

# The role of melatonin in mood disorders

Domenico De Berardis<sup>1-3</sup>Laura Orsolini<sup>3-5</sup>Nicola Serroni<sup>1</sup>Gabiella Girinelli<sup>1-3</sup>Felice Iasevoli<sup>3-6</sup>Carmine Tomasetti<sup>3-6</sup>Monica Mazza<sup>3-7</sup>Alessandro Valchera<sup>3-8</sup>Michele Fornaro<sup>9</sup>Giampaolo Perna<sup>10-12</sup>Monica Piersanti<sup>13</sup>Marco Di Nicola<sup>14</sup>Marilde Cavuto<sup>15</sup>Giovanni Martinotti<sup>2</sup>Massimo Di Giannantonio<sup>2</sup>

<sup>1</sup>NHS, Department of Mental Health, Psychiatric Service of Diagnosis and Treatment, Hospital "G. Mazzini", Teramo, Italy; <sup>2</sup>Department of Neuroscience, Imaging and Clinical Science, Chair of Psychiatry, University G d'Annunzio, Chieti, Italy; <sup>3</sup>Polyedra, Teramo, Italy; <sup>4</sup>United Hospitals, Academic Department of Experimental and Clinical Medicine, Polytechnic University of Marche, Ancona, Italy; <sup>5</sup>School of Life and Medical Sciences, University of Hertfordshire, Hatfield, Hertfordshire, UK; <sup>6</sup>Laboratory of Molecular Psychiatry and Psychopharmacotherapeutics, Section of Psychiatry, Department of Neuroscience, University School of Medicine Federico II, Naples, Italy; <sup>7</sup>Department of Health Sciences, University of L'Aquila, L'Aquila, Italy; <sup>8</sup>Villa S. Giuseppe Hospital, Hermanas Hospitalarias, Ascoli Piceno, Italy; <sup>9</sup>Department of Scienze della Formazione, University of Catania, Catania, Italy; <sup>10</sup>Hermanas Hospitalarias, FoRiPsi, Department of Clinical Neurosciences, Villa San Benedetto Menni, Albese con Cassano, Como, Italy; <sup>11</sup>Department of Psychiatry and Neuropsychology, University of Maastricht, Maastricht, the Netherlands; <sup>12</sup>Department of Psychiatry and Behavioral Sciences, Leonard Miller School of Medicine, University of Miami, Miami, FL, USA; <sup>13</sup>Hospital Pharmacy, Hospital G. Mazzini, ASL 4 Teramo, Italy; <sup>14</sup>Institute of Psychiatry and Psychology, Catholic University of Sacred Heart, Rome, Italy; <sup>15</sup>IASM, L'Aquila, Italy

Correspondence: Domenico De Berardis  
National Health Service, Department of Mental Health,  
Psychiatric Service of Diagnosis and Treatment,  
Hospital "G. Mazzini", Piazza Italia 1, 64100 Teramo, Italy  
Tel +39 0861 4297 08  
Fax +39 0861 4297 09  
Email dodebera@aliceposta.it

**Abstract:** Melatonin (*N*-acetyl-5-methoxytryptamine) has been discovered as a hormone secreted by the pineal gland, even though it is also synthesized in various other organs, tissues, and cells. The circadian rhythm of melatonin is often used as an indicator phase position since it is a well-defined, high-amplitude rhythm controlled by the hypothalamic suprachiasmatic nuclei. Melatonin production is controlled by this endogenous circadian timing system. It peaks during the night and is suppressed by daylight. Mood spectrum disorders, including bipolar disorder (BD), major depressive disorder (MDD), and seasonal affective disorder (SAD), have been observed to be accompanied by circadian dysregulation as well as dysregulation in melatonin secretion. Simultaneously, it has also been documented that disruptions in circadian rhythms, including the sleep/wake cycle, though environmental means can produce mood-related problems in vulnerable individuals. These findings suggested that altered circadian rhythms might be biological markers of these disorders. As melatonin is considered a chronobiotic factor, ie, able to entrain the circadian rhythms of several biological functions (eg, activity/rest, sleep/wake, body temperature, endocrine rhythms, etc), its use may provide a new therapeutic approach for the treatment of affective disorders. However, the available evidence is controversial. This review summarizes the data published so far about reliable evidence on the role of melatonin in affective disorders.

