

## *Antidepressant chronotherapeutics for bipolar depression*

Francesco Benedetti, MD



*Chronotherapeutics refers to treatments based on the principles of circadian rhythm organization and sleep physiology, which control the exposure to environmental stimuli that act on biological rhythms, in order to achieve therapeutic effects in the treatment of psychiatric conditions. It includes manipulations of the sleep-wake cycle such as sleep deprivation and sleep phase advance, and controlled exposure to light and dark. The antidepressant effects of chronotherapeutics are evident in difficult-to-treat conditions such as bipolar depression, which has been associated with extremely low success rates of antidepressant drugs in naturalistic settings and with stable antidepressant response to chronotherapeutics in more than half of the patients. Recent advances in the study of the effects of chronotherapeutics on neurotransmitter systems, and on the biological clock machinery, allow us to pinpoint its mechanism of action and to transform it from a neglected or "orphan" treatment to a powerful clinical instrument in everyday psychiatric practice.*

© 2012, LLS SAS

*Dialogues Clin Neurosci.* 2012;14:401-411.

**Keywords:** bipolar disorder; antidepressant; sleep deprivation; light therapy; sleep phase advance; dawn simulation; serotonin; glutamate; dopamine; noradrenaline

**Author affiliations:** Department of Clinical Neurosciences, Scientific Institute and University Vita-Salute San Raffaele, Milan, Italy

### The need for chronotherapeutics

**C**hronotherapeutics refers to treatments based on the principles of circadian rhythm organization and sleep physiology,<sup>1,2</sup> which control the exposure to environmental stimuli that act on biological rhythms, in order to achieve therapeutic effects in the treatment of psychiatric conditions.<sup>3</sup> These nonpharmaceutical and biologically based clinical interventions include manipulations of the sleep-wake cycle such as sleep deprivation (SD) and sleep phase advance (SPA), and controlled exposure to light and dark. The use of these techniques in everyday clinical practice is almost exclusively limited to the treatment of mood disorders, offering mental health practitioners a set of nonpharmaceutical, rapid, and effective antidepressant modalities for monotherapy or as adjuvants to conventional medication.<sup>1,4</sup> Interest in the clinical use of these techniques stemmed from their efficacy, rapidity of action, and lack of side effects, and also from the possibility of achieving long-lasting therapeutic effects by combining the different chronotherapeutic interventions among themselves or with conventional psychiatric treatments.<sup>5</sup> Clinical treatment algorithms in everyday psychiatric settings that include chronotherapeutic techniques and the monitoring of chronobiological variables proved to be useful to predict outcomes, speed up recovery, shorten hospitalization, and reduce the clinical need for changes in drug prescriptions.<sup>6-9</sup> The results observed in clinical trials pro-

**Address for correspondence:** Francesco Benedetti, MD, Istituto Scientifico Universitario Ospedale San Raffaele, Dipartimento di Neuroscienze Cliniche, San Raffaele Turro, Via Stamira d'Ancona 20, 20127 Milano, Italy (e-mail: benedetti.francesco@hsr.it)

# Clinical research

duced a positive answer to early doubts about the therapeutic usefulness of chronotherapeutics<sup>10</sup> and about the temporary nature of the achieved benefits.<sup>11</sup>

These effects of chronotherapeutics have been particularly evident in difficult-to-treat conditions such as bipolar depression, which has been associated with extremely low success rates of antidepressant drugs in naturalistic settings.<sup>12</sup> Bipolar patients spend a substantial proportion of their time ill,<sup>13</sup> with depression representing their predominant abnormal mood state,<sup>14</sup> but with the repeated use of antidepressant drugs being related to poor prospective response to naturalistic treatment.<sup>15</sup> The clinical need for treatment of their disabling condition and the interplay between the risk of treatment-emergent mania<sup>16,17</sup> and the risk of relapse when discontinuing drug treatments<sup>18</sup> often leads to prolonged and highly complex medication regimens to achieve a sustained response.<sup>19</sup> Nevertheless, there is still a real clinical need for fast-acting antidepressant effects to counteract the rapid breakthrough depression experienced by the patients: hence the interest in chronotherapeutics, which act without the delay inherent to traditional antidepressant treatments.<sup>3,20</sup>

Paralleling these clinical achievements in recent years, basic research in the last decade has substantially improved knowledge about the biological mechanisms that control the molecular machinery of the master clock,<sup>21</sup> and link it with the neurotransmitter systems that are involved in mood regulation and targeted by antidepressant drugs.<sup>22</sup> Confirming the classical belief that man and his environment are inseparable, it is now established that exposure to environmental stimuli that act on the transcription of clock genes will lead to major changes in the same brain neurotransmitter function involved in psychiatric conditions,<sup>3</sup> and that from a clinical point of view the choice will be restricted between the potentially detrimental random exposure to these stimuli, which could even precipitate bipolar illness episodes,<sup>23,24</sup> and the direct control by the psychiatrist in order to achieve a therapeutic effect.

The present review focuses on recent achievements in the chronotherapeutic treatment of bipolar depression and on the recently discovered molecular mechanisms that clearly link chronotherapeutics with the usual antidepressant drug treatments of this disorder.

## Techniques

The first studies published in clinical samples used single chronotherapeutic techniques to treat depression,

but the clinical need for rapid and sustained improvement of patients prompted the combination of different techniques among themselves and with usual antidepressant drug treatments.

