, sertraline and fluoxetine. Moreover, data suggest that agomelatine was not associated with discontinuation symptoms, even if this potential side effect warrants further investigation, especially regarding long-term risks. The incidence of relapse over six months was significantly lower with agomelatine [60]. A recent clinical study has shown an early impact of agomelatine treatment on sleep quality and alertness at awakening, indicating that agomelatine could be an effective antidepressant agent in the acute phase of MDD [61]. Thus, it may be forecasted that the development of novel melatonergic compounds would greatly advance the treatment of depressive disorders.

2.5. *Schizophrenia*

Several studies have reported abnormal functioning of melatonin in the pathophysiology of schizophrenia [62–64]. In the past, alteration in melatonin secretion has been linked to pineal calcification and pineal calcification size has been used to detect the development and prognosis of schizophrenia. Melatonin has been reported as a biomarker of schizophrenia which could be used to identify the type of schizophrenia in patients [62]. MT_1 and MT_2 melatonin receptor has been reported as potential targets to improve psychotic symptoms [63]. Important link between the promoter of the melatonin receptor 1A gene and schizophrenic disorder has been reported and a higher change in melatonin level is reported in monozygotic twins discordant for schizophrenia [64]. Psychosis and dreaming, including delusions, hallucinations, bizarre thinking and perceptual distortions, have many similarities, leading to the hypothesis that SCN which regulates sleep and wakefulness could be involved in the pathogenesis of schizophrenia [65]. It was hypothesized that altered functioning of SCN could contribute to schizophrenia through several different, not necessarily mutually exclusive, mechanisms, including "rapid eye movement sleep (dream) rebound" phenomenon, damaged neuronal pathways connecting SCN to the brain regions affected by schizophrenia, and the SCN dysfunction induced dysregulation of gene expression in different parts of the body, including the brain [65]. Melatonin has been reported to prevent metabolic side effects of antipsychotic agents. Olanzapine induced body weight gain and visceral adiposity in rodents has been linked to low plasma melatonin level, indicating possible use of melatonin in the management of weight gain caused by antipsychotic medications [66]. In schizophrenia, long-term treatments with benzodiazepines often present with withdrawal symptoms due to the development of dependence. Melatonin has been reported to lower benzodiazepines intake [67,68]. Controlled-release melatonin formulation may help withdraw benzodiazepine therapy while maintaining good sleep quality. A randomized clinical trial (NCT01431092) is evaluating the role of melatonin in long-term benzodiazepine withdrawal treatment in schizophrenia patients and the result is being awaited [69].

In 2014, Modabbernia et al. [70] reported a randomized double-blind placebo-controlled study on 48 patients with first-episode schizophrenia who were eligible for olanzapine treatment. The patients were randomized to receive olanzapine plus either melatonin 3 mg/day or matched placebo for eight weeks. Anthropometric and metabolic parameters as well as psychiatric symptoms using the Positive and Negative Syndrome Scale (PANSS) were assessed at baseline, week 4, and week 8. Primary outcome measure was the change from baseline in weight at week 8. Thirty-six patients were made to have at least one post-baseline measurement. At week eight, melatonin was associated with significantly less weight gain, increase in waist circumference and triglyceride concentration than the placebo. Changes in cholesterol, insulin, and blood sugar concentrations remained nearly the same between the two groups. Patients in the melatonin group were reported to have experienced significantly greater reduction in their PANSS scores than the placebo group. No serious adverse events were reported. The study findings showed that in patients treated with olanzapine, short-term melatonin treatment had attenuated weight gain, abdominal obesity, and hypertriglyceridemia. It might also provide additional benefit for treatment of psychosis. Thus, it was concluded that the use of short term melatonin treatment in patients with first episodes of schizophrenia who were on olanzapine treatment could prevent the metabolic side-effects, viz weight gain, abdominal obesity, and hypertriglyceridemia.

Agomelatine has been reported to possess favorable efficacy in psychotic disorders [52]. Agomelatine, due to its $5HT_{2c}$ receptor antagonism, causes enhanced release of both norepinephrine and dopamine at the fronto-cortical dopaminergic and noradrenergic pathways, which indirectly stimulates the release of brain-derived neurotrophic factor [58].