**Keywords:** melatonin, melatonergic system, mood disorders, depression, seasonal affective disorder, bipolar disorder

## Introduction

Melatonin (chemically, *N*-acetyl-5-methoxytryptamine) is an indolamine hormone isolated and characterized, in 1958, by the dermatologist Aaron Lerner who found, in extracts of bovine pineal glands, an amphibian skin-lighting factor, subsequently called melatonin due to its ability of inducing contraction of stellate amphibian melanophores.<sup>1</sup> It is mainly synthesized, as a derivative of the amino acid tryptophan, by the parenchymal cells of the pineal gland,<sup>2</sup> and then rapidly secreted into the blood vascular system and cerebrospinal fluid. Secondary sources are retina, gut, skin, platelets, bone marrow, and other structures.<sup>3-8</sup> The synthesis involves three enzymatic steps. The first is the metabolism of l-tryptophan to serotonin (or 5-hydroxytryptamine). The second step is the *N*-acetylation by the enzyme serotonin *N*-acetyltransferase (SNAT) to yield *N*-acetylserotonin. The physiological regulation of SNAT, with its sharp increase in activity at night, is considered the major regulatory step in melatonin synthesis.<sup>9,10</sup> The final step of the synthesis pathway is the conversion of *N*-acetylserotonin to melatonin by the action of the enzyme hydroxyindole-*O*-methyltransferase (HIOMT).

The day/night changes of HIOMT are less prominent; however, HIOMT gene transcription has also been described to have a day/night rhythm.<sup>11</sup>

Melatonin is secreted by the pineal gland by simple diffusion. Its lipophilicity contributes to its easy passive diffusion across cell membranes as well as through cell layers.<sup>12</sup> About 60%–70% of melatonin in the plasma is bound to albumin.<sup>13,14</sup> Its plasma half-life after intravenous infusion is about 30 minutes,<sup>15</sup> but a biphasic elimination pattern with half-lives of about 3 and 45 minutes has also been observed following oral administration.<sup>16</sup> The circulating melatonin is rapidly converted to 6-hydroxymelatonin in the liver, which clears 92%–97% of circulating melatonin in a single pass. The 6-hydroxymelatonin is then conjugated and excreted in urine. The sulfate derivative of 6-hydroxymelatonin accounts for 50%–80% of the excreted melatonin and the glucuronide derivative for 5%–30%. The remaining melatonin is excreted either unchanged (less than 1%), as 5-methoxyindoleacetic acid (0.5%), or as the nonindolic metabolite *N*-acetyl-5-methoxykynurenamine (15%).<sup>17,18</sup>

The rhythm of melatonin synthesis and secretion is entrained to a circadian period largely by the environmental alteration of light and darkness.<sup>19</sup> Light is perceived by a sub-type of retinal ganglion cells, which transmits photic stimuli to the suprachiasmatic nucleus (SCN) of the hypothalamus through the retino-hypothalamic tract.<sup>20–22</sup> The SCN, in turn, conveys the signal to the pineal gland through a multisynaptic pathway and is responsible of the circadian rhythm of melatonin, which is characterized by a gradual rise suddenly after the time of lights off and by a peak at the middle of the night (around 03:00–04:00 am), with a subsequent slow decline during the second part of the night.<sup>19</sup> This remarkable diurnal variation is also determined by the secretion of norepinephrine, released at night from postganglionic sympathetic nerves that innervate the pineal gland. The stimulation of the sympathetic nerves on the pineal gland is strictly connected to the environmental light–dark cycle.<sup>2,13</sup> Furthermore, melatonin synthesis depends upon tryptophan availability<sup>23</sup> and other nutritional factors such as folate status and vitamin B<sub>6</sub>, a coenzyme in tryptophan decarboxylation which is able to stimulate melatonin production.<sup>24–26</sup>