## Sleep deprivation

Antidepressant effects of sleep deprivation were first reported in 1959,<sup>25</sup> but the first experimental trials to test its clinical efficacy were performed in the 1970s.<sup>26,27</sup> The amazingly rapid effects of the treatment, which is usually able to restore euthymia in the morning soon after a single night awake, are closely linked to the wake period and are usually rapidly lost after restoring an undisturbed night sleep.<sup>11</sup> To achieve the best results the wake period includes the extension of daytime wakefulness into the night, and lasts about 36 hours until the evening of the day after (total sleep deprivation), but it can also be limited to the second half of the night and the following day, thus allowing sleep during the first half of the night,<sup>28</sup> with little disadvantage<sup>29</sup>: in both cases, the mood amelioration is obtained during the prolonged wake, and in the presence of light.<sup>30</sup> This link between mood and wake, together with the observation that during the nights of undisturbed sleep patients sleep better and deeper than usual,<sup>31</sup> justified the recent use of the term “wake therapy” to refer to this treatment.<sup>2</sup>

In the absence of combined treatments, not more than 5% of responders to wake will maintain a stable euthymia in the days of subsequent normal sleep,<sup>20</sup> thus limiting the diffusion of this technique alone.<sup>32</sup> Soon in the early studies, however, SD was observed to produce rapid benefits in the broadly defined depressive syndrome: in endogenous, reactive, unipolar, bipolar, secondary, and schizoaffective depression; in the elderly and in children; in depression secondary to Parkinson's disease or schizophrenia; or associated with pregnancy and postpartum and premenstrual dysphoric disorder,<sup>10,20</sup> and with better effects observed in endogenous primary depression compared with reactive and/or secondary depression, and in the treatment of Bipolar Disorder compared with Primary Depressive Disorder.<sup>33</sup>

In order to prevent the relapse into depression after SD, single-night SD or repeated SD was combined with serotonergic antidepressants, lithium salts, or other chronotherapeutic techniques.<sup>4</sup> The simple repetition of SD over time has been tested for many schedules, including twice in 1 week,<sup>34</sup> or twice a week for 3 weeks<sup>35,36</sup> or

for a month,<sup>37</sup> or for twice in 1 week followed by partial SD twice,<sup>38</sup> etc. Repeated SD once a week has also been proposed as a prophylactic treatment: preliminary studies in small samples showed that SD reduced the frequency of relapses and increased the duration of normothymia in roughly one half of the patients.<sup>39,40</sup>

Our group developed a treatment schedule based on repeated total SD, three times during 1 week, resulting in a lengthening of the sleep-wake period from the usual 24 to 48 hours.<sup>41-49</sup> When combined with light therapy and with lithium salts, the mainstay for the long-term treatment of bipolar disorder, this therapy is able to trigger an acute response also in patients drug resistant to both serotonergic and tricyclic antidepressants, and to lead to a stable euthymia for 9 months in roughly 60% of bipolar patients without a history of drug resistance.<sup>47</sup> Despite early concerns due to the close link between sleep loss and the onset of mania,<sup>50</sup> this result is achieved with a risk of switch which is around 6% and leads to easily controlled manic reactions,<sup>51</sup> thus comparable to the reported switch rate for placebo. Considering the 15%-to-25% risk of treatment-emergent mania linked with antidepressant drug treatment in bipolar patients,<sup>16,17</sup> and the 30% of responders maintaining euthymia when discontinuing drug treatments before 6 months,<sup>18</sup> these data warrant the highest clinical interest in using these techniques as first-choice treatments for bipolar depression.

### Light therapy

The scientific approach to the treatment of depression with bright light started in the 1980s.<sup>52-54</sup> Early on, antidepressant bright light therapy (LT) was administered 1 to 2 hours before the usual time of awakening.<sup>55</sup> This phase-advancing administration of light in the early morning was then proven to have better antidepressant effects than the simple increase of the subjective photoperiod obtained by exposing the patients to light in the evening.<sup>56</sup> A correlation was then observed between the magnitude of phase advances to morning LT and improvement in depression ratings, with maximum effects with phase advances of 1.5 to 2.5 hours (about 7.5 to 9 hours after the dim-light melatonin onset the evening before).<sup>57</sup> Since scores on the Morningness-Eveningness Questionnaire (MEQ) are strongly correlated with sleep midpoint and melatonin secretion, a predictive algorithm based on MEQ scores was then developed to define the individual optimal timing of LT

administration,<sup>58</sup> and proven successful even when used in common clinical settings, and when giving light in combination with antidepressants.<sup>59</sup> Over the years, other treatment algorithms have been proposed,<sup>60</sup> and research is currently identifying the most effective treatment schedule as a function of seasonality and other individual characteristics.<sup>61</sup>

Given that LT is, however, useful, even when given at midday,<sup>62</sup> the clinical use of LT followed a pattern of evolving applications in any kind of depressive syndrome.<sup>63</sup> The APA Committee on Research on Psychiatric Treatments<sup>64</sup> and a Cochrane review<sup>65</sup> concluded that light treatment for nonseasonal major depression is efficacious, with effect sizes equivalent to those in most antidepressant pharmacotherapy trials. When combined with standard antidepressant drug treatments LT hastens recovery, with benefits that can be perceived by the patients during the first week of treatment.<sup>59,66</sup> After 1 month of treatment, patients treated with light show a net benefit, in respect to placebo, that can be quantified in an approximately 30% better reduction in the severity of depression: remarkably, these values are very similar for early studies performed with the combination of light and tricyclic antidepressants, and for new studies combining light and selective serotonergic drugs.<sup>59,66,67</sup> The benefit is also clinically evident in drug-resistant patients, when adding light to ongoing albeit ineffective antidepressants.<sup>68</sup> Similar to SD, LT in nonseasonal major depression does not show a sustained effect after discontinuation, with a complete offset of effect after 1 month,<sup>69</sup> but the relapse can be easily prevented when combining LT with common antidepressant drugs.<sup>70</sup> Again, similarly to SD, LT caused marked benefits in the broadly defined depressive syndrome, including very different psychopathological conditions such as antepartum depression<sup>71</sup> as well as post-stroke depression in the elderly.<sup>72</sup> In the case of bipolar depression, the efficacy of LT alone is questioned, with studies showing either better benefits than in unipolar patients,<sup>73</sup> or worse effects,<sup>74</sup> but the combination of LT with other chronotherapeutic techniques and with lithium salts was proven to lead to stable mood ameliorations and euthymia, even in drug-resistant patients.<sup>45,47</sup> Moreover, some observations suggested that bipolar patients could be sensitive to the antidepressant properties of light at intensities as low as 300 to 500 lux,<sup>45,73</sup> far below the usual 10000-lux standard used in LT of unipolar patients: a finding in agreement