A recent study has reported compelling evidence of decreased peripheral BDNF levels in schizophrenia which was also supported by the previously described reduced cerebral BDNF expression in the psychotic disorders [71]. Thus, agomelatine may be used in the treatment of symptoms associated with schizophrenia. A 16-week, open-label, preliminary study involving 20 outpatients (9 men and 11 women) with schizophrenia was conducted to assess the efficacy of agomelatine combination with clozapine in psychosis [72]. The patients used in this study were stable and receiving clozapine monotherapy at the highest tolerable dose (mean dose 430 mg/day) for at least one year. However, patients were regarded as partial responders to clozapine due to the presence of residual symptoms and according to Brief Psychiatric Rating Scale (BPRS) total scores of more than 25. Agomelatine augmentation of clozapine significantly improved PANSS as well as total score and overall clinical symptoms (measured by BPRS) at week 8. At week 16, significant differences were noted in PANSS rating, depressive symptoms (measured with the Calgary Depression Scale for Schizophrenia) and overall clinical symptoms. At week 8, significant differences were noted in cognitive performances only at Wisconsin Card Sorting Test (WCST) "perseverative errors", but, at week 16, agomelatine treatment significantly improved performances on Stroop task and increased improvement on WCST "perseverative errors". At endpoint, 9 subjects (64.3%) of the 14 patients, who completed the trial, responded to the coadministration of agomelatine (defined as a reduction in PANSS total score >25% between the baseline and follow-up ratings) and no patients reported worsening in clinical symptoms compared to baseline [72]. Agomelatine–clozapine combination was reported to be well tolerated. However, most common adverse effects reported were gastrointestinal symptoms, headache and excessive sleepiness.

There is a need for a bigger randomized blinded comparator trial; involving a large sample size is required to draw any firm conclusions. Thus, melatonin could be utilized as an add-on medication to increase the efficacy of medications in schizophrenia, decrease metabolic side effects and increase life-expectancy of patients on long-term antipsychotic medication.

2.6.   Obsessive–compulsive disorder

Obsessive–compulsive disorder (OCD), characterized as severe persistent intrusive and disturbing thoughts (obsessions) and repetitive stereotypic behaviors (compulsions), is a common chronic neuropsychiatric disorder associated with marked distress and impairment of social and occupational functioning. The manifestations of OCD are frequently associated with anxiety or extreme fear [73]. The etiopathology of OCD remains poorly understood but patients often show hormonal imbalance and disturbance in sleep phase, suggesting dysfunctional circadian rhythms. 24 hour-secretion of melatonin was also found to be reduced as compared to the healthy control subjects and has been associated with the severity of the OCD symptoms, particularly with obsessions. A dysfunction of noradrenergic system followed by a dysregulation of melatonin synthesis and secretion has been reported in OCD. A retrospective study has linked OCD with circadian rhythm sleep disorder which is known as the delayed sleep phase syndrome (DSPS). Patients with OCD typically display DSPS which causes excessive daytime sleepiness leading to disruption in social and occupational functioning [73]. Patients with DSPS usually go to bed and get up much later than normal. They are unable to shift their sleep to an earlier time and, as a result, suffer considerable disruption of social and occupational functioning [74]. Administration of exogenous melatonin has been reported to treat sleep disorders which increased the treatment efficacy, mitigated relapse and protected against the onset of co-morbid psychiatric illnesses in OCD patients [75]. There is a close link between light and melatonin in the regulation of sleep–wake cycle which suggests a possible role for treatment with exogenous melatonin and/or light therapy in OCD patients with DSPS. Thus, melatonin could be developed as a pharmacological means for treating both OCD and DSPS [74]. In 2011, daRocha and Correa presented a case report of an adult male patient with OCD who was unresponsive to clomipramine treatment and also had problem with risperidone or aripiprazole. Augmentation of the therapy with agomelatine has been reported to improve patient's condition possibly by resynchronization of circadian-rhythm [76]. Further, clomipramine and selective serotonin reuptake inhibitors are established medications for OCD but they cause numerous adverse effects, including weight gain and sexual dysfunctions, severely impacting patient's quality of life. Agomelatine is reported to cause no clinically overt adverse effects such as weight gain and sexual dysfunction. In another case report, a 22-year-old female student had severe OCD symptoms which included washing and checking of hands and feet compulsively in response to contamination [77]. Her OCD caused dermatitis in her hands and such cleaning/washing and checking compulsions severely disrupted her social activities. She was receiving medications which included fluvoxamine, venlafaxine, lorazepam, and clomipramine and intake of these medications developed several adverse effects. She was prescribed agomelatine 25 mg/day at bedtime which significantly improved her symptoms without any adverse effects after 2 weeks of therapy and subsequently dose was titrated to 50 mg/day [77]. In yet another case study, agomelatine augmentation of escitalopram therapy successfully treated a young female patient suffering from severe treatment resistant OCD [78]. Another study, in 2013, also highlighted the potential anticompulsive effect of agomelatine [79]. Anticompulsive effect of agomelatine is reported to be mediated via $5HT_{2C}$ antagonism and $MT_{1/2}$ agonism [79]. Thus, melatonergic agents could be promising and may be developed for possible use in OCD in conjunction with existing medications.