Melatonin acts through the activation of specific receptors which are called MT1 and MT2.<sup>27</sup> They belong to the superfamily of seven-transmembrane superfamily G protein-coupled receptors. Their activation leads to the inhibition of the adenylate cyclase with subsequent decrease of intracellular cyclic adenosine monophosphate which, in turn, provokes the inhibition of protein kinase A and of CREB protein

phosphorylation.<sup>28,29</sup> MT2 receptor additionally inhibits the soluble guanylyl cyclase pathway.<sup>30,31</sup> However, depending on the tissue and species, melatonin receptor activation can elicit a variety of second messenger cascades.<sup>27</sup> In fact, MT1 and MT2 were also found in many other tissues (eg, retina, ovary, testis, mammary gland, liver, kidney, skin, immune system, duodenum, adipocytes, myometrium, etc).<sup>3–8</sup>

Melatonin levels can be assessed by measuring its levels in blood, saliva, and by measuring its urinary metabolite, the 6-sulfatoxymelatonin (aMT6s). The most commonly used circadian melatonin phase marker is the dim light melatonin onset (DLMO).<sup>32</sup> DLMO marks the time of the beginning of one's biological night and is also useful for assessing circadian misalignment and for phase typing. It is defined as the interpolated clock time at which the ascending phase of melatonin reaches 20 pg/mL. Some authors use a cut-off of a smaller value, such as 10 pg/mL or even lower.<sup>33</sup> The phase angle difference (PAD) between DLMO and midsleep can be used as a marker for internal circadian alignment and may also be used for phase typing.<sup>34</sup>

Affective disorders such as major depressive disorder (MDD), bipolar disorder (BD), and seasonal affective disorder (SAD) are accompanied by circadian function dysregulations, including changes in biochemical (melatonin and cortisol profiles), actigraphic (sleep/wake patterns), and dimensional (chronotypes) circadian markers, which can occur during acute mood episodes as well as during euthymic periods.<sup>35–37</sup>

In fact, in addition to the classical monoaminergic hypotheses that have been long proposed to explain the pathophysiology of mood spectrum disorders, a strong association between circadian rhythms, dysregulation in melatonin secretion, and mood regulation has been suggested in the light of several preclinical and clinical findings.<sup>38–47</sup>

There is good evidence that melatonin contributes to the entrainment of the circadian rhythms of several biological functions, including activity/rest, sleep/wake, body temperature, heart rate, liver and kidney function, and endocrine rhythms.<sup>45,48–50</sup> Moreover, it is well documented that exogenous melatonin shows a good clinical response for reducing difficulties of falling asleep or improving symptoms associated with poorly coupled circadian rhythms, which may be present in the symptomatology of mood disorders.<sup>51,52</sup> According to these findings, affective disorders caused by circadian dysfunction may be theoretically treatable by manipulating the circadian system using melatonin administration.<sup>46</sup> However, there are contradictory data on its efficacy in the treatment of affective disorders.

The present review aims to provide an overview of data published so far about the potential role of melatonin in affective disorders.

## Methodology/search strategy

PubMed/Medline databases were searched by using the following sets of keywords: ([melatonin] AND [bipolar disorder OR major depression OR depression OR seasonal affective disorder OR affective disorder OR mania]). A selectively targeted literature review of English language studies was carried out. No time restrictions were placed on the electronic search covering the period up to January 2015. Secondary searches were performed using the reference list of identified papers/documents. To be included in the review, studies were required to investigate the circadian melatonin pattern (eg, its alterations) in the affective disorders (BD, MMD, or SAD). All studies not focusing on these specific topics were properly excluded, including animal studies; studies referring to melatonergic drugs; studies on population without a diagnosis of an affective disorder; studies on pregnant women, healthy subjects, or subjects affected with comorbid organic pathologies (eg, neuromuscular diseases); studies focusing on jet lag, sleep disorders, or bright light therapy. The search was performed independently by the authors. Data were compared and discrepancies were settled, if needed. Finally, data were then ranked in three macrocategories, eg, those pertaining to role of melatonin in MMD, those referring to BD, and, finally, those regarding SAD.