# Clinical research

with the proposed supersensitivity of the biological clock to the effects of light as a possible trait marker for bipolar disorder.<sup>75</sup>

Other studies explored the interaction of LT with the circadian changes of sensitivity of the biological clock to the effects of light and defined “dawn simulation” protocols based on the administration of low intensity (400 lux) LT during the last period of the patient’s sleep episode, a treatment with a comparable efficacy to that of bright white LT.<sup>76,77</sup>

## Sleep phase advance and combined treatments

Antidepressant effects of sleep phase-advance (SPA) have been predicted by chronobiological studies of depression (suggesting a misalignment between the biological clock, biological rhythms, and the sleep-wake rhythms) and first described in 1979<sup>78</sup>: the simple act of going to bed and waking up 5 hours earlier leads to a sustained marked improvement of mood in a bipolar depressed patient, an effect then confirmed in unipolar endogenous depression.<sup>79</sup> Remarkably, recent studies on large samples in the general population showed that earlier parental set bedtimes are a protective factor against depression and suicidal ideation during adolescence,<sup>80</sup> thus suggesting a major role for the disruption of the circadian timing in the pathophysiology of depression.<sup>81</sup> Probably because of the difficult match of a phase-advanced sleep schedule with social and environmental cues and expectations, SPA has never spread into clinical settings. When combined with a previous SD, SPA is however able to sustain its effects and prevent the relapse that might occur after restoring night sleep.<sup>82</sup> A short SPA protocol, performed over 3 days, has been shown to be sufficient to achieve this effect and to be synergistic with lithium salts in sustaining a stable euthymia in bipolar depressed patients.<sup>83</sup> This protocol can easily be associated with antidepressant medications,<sup>84</sup> and more recent pilot trials explored the possibility of a “triple chronotherapeutics” for bipolar depression: SD followed by SPA and combined with morning LT, given as adjunctive treatment to lithium and antidepressants, significantly enhanced antidepressant response.<sup>85</sup>

## Mechanisms of action

The mechanism of action of chronotherapeutics has been widely explored for SD, and suggests convergence

of effects between SD and all known antidepressant strategies. Many effective antidepressant treatments target several mechanisms, and a multitarget approach to treatment could overall be better suited for a multifactorial illness such as depression<sup>86</sup>: chronotherapeutics is no exception, and is able to influence the same mechanisms that are targets for other antidepressants.

## Brain monoamines and glutamate

SD potentiates all the monoaminergic systems that are targeted by antidepressant drugs and that have been involved in the pathogenesis of depression, and effects of SD on monoamines are part of its mechanism of action. Research on this topic directly measured changes in monoaminergic neurotransmission in animal models, or studied SD effects in humans with challenge methods, brain imaging, or pharmacogenetic approaches. These methods allowed definition of convergent effects in animal and humans, either healthy or depressed, of SD on serotonin (5-HT), noradrenaline (NA), and dopamine (DA).

In animal models, SD increase 5-HT neurotransmission<sup>87</sup> by enhancing the activity of 5-HT neurons in the dorsal raphe nucleus,<sup>88</sup> increasing brain extracellular 5-HT<sup>89</sup> and 5-HT turnover,<sup>90-92</sup> reducing the sensitivity of 5-HT<sub>1A</sub> inhibitory autoreceptors,<sup>88,93</sup> and increasing the behavioral responsiveness to 5-HT precursors.<sup>94</sup> In a similar way, SD was shown to increase synaptic levels of NA<sup>95</sup> and tyrosine hydroxylase and NA transporter mRNA in the locus coeruleus,<sup>96</sup> and to increase DA activity and behavioral response to DA agonists,<sup>97,98</sup> with an increase of DA receptor binding sites during the early stages of SD (following 12 to 24 hours awake)<sup>99</sup> and a subsequent subsensitivity after more prolonged wake,<sup>100</sup> suggesting downregulation after prolonged stimulation.

Clinical psychobiology confirmed these effects in depressed humans and linked them with the efficacy of chronotherapeutics. SD increased the prolactin response to intravenous tryptophan infusion<sup>101</sup> and decreased plasma levels of prolactin, which is inhibited by DA agonists, thus suggesting DA hyperactivity during SD.<sup>102,103</sup> D2 receptor occupancy decreased in responders to SD, thus suggesting an enhanced DA release in responders,<sup>104</sup> levels of homovanillic acid in the spinal fluid predicted the clinical effects of SD,<sup>105</sup> and eye-blink rate after SD increased in responders, suggesting DA activation.<sup>106</sup> The NA metabolites 3-methoxy-4-hydroxyphenylglycol (MHPG) and MHPG sulfate<sup>107</sup> increased after SD pro-



portionally to severity of depression<sup>108</sup> and clinical response to treatment.<sup>109</sup> Human pharmacogenetics confirmed that gene variants that improve neurotransmission by increasing receptor or transporter density, or decreasing neurotransmitter degradation, also improve the clinical efficacy of SD in bipolar depression when given alone or combined with bright light therapy. This was proven for genotypes influencing the density of the 5-HT transporter<sup>110-112</sup> and of the 5-HT<sub>2A</sub> receptor,<sup>113</sup> or the efficiency of the catechol-O-methyltransferase (COMT) in clearing NA and DA from the synapse.<sup>114</sup> Interestingly, the role of these genetic influences has effect sizes comparable to those observed on response to antidepressant drugs,<sup>115-117</sup> thus strongly suggesting a shared mechanism of action of chronotherapeutics and monoaminergic drugs.