2.7.   Parkinson's disease

Parkinson's disease (PD) is one of the most common neurodegenerative disorders characterized by a progressive loss of dopamine in the substantia nigra and striatum. It has been reported that over 70% of dopaminergic neuronal death takes place before appearance of the first symptoms, making it extremely difficult for an early diagnosis and effective treatment of the disease [80,81]. Levodopa (L-dopa) has been used to restore dopamine content which unfortunately provides only symptomatic relief and also L-dopa intake is associated with certain long-term pro-oxidant damage. The first evidence of a significant relationship between Parkinson's disease and melatonin came from the finding that circulating melatonin concentration was low in PD patients due to diminished pineal activity [82], and subsequently, due to the discovery of its potent antioxidant properties, melatonin was successfully tested in several *in vivo* and *in vitro* PD models. 1-Methyl-4-phenyl-1,2,3,6-tetrahydopyridine (MPTP) is a neurotoxin responsible for the PD syndrome which elicits an irreversible, severe parkinsonian-like signs characterized by all the features observed in PD, i.e., tremor, rigidity, slowness of movement, and postural instability. In 2005, Mayo et al. [80] summarized all the potential pathways involved in the neuroprotective actions of melatonin in MPTP model of PD, which mimics most of the symptoms of PD in humans. MPTP crosses the blood–brain barrier and is converted by glial cells into 1-methyl-4-phenyl pyridinium ion (MPP^+) by monoamine oxidase B. MPP^+ enters into the dopaminergic terminals through the dopamine transporter and accumulates in vesicles or in the mitochondria of dopaminergic neurons and interferes with electron-transport chain producing oxidative stress which eventually triggers apoptosis of dopaminergic neurons. The possible mechanisms through which melatonin may elicit protective actions included (1) potent antioxidant activities scavenging reactive oxidative species, harmful to macromolecules and triggering apoptosis; (2) antiapoptotic activities via the blockade of apoptotic cascade; (3) activation of mitochondrial metabolism; and (4) anti-inflammatory actions, by either blocking microglia activation or inhibition of enzymes such as cyclooxygenase 2 and inducible nitric oxide synthase which produce proinflammatory mediators and nitric oxide, respectively. Thus, melatonin blocks pro-apoptotic cascade at different levels, preventing dopaminergic neuronal death which is responsible for causing parkinsonian signs. Cardiolipin is a phospholipid located in inner mitochondrial membrane which

is needed for several mitochondrial bioenergetic processes and proper functioning of transport proteins. A change in cardiolipin structure and acyl chain composition causes mitochondria to work abnormally under a variety of pathological dysfunctions including PD. Melatonin has been reported to protect mitochondrial membranes from oxidation-reduction damage by stopping cardiolipin oxidation [83].