With the initial set of keywords, some 1,300 studies were identified. Of these, 448 were excluded because they were either focused on preclinical/animal research (328) or were not in English language (120); whilst 674 were did not meet the inclusion criteria. Out of the remaining 181 studies, 101 were excluded because they were duplicated or were not consistent with the aims of this review, leaving a total of 80 documents to be considered for inclusion in this review. A total of 49 studies were deemed of interest for MMD, of which 30 focused on circadian dysregulation in MDD (Table 1); 16 studies referred to BD, of which 8 referred to circadian dysregulation in BD (Table 2); and, finally, 15 focused on SAD, of which 9 focused on circadian dysregulation in SAD (Table 3).

## The role of melatonin in major depressive disorder

Alteration of circadian rhythms in major depression, particularly unipolar depression, were first described more than 30 years ago.<sup>53–55</sup> Several studies have later identified alterations in the melatonin secretory pattern in depression

as well as in dysthymia; firstly, this suggests that, in MDD, the endogenous circadian pacemaker is set abnormally early (misaligned) with respect to the timing of sleep.<sup>56,57</sup> However, subsequent studies have not consistently found that the endogenous circadian pacemaker is set either abnormally early (phase advanced) or late (phase delayed) in individuals with MDD<sup>58</sup> and that there is a large range of circadian dysregulation. In particular, the most consistent findings have been lower nocturnal melatonin levels,<sup>53–55,59–72</sup> phase advance<sup>62,63,70,71,73–76</sup> of melatonin onset<sup>77</sup> or peak,<sup>62,63</sup> a delay in the peak,<sup>72,75,77–80</sup> onset,<sup>63,81,82</sup> or offset<sup>78</sup> of melatonin secretion, as well as a longer duration of aMT6s excretion.<sup>78</sup>

According to these findings, therapeutic strategies aimed at resynchronizing the circadian clock of depressed patients have been developed, such as sleep deprivation and light therapy,<sup>83–86</sup> even though there are contradictory findings.<sup>87–90</sup> Furthermore, it was proposed to be a “low-melatonin syndrome”.<sup>62,91</sup> However, further studies reported that only a subgroup of depressive patients had lower melatonin levels compared to healthy subjects.<sup>62,68,92,93</sup> These patients showed an abnormal response to dexamethasone suppression test (DST).<sup>62,92,94,95</sup>

Conversely, other studies described increased levels in melatonin concentrations in depressive patients.<sup>79,81,96</sup> Therefore, it has been hypothesized that different melatonin patterns may reflect different subcategories of MDD<sup>64,82</sup> and that melatonin levels may be also related to alterations in serotonin and norepinephrine levels.<sup>97,98</sup>

Furthermore, recent studies have found a relationship between severity of unipolar depression and circadian misalignment.<sup>80,82</sup> In addition, clinical evidence that antidepressant drugs as well as mood stabilizers affect the rhythmicity of the melatonin secretion<sup>99–103</sup> has pointed to the possibility of the involvement of melatonin in the pathophysiology of MDD.<sup>98,104–108</sup>

Finally, other studies have not demonstrated significant differences in melatonin pattern nor decrease/phase shift in MDD patients compared with healthy subjects,<sup>74,95,109</sup> only reporting a nonsignificant trend toward higher melatonin levels in MDD patients compared with healthy subjects.<sup>109,110</sup>

Although preclinical<sup>111,112</sup> and some clinical<sup>113,114</sup> data supported melatonin antidepressant potentialities in rodent models, melatonin seems to lack antidepressant activity in humans.<sup>115</sup> In fact, the few studies administering melatonin to depressed patients found improvement of sleep disturbances, but no effect on depressive symptoms<sup>115,116</sup> nor an enhancing<sup>117</sup> effect of existing antidepressant therapies in patients with