Following this line of reasoning, the most striking confirmations of shared influences on monoamines come from combined treatments with chronotherapeutics and drugs. SD showed synergistic interactions with drugs that increase the activity of brain 5-HT,<sup>42,43,85</sup> NA,<sup>118</sup> and DA<sup>46</sup> systems; conversely, DA antagonists block the behavioral<sup>119</sup> and antidepressant<sup>120</sup> effects of SD. Similar synergistic effects have been described for light therapy, which significantly potentiates serotonergic antidepressants,<sup>59,66</sup> is influenced by genotypes influencing the density of the 5-HT transporter,<sup>112</sup> and can prevent the mood-lowering effect of acute tryptophan depletion, which reduces brain 5-HT.<sup>121</sup>

Finally, an increasing interest on glutamatergic neurotransmission in depression stemmed from trials reporting antidepressant effects of the NMDA antagonists ketamine<sup>122</sup> and the glutamatergic modulator riluzole.<sup>123</sup> Glutamatergic neurotransmission follows a strict circadian rhythm, and in animal models it is first enhanced and then markedly depressed during SD.<sup>124</sup> In vivo single proton magnetic resonance spectroscopy (1H-MRS) indicated that glutamatergic transmission is altered by SD, as shown by reduced glutamate concentrations, the changes being proportional to both perceived and observed mood amelioration in bipolar depression.<sup>125</sup> Remarkably, these effects were observed in the anterior cingulate cortex, a brain area which has been widely implicated in providing a neural basis for mood-congruent cognitive biases in depression,<sup>126</sup> and where chronotherapeutics was shown to profoundly change metabolism<sup>127,128</sup> and neural reactivity to stimulus words<sup>48</sup> in responders to treatment.

### **Biological clock and long-lasting effects on biological rhythms**

The hypothesis that several psychiatric conditions may involve primary or secondary changes in biological clocks,<sup>129</sup> and the observations that biological rhythms show a range of abnormalities in mood disorders,<sup>130</sup> make the biological clock a primary candidate to explain the mechanism of action of chronotherapeutic techniques. The molecular machinery which constitutes the biological master clock in the suprachiasmatic nuclei (SCN) is being elucidated,<sup>131</sup> but the systematic study of the relationship between clock and therapeutic interventions in psychiatry is just beginning.<sup>132</sup>

Growing evidence supports the hypothesis that changes in brain monoaminergic functioning influence the function of the biological clock molecular machinery, and the clock and the control of biological rhythms are emerging targets for antidepressant drug treatment.<sup>133,134</sup> New animal models have been used to test the interactions between circadian genes and mood-related neurotransmitter systems, and, conversely, to explore the effects of light on brain circuitries and of antidepressant and mood-stabilizing drugs on the clock.<sup>22</sup> Serotonin modulates the response of the circadian system to light and mediates modification of the period and phase of the central clock by behavioral arousal, while, in turn, the biological clock gene network is expressed in serotonergic raphe neurons,<sup>135</sup> with a close interplay between the two systems leading to strong circadian and seasonal rhythms in serotonergic function.<sup>136</sup> Dopaminergic activity also follows a strong rhythm, and manipulations of clock genes within brain dopaminergic structures leads to abnormal animal behaviors that closely resemble human bipolar disorder,<sup>137-139</sup> while some genetic variants of the same clock genes are associated with a worse bipolar phenotype in human patients.<sup>140,141</sup> The locus coeruleus produces a relatively constant tonic noradrenergic firing throughout all behavioral states, except during rapid eye movement (REM) sleep when NA discharge is absent,<sup>142</sup> and it was hypothesized that modifications of NA activity during chronotherapeutics could be necessary for its effects.<sup>99,143</sup>

Remarkably, all antidepressant chronotherapeutic interventions cause a phase advance of biological rhythms. Light therapy in the morning is the main environmental synchronizer of the internal clock and influences timing and entrainment of the SCN circadian clock by inducing

# Clinical research

CREB.<sup>144</sup> The circadian pacemaker is sensitive to short-duration light pulses with a nonlinear relationship between light duration and the amount of resetting, and a 1-hour bright white light pulse phase shifts the circadian pacemaker following a clear-cut phase-response curve<sup>145</sup>: phase advances are obtained when administering light in the morning, and phase delays when administering it in the evening (the so-called type I phase response).<sup>146</sup> SD directly targets the sleep-wake rhythm and can influence SCN function by modifying vigilance state transitions and sleep states,<sup>147</sup> specifically modifies the binding of the molecular components of the biological clock,<sup>148</sup> and is clinically synergistic with the administration of phase-advancing morning light<sup>149</sup>: in agreement with these findings, an actimetric advance of the activity-rest circadian cycle correlates with positive antidepressant response to SD.<sup>49</sup> Surprisingly, very little data are available on the effects of antidepressant drugs on the biological clock, but a single study showed that fluoxetine induces a phase advance of the SCN in rats,<sup>150</sup> while the antidepressant agomelatine can induce a phase advance in normal humans,<sup>151</sup> thus supporting the hypothesis that chronotherapeutics and drug-induced changes on monoaminergic function may result in similar long-lasting effects on the master clock of depressed patients, possibly correcting yet poorly understood abnormalities in the phase-angle relationships between biological rhythms.<sup>81,152</sup>