Alpha-synuclein (α-synuclein) is known to be involved in the development of PD. Melatonin has been reported to prevent α-synuclein fibril formation and destabilize the preformed α-synuclein fibrils. It reduces α-synuclein-induced cytotoxicity and thus prevents further development of PD symptoms [84]. Melatonin was also shown to inhibit protofibril formation, oligomerization and secondary structure transitions. Melatonin's ameliorative effects were reported due primarily to the inhibition of toxic polymers assembly and protection of neurons from their toxic effects [84]. In a 2013 study, melatonin showed neuroprotective effects against mutant α-synuclein-induced injury in the substantia nigra [85]. In 2002, Antolín et al. [86] developed a chronic experimental model to study PD. They administered a low-dose of MPTP, 15 mg/kg, body weight, for 35 days, to mice to induce nigral cell death. The mouse model emulated the chronic condition of PD in humans. The researchers observed that treatment of melatonin, 500 μg/kg, body weight, prevented the neuron cell death and damage caused by the long-term MPTP treatment. Antolín and his colleagues proposed that melatonin may be a potential therapy agent to prevent the disease and/or its progression [86]. Another study in rats treated (via drinking water), chronically, with physiological concentrations of melatonin (0.4 μg/ml and 4.0 μg/ml) after partial lesioning with 6-hydroxydopamine (6-OHDA) in the striatum has also supported that physiological levels of melatonin have a protective role in parkinsonian neurodegeneration in the nigrostriatal system [87].

A study involving unilateral 6-OHDA lesion rats and patients with PD has correlated the serum melatonin levels with the severity of PD. The study found significantly higher levels of serum melatonin than control groups during the morning period, in both animal and human subjects with PD [88]. Another study reported that chronic administration of melatonin orally improved 6-OHDA-induced neurotoxicity. The animals treated with melatonin and L-dopa performed well in various motor tasks without dyskinesia compared to animals treated with L-DOPA alone [88]. In 2012, Gutierrez-Valdez et al. [89], and in 2014, Yildirim et al. [90], showed other probable mechanism of melatonin in PD. They reported that melatonin delayed the cellular and behavioral alterations produced by 6-OHDA-induced neurotoxicity and prevented dopaminergic neuronal death by increasing the levels of *Bcl-2* protein (an important anti-apoptotic protein) and decreasing the caspase-3 activity in PD [89,90]. In rotenone-induced animal model, rotenone and melatonin combination have shown neuroprotective effects which have been linked to the inhibition of *Omi* and *Bax*-induced autophagy [91,92]. In another study, prolonged melatonin treatment after dopaminergic neuronal lesion did not alter motor-function but produced antidepressant-like effects in the forced swim-test and prevented rotenone-induced dopamine reduction in the striatum, indicating neuroprotective and antidepressant-like effects of melatonin in PD [93]. Levodopa (L-DOPA) is an established medication used to reduce the symptoms of PD, but it poses serious side effects following chronic use. In 2013, Naskar et al. [94] reported that melatonin potentiated the effects of low dose L-DOPA in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced experimental model of PD [94]. Treatment with L-dopa ameliorated motor performance in mice and significant improvement of motor response was noted following treatment with combined dose of L-dopa and melatonin [95]. A recent study also confirmed that combination of melatonin and L-DOPA reduced the doses of L-DOPA by 60%. Thus, addition of melatonin might help to lower the doses of L-DOPA which may reduce side effects caused by the chronic use of L-DOPA improving clinical outcome [95]. In 2013, Zaitone et al. [96] reported that combination of melatonin and L-DOPA also increased the level of oxidative enzymes, e.g. lipid peroxidation, glutathione and other antioxidant enzymes. Oxidative stress and free radicals from mitochondrial impairment and dopamine metabolism have been reported to play key roles in PD etiology. Studies with melatonin have reported increased antioxidant capacity of cells due to enhanced synthesis of antioxidant enzymes including superoxide dismutase, glutathione peroxidase, and glutathione reductase, and increased glutathione levels. Melatonin is reported to maintain mitochondrial homeostasis, reduce generation of oxidative species and protect the production of mitochondrial adenosine triphosphate by stimulating Complexes I and IV activities. Melatonin's neuroprotective activities have been tested successfully both in *in vivo* and *in vitro* models of PD [97,98]. Moreover, melatonin is safe at higher doses and could readily cross the blood–brain barrier [98]. The efficacy of melatonin in preventing oxidative damage in either cultured neuronal cells or in the brains of animals treated with various neurotoxic agents have suggested that melatonin could be a novel neuroprotective drug to be used in treatment of neurodegenerative disorders [99]. Melatonin production has been reported to decline in elderly people, suggesting it to be one of the primary contributing factors for development of age-associated neurodegenerative diseases, and melatonin therapy treated chronic fatigue syndrome, improved sleep and quality of life in PD patients [100]. A case reported in 2013 by De Berardis et al. [60] reported improved sleep efficiency and disappearance of intra-sleep awakening by the treatment of agomelatine in PD patients with depression.