**Table I** Melatonin circadian pattern in MDD: summary of the findings from literature

Author(s)	Findings
Mendlewicz et al <sup>53</sup>	• Significant lower nocturnal M levels in MDD
Wetterberg <sup>54</sup>	• Significant lower nocturnal M levels in MDD
Claustrat et al <sup>59</sup>	• Significant lower nocturnal M levels in MDD
Parry and Newton <sup>61</sup>	• Significant lower nocturnal M levels in MDD compared to HC • Estrogen treatment increases M levels whilst progesterone antagonizes these effects
Beck-Friis et al <sup>62</sup>	• Significant lower nocturnal M levels in MDD compared to HC • Phase advance of M onset in MDD
Nair et al <sup>63</sup>	• Significant lower nocturnal M levels in MDD compared to HC • Phase delay of M onset
Brown et al <sup>64</sup>	• Significant lower nocturnal M levels in MDD (melancholic subgroup) compared to HC
McIntyre et al <sup>65</sup>	• Significant lower nocturnal M levels in MDD compared to HC
Frazer et al <sup>66</sup>	• Significant lower nocturnal M levels in MDD compared to HC
McIntyre et al <sup>67</sup>	• Significant lower nocturnal M levels in MDD compared to HC
Fountoulakis et al <sup>68</sup>	• Significant lower nocturnal M levels in melancholic depressed patients compared to atypical and undifferentiated depressed
Paparrigopoulos <sup>69</sup>	• Significant lower nocturnal M levels in MDD compared to HC
Wehr et al <sup>70</sup>	• Phase advance of M onset in MDD
Buckley and Schatzberg <sup>71</sup>	• Phase advance in MDD compared to HC • Significant lower nocturnal M levels in MDD compared to HC
Khaleghipour et al <sup>72</sup>	• Significant lower nocturnal M levels in MDD compared to HC • Phase delay of M peak in MDD compared to HC
Voderholzer et al <sup>74</sup>	• No difference between night time levels of M in MDD and HC • Phase advance of M onset in MDD
Crasson et al <sup>75</sup>	• Significant lower nocturnal M levels in MDD compared to HC • Phase-shifted M secretion in MDD compared to HC • Urinary aMT6s concentrations enhanced in the morning compared to night time levels in MDD (compared to HC)
Wehr and Goodwin <sup>76</sup>	• Phase advance of M onset in MDD
Tuunainen et al <sup>78</sup>	• Correlation between delayed offset of aMT6s excretion and MDD • Phase delay of M offset in MDD
Rubin et al <sup>77</sup>	• Significant higher nocturnal M levels in MDD compared to HC
Emens et al <sup>79</sup>	• Phase delay of M onset is correlated with depression severity
Parry et al <sup>80</sup>	• Increased M secretion into the morning in MDD compared to HC • Phase delay in MDD compared to HC
Hasler et al <sup>81</sup>	• No significant group differences in the PAD between MDD and HC • A greater heterogeneity in PAD among MDD patients
Robillard et al <sup>82</sup>	• No significant group difference in the PAD between MDD and BD • Phase delay of M onset in young people with MDD and BD
Rahman et al <sup>91</sup>	• Low M secretion may desynchronize endogenous rhythms allowing subsyndromal MDD
Beck-Friis et al <sup>92</sup>	• Significant lower nocturnal M levels in MDD and BD compared to HC
Carvalho et al <sup>94</sup>	• No significant differences in M secretion between MDD and HC • No decrease nor a phase shift in MDD
Sekula et al <sup>110</sup>	• No difference between nighttime levels of M in MDD and HC • Only a trend toward higher M levels in MDD
Shafii et al <sup>96</sup>	• Significant higher nocturnal M levels in MDD compared to HC
Thompson et al <sup>109</sup>	• No difference between night-time levels of M in MDD and HC • Only a nonsignificant trend toward higher M levels in MDD

**Abbreviations:** PAD, phase angle difference; MDD, major depressive disorder; BD, bipolar disorder; HC, healthy controls; M, melatonin; aMT6s, 6-sulfatoxymelatonin.

treatment-resistant depression.<sup>118</sup> To date, according to a recent metaanalysis,<sup>119</sup> there is no clear evidence of a therapeutic or prophylactic effect of melatonin in MDD.