## Brain plasticity and metabolism

Genes of the biological clock are expressed in many brain structures other than in the SCN<sup>153,154</sup> and their genetic variants can bias “non-clock” brain functions such as information processing and decision making in bipolar depression.<sup>155</sup> Several findings suggest that at the cellular level clock genes could provide a mechanism for the control of circadian gene expression and of responsiveness to stimuli,<sup>156</sup> which in psychiatric conditions may influence the complex relationship between susceptibility and precipitating factors for depression, thus biasing core characteristics of the illness such as age at onset,<sup>157</sup> recurrence of illness,<sup>158</sup> or its occurrence in specific risk periods such as the postpartum period.<sup>159</sup>

The close link between the clock machinery and core metabolic cellular processes is confirmed by the study of protein modulators such as glycogen synthase kinase 3- $\beta$  (GSK3- $\beta$ ), which is a core constituent of the mammalian circadian clock and affects circadian rhythm gen-

eration by modifying the stability of circadian clock molecules.<sup>160</sup> This kinase is also an essential element of the Wnt/beta-catenin pathway, which is involved in the control of gene expression, cell behavior, cell adhesion, and cell polarity, and plays major roles in neurodevelopment and in regulation of neuronal polarity, neuronal plasticity, and cell survival.<sup>161</sup> It regulates the activity of many targets including transcriptional factors, enzymes, and cytoskeletal proteins,<sup>162</sup> and is considered a primary regulator in a range of cellular processes including differentiation, growth, motility, and apoptosis.<sup>163</sup> GSK-3 influences the susceptibility of neurons to harmful stimuli (neuronal resilience), because increasing GSK-3 activity increases apoptosis in neuronal cells, while inhibiting GSK has neuroprotective effects,<sup>164</sup> and because its inhibition occurs in response to brain-derived neurotrophic factor (BDNF) and other neurotrophins.<sup>165</sup>

These mechanisms provide a target for the convergent effects of chronotherapeutics and antidepressant drugs on the biological clock and on neurotransmitter systems. Control of the phosphorylation/activity status of GSK-3 $\beta$  is considered an important mechanism of serotonin (5-HT) and dopamine (DA) action on brain and behavior,<sup>166</sup> because GSK3- $\beta$  is inhibited by lithium, valproate, and several antidepressants such as selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, and tricyclic antidepressants.<sup>165,167</sup> Confirming the role of these mechanisms for bipolar disorder and chronotherapeutics, promoter gene variants were associated with less detrimental clinical features, including a delayed onset of illness,<sup>168</sup> a better clinical response to lithium,<sup>169,170</sup> and a better response to sleep deprivation<sup>171</sup>: this effect was so strong as to overcome the detrimental influence on SD response of genotypes negatively affecting serotonergic function.<sup>111,172</sup>

Molecular mechanisms involved in brain plasticity are likely to play a major role in antidepressant response and long-term mood stabilization of bipolar patients.<sup>173</sup> Accumulating evidence suggests then that plastic processes occurring during wakefulness result in a net increase in synaptic strength in many brain circuits, and that synaptic strength is downscaled to baseline levels during sleep,<sup>174</sup> when effective cortico-cortical connectivity is broken down.<sup>175</sup> In agreement with the predictions of this “synaptic homeostasis hypothesis” of sleep,<sup>176</sup> a recent study showed that in healthy humans prolonged wakefulness is associated with significant changes in the state of cortical circuits involving a steady

increase in the excitability of human cortical circuits that is rebalanced during sleep.<sup>177</sup> These effects have been related with the circadian rhythms of glutamatergic neurotransmission and with increased synaptic weights in animal models,<sup>178</sup> thus supporting the hypothesis that these mechanisms could provide a new basis in conceptualizing the link between chronotherapeutics and brain homeostasis in bipolar depression.

### Conclusion

In conclusion, chronotherapeutics has now been proven to be a powerful clinical instrument for the treatment of depression in everyday clinical practice. Rapidity of effects and lower rates of switch into mania with respect

to available antidepressant drugs make chronotherapeutic combinations a first-choice option for the hospital treatment of patients with a major depressive episode in the course of bipolar disorder. Antidepressant efficacy in nearly one half of drug-resistant patients makes it mandatory for the clinician to prescribe these treatments to these difficult-to-treat patients. Single techniques, such as light therapy, can be easily prescribed to outpatients in combination with the usual antidepressant drug treatments. In all cases, chronotherapeutic techniques should be combined with mood-stabilizing treatments, such as lithium salts, which are the mainstay of the long-term psychiatric management of bipolar disorder and which can enhance and sustain the acute antidepressant effects of chronotherapeutics. □

#### **Cronoterapia antidepressiva para la depresión bipolar**

*La cronoterapia se refiere a los tratamientos basados en los principios de la organización del ritmo circadiano y de la fisiología del sueño, mediante el control de la exposición a los estímulos ambientales que actúan sobre los ritmos biológicos con el fin de conseguir efectos terapéuticos en el tratamiento de los cuadros psiquiátricos. Esta terapia incluye manipulaciones del ciclo sueño-vigilia como la privación de sueño y el avance de fase, junto con la exposición controlada a la luz y a la oscuridad. Los efectos antidepressivos de la cronoterapia son evidentes en cuadros de difícil tratamiento como la depresión bipolar, la cual se ha asociado con resultados de éxito extremadamente bajos para los fármacos antidepressivos en estudios naturalísticos y con una respuesta antidepressiva estable a la cronoterapia en más de la mitad de los pacientes. Avances recientes en el estudio de los efectos de la cronoterapia en los sistemas de neurotransmisión y en la maquinaria del reloj biológico, permiten identificar su mecanismo de acción y transformarla desde un rechazo o un "tratamiento huérfano" a un poderoso instrumento clínico en la práctica psiquiátrica cotidiana.*