Accumulating evidence have favored the use of melatonin in PD; however, there are some studies which have reported no efficacy of melatonin in PD. In 1999, Willis and Armstrong [101] reported that melatonin enhanced behavioral impairment and dopamine degeneration and indicated that melatonin receptor antagonist could serve to promote clinical recovery in PD. They indicated that melatonin could not be a universal remedy as suggested and may pose considerable problems in neurological diseases characterized by dopamine degeneration [101]. The finding of a study showed that chronic administration of a high pharmacological dose of melatonin was ineffective in protecting nigral dopaminergic neurons from neurotoxic effects of MPTP [102]. The rat rotenone model has been reported to reproduce many of the pathological features of the human disease, including apomorphine-responsive behavioral deficits, DA depletion, loss of striatal dopamine terminals and nigral dopaminergic neurons, and α-synuclein/

polyubiquitin-positive cytoplasmic inclusions reminiscent of Lewy bodies. Therefore, this model is well-suited to examine potential neuroprotective agents. In a review in 2008 Willis [103] reported that melatonin have a tendency to induce PD-like behavioral toxicity and presented abundant evidence to describe PD as an endocrine disorder of melatonin hyperplasia. In 2010, Tapias et al. [104] investigated the neuroprotective potential of melatonin in the rotenone PD model. The researchers noted that melatonin potentiated the striatal catecholamine depletion, striatal terminal loss, and nigral dopaminergic neuron loss. They indicted melatonin alone for causing the changes in the striatal catecholamine content. Thus, the findings of Tapias et al. suggested that melatonin is not neuroprotective in the rotenone model of PD and could even exacerbate neurodegeneration [104]. Further, some clinical studies were also attempted which have shown no therapeutic benefit with the use of melatonin in PD. The data from one of the studies demonstrated that melatonin had no significant protective effects against the long-term MPTP induced depletion of the striatal dopamine and 3,4-dihydroxyphenylacetic acid in the C57BL/6 mouse [105].

In 2005, Dowling et al. [106] conducted a multi-site double-blind placebo-controlled cross-over trial involving 40 subjects who completed a 10-week protocol. The study comprised of a 2-week screening period, 2-week treatment periods, and 1-week washouts between treatments. Actigraphy and diaries were used to assess nocturnal sleep. Epworth Sleepiness Scale (ESS), Stanford Sleepiness Scale (SSS), and General Sleep Disturbance Scale (GSDS) were used to measure daytime sleepiness and motor function. Patients received melatonin or placebo 30 minutes before bedtime. Using actigraphic measures, melatonin 50 mg significantly increased nocturnal sleep time (10 minutes) versus placebo (P < 0.05). Subjective outcome measures using the GSDS showed that melatonin 5 mg significantly improved overall sleep quality compared to placebo (P < 0.05), but this was not the case for melatonin 50 mg. Melatonin did not significantly improve excessive daytime sleepiness versus placebo, according to the ESS and Stanford Sleepiness Scale. Two patients had reported minor adverse events with melatonin. The investigators noted that although 50 mg melatonin had significantly improved total sleep time on actigraphy compared to 5 mg or placebo, the improvement was merely 10 min which might not be clinically significant [106]. In 2007, Medeiros et al. [107] also failed to detect any motor effect of melatonin. Medeiros et al. conducted a clinical study on 18 PD patients who were on Hoehn and Yahr scale from I to III. Patients were assessed for motor dysfunction using Unified Parkinson's Disease Rating Scale (UPDRS) II, III and IV before receiving treatment. Pittsburgh Sleep Quality Index (PSQI) and ESS were used to assess the subjective sleep quality and daytime somnolence, respectively. All patients received full polysomnography (PSG) test. Patients were randomly chosen to receive melatonin (3 mg) or placebo one hour before bedtime for four weeks, and test parameters were repeated at the end of treatment. The initial finding of the study showed that 14 patients (70%) had PSQI rating of more than 6, indicating poor quality sleep, and eight (40%) showed ESS rating of more than 10, suggesting excessive daytime sleepiness. PSG findings indicated increased sleep latency, REM sleep without atonia, and reduced sleep efficiency. The findings of the study suggested that melatonin had significantly improved subjective quality of sleep as evaluated by the PSQI index but because PSG ab-