## The role of melatonin in bipolar disorder

Chronobiological models have contributed to a better understanding of the pathophysiology of BD. Circadian function

dysregulations, changes in the timing, and phase position are associated with BD, including melatonin secretion and sleep/wake patterns.<sup>86,98,119</sup> In particular, it has been noted that in manic patients phase alterations such as phase advance in melatonin levels<sup>120,121</sup> and delayed peak melatonin secretion are accompanied by lower melatonin levels.<sup>86</sup>

Although melatonin has proved to be a reliable marker of circadian phase, few studies have focused on this measure in

**Table 2** Melatonin circadian pattern in BD: summary of the findings from literature

Author(s)	Findings
Robillard et al <sup>82</sup>	<ul style="list-style-type: none"> <li>No significant group difference in the PAD between MDD and BD</li> <li>Longer phase delay of M onset in BD compared to MDD</li> </ul>
Lam et al <sup>87</sup>	<ul style="list-style-type: none"> <li>Significant lower nocturnal M levels in BD compared to HC and MDD</li> </ul>
Beck-Friis et al <sup>92</sup>	<ul style="list-style-type: none"> <li>Significant lower nocturnal M levels in MDD and BD compared to HC</li> </ul>
Lewy et al <sup>120</sup>	<ul style="list-style-type: none"> <li>Significant lower nocturnal M levels in BD during depressed phase</li> <li>Significant higher nocturnal M levels in BD during manic phase</li> <li>Phase advance of M onset in BD</li> </ul>
Kennedy et al <sup>121</sup>	<ul style="list-style-type: none"> <li>Significant lower nocturnal M levels in BD during depressed phase</li> <li>Significant higher nocturnal M levels in BD during manic phase</li> <li>Phase advance of M onset in BD</li> </ul>
Kennedy et al <sup>122</sup>	<ul style="list-style-type: none"> <li>No significant differences in M secretion among several BD states</li> <li>Significant lower nocturnal M levels in BD compared to HC</li> <li>No significant differences in aMT6s levels between BD and HC</li> </ul>
Souetre et al <sup>177</sup>	<ul style="list-style-type: none"> <li>Significant lower nocturnal M levels in BD during depressed phase</li> <li>Significant higher nocturnal M levels in BD during manic phase</li> <li>Restoration of M levels during the remission of BD</li> </ul>
Lewys et al <sup>123</sup>	<ul style="list-style-type: none"> <li>Significant lower nocturnal M levels in BD during depressed phase</li> <li>Significant higher nocturnal M levels in BD during manic phase</li> </ul>

**Abbreviations:** PAD, phase angle difference; MDD, major depressive disorder; BD, bipolar disorder; M, melatonin; HC, healthy controls.

BD and have yielded contradictory findings. Some studies reported phase disturbances<sup>82,86,120,121</sup> in the melatonin secretion in BD whilst others reported no phase variations.<sup>122</sup> Subjects affected by BD have demonstrated significantly lower peak nocturnal melatonin levels when compared to healthy controls<sup>86,87,92,122</sup> and unipolar depressive patients.<sup>87,122</sup> Furthermore, both euthymic and acutely ill bipolar patients have also demonstrated a hypersensitive pineal response to ocular light exposure when compared to controls.<sup>57,89</sup> Some studies, which specifically evaluated patients affected with BD, reported a reduction in melatonin secretion during the depressed phase and an increase in the manic phase of the illness whilst a restoration during the remission of symptomatology.<sup>120,121,123</sup> These findings suggested that melatonin levels in BD might be more a “trait marker” rather than a “state marker”.<sup>122</sup>

It remains unclear whether these findings indicate a primary dysfunction of the circadian timing system or whether

**Table 3** Melatonin circadian pattern in SAD: summary of the findings from literature

Author(s)	Findings
Lewy et al <sup>34</sup>	<ul style="list-style-type: none"> <li>Most SAD are phase-delayed</li> <li>A SAD subgroup is phase-advanced</li> </ul>
Lewy et al <sup>141</sup>	<ul style="list-style-type: none"> <li>Phase delay of M onset during the winter in SAD</li> </ul>
Wehr et al <sup>142</sup>	<ul style="list-style-type: none"> <li>Phase delay of M onset during the winter rather than summer in SAD</li> <li>Phase delay of M offset in SAD compared to HC</li> <li>Higher M levels in SAD compared to HC</li> </ul>
Kárádóttir and Axelsson <sup>143</sup>	
Danilenko et al <sup>144</sup>	<ul style="list-style-type: none"> <li>Higher M levels during winter in SAD compared to HC</li> </ul>
Lewy et al <sup>148</sup>	<ul style="list-style-type: none"> <li>Phase delay of M onset during the winter in SAD</li> </ul>
Terman et al <sup>149</sup>	<ul style="list-style-type: none"> <li>Phase delay of M onset in SAD</li> </ul>
Dahl et al <sup>150</sup>	<ul style="list-style-type: none"> <li>Phase delay of M onset in SAD compared to HC</li> </ul>
Checkley et al <sup>151</sup>	<ul style="list-style-type: none"> <li>No significant differences in circadian rhythms between SAD and HC</li> </ul>

**Abbreviations:** SAD, seasonal affective disorder; M, melatonin; HC, healthy controls.

they may be secondary to sleep disturbances, a prominent characteristic in BD.