#### **Chronothérapie antidépressive pour la dépression bipolaire**

*La chronothérapie se rapporte aux traitements dont les principes reposent sur l'organisation des rythmes circadiens et la physiologie du sommeil, qui contrôlent l'exposition aux stimuli environnementaux agissant sur les rythmes biologiques, afin de pouvoir traiter les pathologies psychiatriques. Elle comprend des manipulations du cycle veille-sommeil comme la privation de sommeil et l'avance de phase du sommeil ainsi qu'une exposition contrôlée à la lumière et à la nuit. Les effets antidépresseurs de la chronothérapie sont évidents dans des pathologies difficiles à traiter comme la dépression bipolaire, qui a été associée à des taux de succès extrêmement faibles des antidépresseurs dans les échantillons naturalistes et à une réponse antidépressive stable à la chronothérapie chez plus de la moitié des patients. Des progrès récents dans l'étude des effets de la chronothérapie sur les neurotransmetteurs et sur l'horloge biologique nous permettent d'identifier son mécanisme d'action et de faire de ce traitement « orphelin » ou négligé un instrument clinique puissant en pratique psychiatrique quotidienne.*

# Clinical research

## REFERENCES

1. Wirz-Justice A, Terman M. Chronotherapeutics (light and wake therapy) as a class of interventions for affective disorders. *Handb Clin Neurol*. 2012;106:697-713.
2. Wirz-Justice A, Benedetti F, Berger M, et al. Chronotherapeutics (light and wake therapy) in affective disorders. *Psychol Med*. 2005;35:939-944.
3. Benedetti F, Barbini B, Colombo C, Smeraldi E. Chronotherapeutics in a psychiatric ward. *Sleep Med Rev*. 2007;11:509-522.
4. Wirz-Justice A, Benedetti F, Terman M. *Chronotherapeutics for Affective Disorders. A Clinician's Manual for Light and Wake Therapy*. Basel, Switzerland: Karger; 2009.
5. Wirz-Justice A. Chronobiology and mood disorders. *Dialogues Clin Neurosci*. 2003;5:315-325.
6. Benedetti F, Barbini B, Campori E, Colombo C, Smeraldi E. Patterns of mood variation during antidepressant treatment. *J Affect Disord*. 1998;49:133-139.
7. Benedetti F, Colombo C, Barbini B, Campori E, Smeraldi E. Morning sunlight reduces length of hospitalization in bipolar depression. *J Affect Disord*. 2001;62:221-223.
8. Bauer M, Pfennig A, Linden M, Smolka MN, Neu P, Adli M. Efficacy of an algorithm-guided treatment compared with treatment as usual: a randomized, controlled study of inpatients with depression. *J Clin Psychopharmacol*. 2009;29:327-333.
9. Bauer M, Glenn T, Whybrow PC, et al. Changes in self-reported sleep duration predict mood changes in bipolar disorder. *Psychol Med*. 2008;38:1069-1071.
10. Leibenluft E, Wehr TA. Is sleep deprivation useful in the treatment of depression? *Am J Psychiatry*. 1992;149:159-168.
11. Wu JC, Bunney WE. The biological basis of an antidepressant response to sleep deprivation and relapse: review and hypothesis. *Am J Psychiatry*. 1990;147:14-21.
12. Post RM, Leverich GS, Altshuler LL, et al. Differential clinical characteristics, medication usage, and treatment response of bipolar disorder in the US versus The Netherlands and Germany. *Int Clin Psychopharmacol*. 2011;26:96-106.
13. Altshuler LL, Kupka RW, Helleman G, et al. Gender and depressive symptoms in 711 patients with bipolar disorder evaluated prospectively in the Stanley Foundation bipolar treatment outcome network. *Am J Psychiatry*. 2010;167:708-715.
14. Kupka RW, Altshuler LL, Nolen WA, et al. Three times more days depressed than manic or hypomanic in both bipolar I and bipolar II disorder. *Bipolar Disord*. 2007;9:531-535.
15. Post RM, Leverich GS, Altshuler LL, et al. Relationship of prior antidepressant exposure to long-term prospective outcome in bipolar I disorder outpatients. *J Clin Psychiatry*. 2012;73:924-930.
16. Frye MA, Helleman G, McElroy SL, et al. Correlates of treatment-emergent mania associated with antidepressant treatment in bipolar depression. *Am J Psychiatry*. 2009;166:164-172.
17. Gao K, Kemp DE, Ganocy SJ, et al. Treatment-emergent mania/hypomania during antidepressant monotherapy in patients with rapid cycling bipolar disorder. *Bipolar Disord*. 2008;10:907-915.
18. Altshuler L, Suppes T, Black D, et al. Impact of antidepressant discontinuation after acute bipolar depression remission on rates of depressive relapse at 1-year follow-up. *Am J Psychiatry*. 2003;160:1252-1262.
19. Post RM, Altshuler LL, Frye MA, et al. Complexity of pharmacologic treatment required for sustained improvement in outpatients with bipolar disorder. *J Clin Psychiatry*. 2010;71:1176-1186.
20. Benedetti F, Colombo C. Sleep deprivation in mood disorders. *Neuropsychobiology*. 2011;64:141-151.