normalities could not be reversed, melatonin was ineffective in treating the motor dysfunction [107]. Thus, based on these two studies, there is insufficient evidence on the efficacy of melatonin at doses of 3 to 5 mg and 50 mg for the treatment of insomnia in PD. Although melatonin at 3 to 5 mg had acceptable risk without specialized monitoring, there is an insufficient evidence for melatonin at 50 mg.

2.8. Alzheimer's disease

Alzheimer's disease (AD) is known as an old-age senile neurodegenerative disease which causes a progressive loss of cognition, memory and other neurobehavioral disorders [108]. Melatonin level has been reported to be reduced to nearly half in elderly patients with AD compared to the young control subjects [109]. In the postmortem brain from AD patients MT_1 and MT_2 immunoreactivities were found to be affected compared to age-matched controls. An increase in MT_1 and a decrease in MT_2 immunoreactivity was noted in the hippocampus of AD patients [110,111]. Accumulation of β-amyloid (Aβ) peptide in the brain is known to be involved in the pathophysiology of AD. Studies have reported antiamyloidogenic and anti-apoptotic activities of melatonin in AD [112,113]. Melatonin has been reported to inhibit Aβ fibril formation and also the production of Aβ [112]. Reduction in the levels of melatonin precursors including tryptophan and serotonin has been linked to the appearance of AD symptoms in the elderly, indicating the involvement of melatonin in the pathophysiology of AD [113]. Melatonin has been reported to upregulate the expression of messenger ribonucleic acid (mRNA) for amyloid precursor protein (APP) and the pretreatment of melatonin resulted in a significant reduction of mRNA for APP in PC12 cells [114]. A study involving the analyses of isolated-brain mitochondria from mice indicated reduction in mitochondrial Aβ levels by two- to fourfold in different brain regions, and a near complete restoration of mitochondrial respiratory rates, membrane potential, and ATP levels has been noted following the treatment of melatonin [114]. In 2012, Garcia-Mesa et al. [115] reported that administration of melatonin together with proper physical exercise could act synergistically to prevent AD symptoms [115]. In a study, melatonin was found to protect neuronal and astrocytic death induced by aggregated full length Aβ 1–40 and the fragments Aβ 25–40 and Aβ 1–28. Melatonin showed no effect on the process of fibrillation of Aβ and did not alter Aβ-induced calcium signaling in astrocytes, but significantly reduced the rate of production of Aβ-induced reactive oxygen species and also protected astrocytes against the mitochondrial depolarization. Thus, scavenging of reactive oxygen species by melatonin was indicated to be the primary effect of melatonin in protecting neurons and astrocytes against Aβ toxicity [116].

2.9. Tardive dyskinesia

Tardive dyskinesia (TD) is one of the most disturbing side effects of antipsychotic medications. The pathophysiology of TD has been reported to involve dopamine receptor supersensitivity and oxidative stress-induced neurotoxicity in the nigrostriatal system. In a study, Shamir et al. suggested the use of melatonin in the treatment of TD because of its excellent antioxidant

activities [117]. In addition, attenuation of dopaminergic activity in the striatum has been reported with melatonin use which may cause the release of dopamine from hypothalamus. This could potentially lead to prevention of the disabling side effect of antipsychotic agents [117]. A double-blind, placebo-controlled, crossover study has reported the efficacy of melatonin (10 mg/day for 6 weeks) in 22 patients with schizophrenia and TD. The study showed a significant decrease in the abnormal-involuntary-movement scale (AIMS) score compared to placebo following treatment with melatonin (10 mg/day for 6 weeks) [118]. Another randomized, double blind, placebo controlled study also reported the efficacy of melatonin (20 mg/day) for a period of 12 weeks in 7 patients with TD, and 6 PD patients receiving placebo. The AIMS score was used to assess the severity of TD initially and after 4, 8 and 12 weeks respectively. Psychiatric evaluation was also performed following the Brief Psychiatric Rating Scale. Two patients receiving melatonin showed considerable improvement (>60%) in AIMS score [119], indicating that melatonin could be beneficial in TD. However, still several studies are needed to confirm melatonin efficacy and soliciting its use in TD.