Sleep disturbance is a hallmark of BD. Sleep disturbances have been associated with a worse course of illness,<sup>124,125</sup> increased symptom severity, and impairments in functioning and quality of life.<sup>124–126</sup> In fact, patients affected with BD exhibit marked reduction in sleep during the night prior to switching from depressive to manic phase of the illness.<sup>76,127–129</sup> A case report evaluation efficacy of melatonin administration in a young refractory BD patient showed relief from insomnia and manic episode.<sup>130</sup> An open-label study reported that melatonin administration was associated with increased sleep duration as well as decrease in manic symptoms.<sup>129</sup> A recent prospective naturalistic study reported sleep and mood improvement after administration of exogenous melatonin.<sup>131</sup> Melatonin did not have a beneficial effect in another study conducted on bipolar patients.<sup>132</sup>

## The role of melatonin in seasonal affective disorder or winter depression

The role of melatonin in the seasonal changes in physiology and behavior of various photoperiodic species has been extensively documented.<sup>89</sup> In fact, the seasonal alterations of the natural photoperiod at high latitudes have a repercussion on melatonin secretion,<sup>133</sup> and the melatonin rhythm is delayed during winter compared with the summer.<sup>134</sup> Some studies reported that these alterations in melatonin secretion were also found in healthy subjects.<sup>135–138</sup>

SAD or winter depression affects upward of 10% of the population at temperate latitudes.<sup>139</sup> It is characterized by



recurrent depressive episodes during the short photoperiod (usually, fall/winter months) and euthymia during spring/summer periods. Individuals with SAD are negatively affected by the shorter days and later sunrise of the winter months and develop a syndrome characterized by carbohydrate craving, lethargy, fatigue, and sadness.<sup>36</sup>

Changes in duration and/or phase of melatonin secretion during this period (the so called “phase shift hypothesis”)<sup>140</sup> were hypothesized to play a role in the pathogenesis of SAD and prompted its treatment with phototherapy.<sup>141</sup> In patients affected with SAD, the most prominent marker of seasonal variations may be represented by the change in the melatonin offset.<sup>142</sup> In fact, it seems that these patients generate a biological signal indicative of the seasonal change, like photoperiodic animals do.<sup>142,143</sup> In addition, several studies have documented higher daytime melatonin levels during the winter season in patients affected with SAD compared to healthy controls<sup>142–144</sup> and phase delay of circadian rhythms during the winter months.<sup>141,142,145–150</sup> However, other studies underlined no significant differences in circadian rhythms between SAD patients compared with the healthy controls evaluated.<sup>151</sup>

Although phototherapy is an effective treatment of SAD, because it induces a phase advancing<sup>141,144,149,150</sup> of circadian rhythms by correcting the PAD between circadian and sleep–wake schedules, the beneficial effect of this treatment does not seem to be supported by changes in melatonin.<sup>121,143,145,146,152</sup>

Studies focusing on efficacy of melatonin administration in SAD patients showed contradictory findings.<sup>153</sup> In fact, although some studies reported a significant improvement of mood symptomatology,<sup>148,154</sup> no significant differences were demonstrated after administering exogenous melatonin compared with the placebo group.<sup>155,156</sup> However, the phase shift hypothesis supports its efficacy in the treatment of seasonal circadian dysregulation in SAD patients, due to its capability to cause phase advances (when taken during evening) or phase delays (when taken during morning).<sup>34,140</sup>

## Current melatonergic drugs on the market

In the last years, advances in medicinal chemistry led to the discovery of compounds that are specific and selective agonists and antagonists for melatonin receptors. Amongst them, some melatonergic drugs are on the market and are currently used in the clinical practice whilst others are also under evaluation (Table 4).<sup>157–175</sup>