21. Dibner C, Schibler U, Albrecht U. The mammalian circadian timing system: organization and coordination of central and peripheral clocks. *Annu Rev Physiol*. 2010;72:517-549.
22. McClung CA. Circadian rhythms and mood regulation: insights from pre-clinical models. *Eur Neuropsychopharmacol*. 2011;21(suppl 4):S683-S693.
23. Jauhar P, Weller MP. Psychiatric morbidity and time zone changes: a study of patients from Heathrow airport. *Br J Psychiatry*. 1982;140:231-235.
24. Young DM. Psychiatric morbidity in travelers to Honolulu, Hawaii. *Compr Psychiatry*. 1995;36:224-228.
25. Schulte W. Sequelae of sleep deprivation. *Medizinische Klinik (Munich)*. 1959;54:969-973.
26. Pflug B, Tolle R. Therapy of endogenous depression using sleep deprivation. Practical and theoretical consequences. *Nervenarzt*. 1971;42:117-124.
27. Pflug B, Tolle R. Disturbance of the 24-hour rhythm in endogenous depression and the treatment of endogenous depression by sleep deprivation. *Int Pharmacopsychiatry*. 1971;6:187-196.
28. Schilgen B, Tolle R. Partial sleep deprivation as therapy for depression. *Arch Gen Psychiatry*. 1980;37:267-271.
29. Giedke H, Wormstall H, Haffner HT. Therapeutic sleep deprivation in depressives, restricted to the two nocturnal hours between 3:00 and 5:00. *Prog Neuropsychopharmacol Biol Psychiatry*. 1990;14:37-47.
30. Wehr TA, Rosenthal NE, Sack DA, Gillin JC. Antidepressant effects of sleep deprivation in bright and dim light. *Acta Psychiatr Scand*. 1985;72:161-165.
31. Benedetti F, Dall'aspezia S, Cigala Fulgosi M, et al. Actimetric evidence that CLOCK 3111 T/C SNP influences depressive insomnia and activity patterns in bipolar depression. *Am J Med Genet B Neuropsychiatr Genet*. 2007;144:631-635.
32. Voderholzer U. Sleep deprivation and antidepressant treatment. *Dialogues Clin Neurosci*. 2003;5:366-369.
33. Barbini B, Colombo C, Benedetti F, Campori E, Bellodi L, Smeraldi E. The unipolar-bipolar dichotomy and the response to sleep deprivation. *Psychiatry Res*. 1998;79:43-50.
34. van den Burg W, van den Hoofdakker RH. Total sleep deprivation on endogenous depression. *Arch Gen Psychiatry*. 1975;32:1121-1125.
35. Wiegand MH, Lauer CJ, Schreiber W. Patterns of response to repeated total sleep deprivations in depression. *J Affect Disord*. 2001;64:257-260.
36. Kundermann B, Strate P, Hemmeter-Spernal J, Huber MT, Krieg JC, Lautenbacher S. Mid-term effects of serial sleep deprivation therapy implemented in cognitive-behavioral treatment on the neuroendocrine response to clomipramine in patients with major depression. *J Psychiatr Res*. 2009;43:711-720.
37. Papadimitriou GN, Christodoulou GN, Trikkas GM, Malliaras DE, Lykouras EP, Stefanis CN. Sleep deprivation psychoprophylaxis in recurrent affective disorders. *Bibl Psychiatry*. 1981;56-61.
38. van Bommel AL, van den Hoofdakker RH. Maintenance of therapeutic effects of total sleep deprivation by limitation of subsequent sleep. A pilot study. *Acta Psychiatr Scand*. 1981;63:453-462.
39. Christodoulou GN, Malliaras DE, Lykouras EP, Papadimitriou GN, Stefanis CN. Possible prophylactic effect of sleep deprivation. *Am J Psychiatry*. 1978;135:375-376.
40. Papadimitriou GN, Christodoulou GN, Katsouyanni K, Stefanis CN. Therapy and prevention of affective illness by total sleep deprivation. *J Affect Disord*. 1993;27:107-116.
41. Benedetti F, Barbini B, Colombo C, Smeraldi E. Chronotherapeutics in a psychiatric ward. *Sleep Med Rev*. 2007;11:509-522.
42. Benedetti F, Barbini B, Lucca A, Campori E, Colombo C, Smeraldi E. Sleep deprivation hastens the antidepressant action of fluoxetine. *Eur Arch Psychiatry Clin Neurosci*. 1997;247:100-103.
43. Smeraldi E, Benedetti F, Barbini B, Campori E, Colombo C. Sustained antidepressant effect of sleep deprivation combined with pindolol in bipolar depression - a placebo-controlled trial. *Neuropsychopharmacology*. 1999;20:380-385.
44. Benedetti F, Colombo C, Barbini B, Campori E, Smeraldi E. Ongoing lithium treatment prevents relapse after total sleep deprivation. *J Clin Psychopharmacol*. 1999;19:240-245.
45. Colombo C, Lucca A, Benedetti F, Barbini B, Campori E, Smeraldi E. Total sleep deprivation combined with lithium and light therapy in the treatment of bipolar depression: replication of main effects and interaction. *Psychiatry Res*. 2000;95:43-53.
46. Benedetti F, Campori E, Barbini B, Fulgosi MC, Colombo C. Dopaminergic augmentation of sleep deprivation effects in bipolar depression. *Psychiatry Res*. 2001;104:239-246.
47. Benedetti F, Barbini B, Fulgosi MC, et al. Combined total sleep deprivation and light therapy in the treatment of drug-resistant bipolar depression: acute response and long-term remission rates. *J Clin Psychiatry*. 2005;66:1535-1540.