2.10. Attention-deficit/hyperactivity disorder

Sleep disorders are the most common psychiatric disorders observed in children with attention-deficit/hyperactivity disorder (ADHD). A long-term study evaluated the safety and efficacy of long-term (mean time up to 3.7 years) melatonin in children with ADHD and chronic sleep onset insomnia using questionnaires answered by parents of patients [120]. The study surveyed parents whose children were treated with melatonin on average, 3.7 years. The long-term melatonin treatment was effective against sleep problems in 88% of the cases and improved behavior and mood in 71% and 61%, respectively, with no serious adverse effects [120]. Two controlled studies further evaluated the role of melatonin in sleep disorder treatment in children with ADHD. The first study was a double-blind, placebo controlled, 30-day crossover trial conducted on 27 stimulant-treated children (6 to 14 years of age) with ADHD. Non-responders to sleep-hygiene guidelines were treated with melatonin (5 mg/day, 20 minutes before bedtime) or placebo. Patients who were given melatonin experienced significant reduction in sleep-onset latency compared to those treated with placebo. The best results were obtained when both sleep–hygiene was taken care of with melatonin intervention [121]. The second study was also a randomized, double-blind, placebo-controlled trial that recruited 105 medication-free children (6 to 12 years of age) with diagnosed ADHD and chronic sleep-onset insomnia. Participants were treated with melatonin (3–6 mg, body weight) or placebo for 4 weeks. Participants who were treated with melatonin reported significant increase in sleep-onset, total sleeping time in comparison with no significant adverse effect on the behavior, cognition, or quality of life [122]. Minor adverse effects noted with melatonin treatment were similar to placebo in either of the two studies. A review of clinical studies on efficacy and safety of melatonin in sleep disorders in children with ADHD reported melatonin to be well-tolerated and effective in pediatric patients [123]. A recent study has recommended that treatment with melatonin in chronic sleep onset insomnia in ADHD should be best reserved for children suffering from persistent insomnia. Melatonin intake may impact normal pubertal and endocrine system development in children [124].

2.11. Autism

Autism or autism spectrum disorders (ASD) is a neurodevelopmental disorder characterized by impaired social interaction, verbal and non-verbal communication, and restricted and repetitive behavior [125]. Children with a history of developmental regression are reported to develop disturbed sleep-pattern in comparison to children without regression. The regulation of sleep in children with ASD has remained poorly understood. Genetic anomaly related to melatonin synthesis and altered modulation of the synaptic transmission by melatonin which causes circadian abnormalities could cause autism in children [126,127]. A bifurcation of the sleep/wake cycle with increased sensitivity to external noise and short-sleep duration which causes irregular sleep-onset and wake-up times are also suggested in the pathogenesis of ASD. In ASD, low levels of melatonin and melatonin metabolite has been noted as compared to control subjects, and their exogenous administration have shown improvement in sleep parameters and daytime behavior, and minimized side effects [128,129]. In 2014, Rossignol and Frye provided an evidence-based exogenous use of melatonin for abnormal sleep parameters in ASD [130]. Hyperserotonemia and deficit in melatonin in 35–46% and 45–57%, respectively, have been reported of ASD patients. Both hyperserotonemia and low melatonin levels have been correlated with the disruption of serotonin–NAS–melatonin pathway which was suggested to serve as a useful biomarker for a characterization of a large group of ASD patients [131]. One of the published literatures reported three cases of autistic disorder which showed that nocturnal symptoms had improved with the use of ramelteon, a selective melatonin receptor agonist. The Clinical Global Impression-Improvement Scale for assessing insomnia and behavior showed that 2 mg dose of ramelteon improved in two cases and 8 mg dose of ramelteon in the third case, indicating that ramelteon was effective not only for insomnia, but also effectively reduced behavioral problems in patients with autistic disorder [132]. Thus, the conclusion drawn from the past and present published literatures indicates that melatonin could be an effective, safe, and a well-tolerated option to treat sleep disorders in children with ASD [133].