For a more comprehensive review see Carocci et al.<sup>176</sup>

## Discussion and summary

The present narrative review aimed to summarize available evidence on circadian melatonin dysregulation in affective disorders. However, the findings provided here include a large number of contradictory data. Most of the studies

**Table 4** Current melatonergic drugs on the market or under evaluation

Melatonergic drug	Trade names	Approval	Pharmacological actions	Chronobiotic effects	Clinical effects	
					Sleep	Mood
Agomelatine (Servier)	Valdoxan® Melitor® Thymanax®	EMA (2009)	MT <sub>1</sub> /MT <sub>2</sub> nonselective agonist 5-HT-2 <sub>c</sub> antagonist 5-HT-2 <sub>a</sub> antagonist	Phase advance and entrains circadian system	Significant benefits in MDD	Significant benefits in MDD and SAD
Ramelteon (Takeda Pharmaceutical Company)	Rozerem®	FDA (2005)	MT <sub>1</sub> /MT <sub>2</sub> nonselective agonist	Phase advance	Significant benefits in insomnia	N/A
Tasimelteon (VEC-162; Vanda Pharmaceuticals)	Hetlioz®	FDA (2014)	MT <sub>1</sub> /MT <sub>2</sub> nonselective agonist	Phase advance and phase delay	Significant benefits in non-24-hour sleep–wake disorder	N/A
TIK-301 (PD-6735, LY-156, 735; Tikvah Pharmaceuticals)	–	–	MT <sub>1</sub> /MT <sub>2</sub> nonselective agonist	Promotes phase advance	Significant benefits in insomnia	N/A
UCM765	–	–	MT <sub>2</sub> selective partial agonist	N/A	N/A	N/A
IIK7	–	–	MT <sub>1</sub> /MT <sub>2</sub> full agonist	N/A	N/A	N/A
UCM793	–	–	MT <sub>1</sub> /MT <sub>2</sub> nonselective agonist	N/A	N/A	N/A
UCM924	–	–	MT <sub>2</sub> selective partial agonist	N/A	N/A	N/A
Neu-PII (Neurim Pharmaceuticals Ltd)	–	–	MT <sub>1</sub> /MT <sub>2</sub> nonselective agonist	N/A	N/A	N/A

**Abbreviations:** EMA, European Medicines Agency; MT, melatonin receptor; MDD, major depressive disorder; SAD, seasonal affective disorder; N/A, not available; FDA, US Food and Drug Administration.

retrieved present a greater heterogeneity in sample number and characteristics and in inclusion and exclusion criteria. For example, the extreme variability in melatonin pattern in MDD may suggest, both, the existence of different subgroups of depressive patients (eg, with different degrees of severity or a seasonal vulnerability) and an inaccurate initial selection of MDD patients (eg, an inclusion of subsyndromal BD or SAD patients). In addition, it could be argued that most data may be influenced by the choice of the age of the sample. In fact, a different circadian alignment according to the age has been reported. Another limitation may be represented by the small sample size used in most studies analyzed here, which may limit the generalizability of data.

SAD and mood disturbances (MDD and BD) caused by circadian malfunction are theoretically treatable by manipulating the circadian system using chronobiotic drugs, chronotherapy, or bright light therapy. There is no doubt that melatonin has chronobiotic properties as well as the ability to induce transient sleepiness or sleep. However, very few and contradictory evidence exist about its role in mood disorders and its potentiality in the treatment of these disorders. In fact, although melatonin appears to be well tolerated and is an effective treatment for a number of sleep disorders related to circadian rhythm disturbance, there is no conclusive confirmation about its efficacy in the treatment of mood disorders. However, due to the well-documented alterations in circadian rhythms and in melatonin secretion in mood disorders, more effective melatonin analogs (eg, agomelatine, tasimelteon, etc) have been developed and studied in order to obtain a reliable and effective drug for the treatment of mood disorders.

Further studies are necessary in order to better characterize the effect of exogenous melatonin and novel melatonergic drugs on the circadian system of MDD, BD, and SAD patients.

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