3. Downsides of melatonin use as novel neuropsychatric agent

Uncontrolled use of apparently any innocuous chemical substance is associated with some kind of danger. The same may also apply for melatonin use which has been largely reported as safe. However, the absence of adverse effects in healthy subjects taking melatonin for various reasons does not mean complete safety, particularly in patients who are unwell [134]. Acute exogenous administration of melatonin has been reported to cause sedation, fatigue, self-reported vigor and a reduced body temperature in healthy subjects. It is said that

the timing is critical for melatonin to be effective and if given at wrong time for sleep disorders or jet lag, it may increase daytime sleepiness and worsen mental performance. Drowsiness and a small fall in body temperature are commonly reported effects particularly after daytime administration when endogenous concentrations of melatonin are low. Melatonin use has been reported to cause headache, altered light adaptation, and loss of visual acuity and reduced vision which had improved after stopping melatonin. Melatonin use was also associated with some cases of retinal damage. Melatonin increased seizure activity in children with pre-existing neurological disorders and a recurring convulsion was reported upon continued use. Melatonin withdrawal upon chronic use was associated with tardive dyskinesia and akathisia as melatonin blocks dopamine receptors. These are some of the serious conditions associated with melatonin use which have high death rate and low recovery rate. Therefore, melatonin is recommended with caution in patients with organic brain damage. In several depressed patients, it has caused mixed affective state after taking melatonin. Confusion, hallucination, and paranoia were also associated with melatonin use. Gynecomastia has been attributed to melatonin. Increased blood glucose levels have been noted in healthy individuals and in patients with Parkinsonism who took melatonin. Melatonin treatment chronically has been reported to cause withdrawal symptoms. Unentrained sleep–wake cycle has been noted after melatonin was stopped. Involuntary movements of the lip and tongue, restlessness and insomnia developed when melatonin was abruptly withdrawn. Melatonin has been reported to interact with antidepressants. It may cause drowsiness, dizziness and acute psychosis if taken with fluoxetine, trazodone and paroxetine. If taken with amitriptyline and chlordiazepoxide, melatonin may cause lethargy, confusion, and disorientation. Overdose of melatonin may cause drowsiness, dizziness, blurred vision and confusion in patients with MDD. Fluvoxamine increases the systemic availability of oral melatonin probably by reducing first pass clearance [134].

4. Conclusion

Over the last decades, accumulating evidence from both experimental and clinical studies has highlighted immense therapeutic potential of melatonin in several diseases including CNS disorders. Neurons are highly susceptible to oxidative stresses leading to lipid peroxidation and generation of reactive oxygen/nitrogen species which are implicated in almost all the neuropsychiatric and neurodegenerative disorders. Melatonin and its metabolites, e.g. AFMK, AMK have been confirmed to have an excellent antioxidant with powerful free radical scavenging properties, making it one of the most suitable novel therapeutic agents to be tried in such disorders involving oxidative stress. A gathering body of evidence suggests that melatonin is a pleiotropic regulator molecule orchestrating diverse physiological function and involves all the melatonin receptors; however, precise pleiotropic mechanisms of melatonin remain to fully be deciphered. Ramelteon and agomelatine are two clinically successful melatonin compounds which elicit hypnotic and chronobiotic efficacy via MT_1 and MT_2 receptor.

Altered circadian rhythm due to disturbed melatonin secretion has been ascribed to development of several neurological disorders and augmented lipid peroxidation. Agomelatine therapy has been prescribed in depression associated insomnia, and ramelteon in chronic insomnia in non-psychiatric patients. Selectivity and specificity are two important components for the success of any novel compounds, and therefore, development of selective and specific melatonergic compounds are warranted to target brain disorders for which limited therapeutic options are currently available, and hence, researches involving melatonin in neuropsychiatric disorders is very promising.

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