48. Benedetti F, Bernasconi A, Blasi V, et al. Neural and genetic correlates of antidepressant response to sleep deprivation: a fMRI study of moral valence decision in bipolar depression. *Arch Gen Psychiatry*. 2007;64:179-187.
49. Benedetti F, Dallaspazia S, Fulgosi MC, Barbini B, Colombo C, Smeraldi E. Phase advance is an actimetric correlate of antidepressant response to sleep deprivation and light therapy in bipolar depression. *Chronobiol Int*. 2007;24:921-937.
50. Wehr TA. Sleep loss: a preventable cause of mania and other excited states. *J Clin Psychiatry*. 1989;50(suppl):8-16.
51. Colombo C, Benedetti F, Barbini B, Campori E, Smeraldi E. Rate of switch from depression into mania after therapeutic sleep deprivation in bipolar depression. *Psychiatry Res*. 1999;86:267-270.
52. Kripke D. Photoperiodic mechanisms for depression and its treatment. In: Perris C, Struwe G, Jansson B, eds. *Biological Psychiatry*. Amsterdam, the Netherlands: Elsevier; 1981:1249-1252.
53. Kripke DF, Risch SC, Janowsky D. Bright white light alleviates depression. *Psychiatry Res*. 1983;10:105-112.
54. Lewy AJ, Kern HA, Rosenthal NE, Wehr TA. Bright artificial light treatment of a manic-depressive patient with a seasonal mood cycle. *Am J Psychiatry*. 1982;139:1496-1498.
55. Parry BL, Maurer EL. Light treatment of mood disorders. *Dialogues Clin Neurosci*. 2003;5:353-365.
56. Terman M, Terman JS. Bright light therapy: side effects and benefits across the symptom spectrum. *J Clin Psychiatry*. 1999;60:799-808.
57. Terman JS, Terman M, Lo ES, Cooper TB. Circadian time of morning light administration and therapeutic response in winter depression. *Arch Gen Psychiatry*. 2001;58:69-75.
58. Terman M, Terman JS. Light therapy for seasonal and nonseasonal depression: efficacy, protocol, safety, and side effects. *CNS Spectr*. 2005;10:647-663.
59. Benedetti F, Colombo C, Pontiggia A, Bernasconi A, Florita M, Smeraldi E. Morning light treatment hastens the antidepressant effect of citalopram: a placebo-controlled trial. *J Clin Psychiatry*. 2003;64:648-653.
60. Lewy AJ, Lefler BJ, Emens JS, Bauer VK. The circadian basis of winter depression. *Proc Natl Acad Sci U S A*. 2006;103:7414-7419.
61. Dallaspazia S, Benedetti F, Colombo C, et al. Optimized light therapy for non-seasonal major depressive disorder: effects of timing and season. *J Affect Disord*. 2012;138:337-342.
62. Wirz-Justice A, Graw P, Krauchi K, et al. Light therapy in seasonal affective disorder is independent of time of day or circadian phase. *Arch Gen Psychiatry*. 1993;50:929-937.
63. Terman M. Evolving applications of light therapy. *Sleep Med Rev*. 2007;11:497-507.
64. Golden RN, Gaynes BN, Ekstrom RD, et al. The efficacy of light therapy in the treatment of mood disorders: a review and meta-analysis of the evidence. *Am J Psychiatry*. 2005;162:656-662.
65. Tuunainen A, Kripke DF, Endo T. Light therapy for non-seasonal depression. *Cochrane Database Syst Rev*. 2004;CD004050.
66. Martiny K, Lunde M, Uden M, Dam H, Bech P. Adjunctive bright light in non-seasonal major depression: results from clinician-rated depression scales. *Acta Psychiatr Scand*. 2005;112:117-125.
67. Kripke DF. Light treatment for nonseasonal depression: speed, efficacy, and combined treatment. *J Affect Disord*. 1998;49:109-117.
68. Prasko J, Brunovsky M, Latalova K, et al. Augmentation of antidepressants with bright light therapy in patients with comorbid depression and borderline personality disorder. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. 2010;154:355-361.
69. Martiny K, Lunde M, Uden M, Dam H, Bech P. The lack of sustained effect of bright light, after discontinuation, in non-seasonal major depression. *Psychol Med*. 2006;36:1247-1252.
70. Martiny K, Lunde M, Simonsen C, et al. Relapse prevention by citalopram in SAD patients responding to 1 week of light therapy. A placebo-controlled study. *Acta Psychiatr Scand*. 2004;109:230-234.
71. Wirz-Justice A, Bader A, Frisch U, et al. A randomized, double-blind, placebo-controlled study of light therapy for antepartum depression. *J Clin Psychiatry*. 2011;72:986-993.
72. Sondergaard MP, Jarden JO, Martiny K, Andersen G, Bech P. Dose response to adjunctive light therapy in citalopram-treated patients with post-stroke depression. A randomised, double-blind pilot study. *Psychother Psychosom*. 2006;75:244-248.
73. Deltito JA, Moline M, Pollak C, Martin LY, Maremmanni I. Effects of phototherapy on non-seasonal unipolar and bipolar depressive spectrum disorders. *J Affect Disord*. 1991;23:231-237.
74. Dauphinais DR, Rosenthal JZ, Terman M, DiFebo HM, Tuggle C, Rosenthal NE. Controlled trial of safety and efficacy of bright light therapy vs. negative air ions in patients with bipolar depression. *Psychiatry Res*. 2012;196:57-61.
75. Lewy AJ, Nurnberger JJ Jr, Wehr TA, et al. Supersensitivity to light: possible trait marker for manic-depressive illness. *Am J Psychiatry*. 1985;142:725-727.
76. Terman M, Schlager D, Fairhurst S, Perlman B. Dawn and dusk simulation as a therapeutic intervention. *Biol Psychiatry*. 1989;25:966-970.
77. Terman M, Terman JS. Controlled trial of naturalistic dawn simulation and negative air ionization for seasonal affective disorder. *Am J Psychiatry*. 2006;163:2126-2133.
78. Wehr TA, Wirz-Justice A, Goodwin FK, Duncan W, Gillin JC. Phase advance of the circadian sleep-wake cycle as an antidepressant. *Science*. 1979;206:710-713.
79. Souetre E, Salvati E, Pringuey D, Plasse Y, Savelli M, Darcourt G. Antidepressant effects of the sleep/wake cycle phase advance. Preliminary report. *J Affect Disord*. 1987;12:41-46.
80. Gangwisch JE, Babiss LA, Malaspina D, Turner JB, Zammit GK, Posner K. Earlier parental set bedtimes as a protective factor against depression and suicidal ideation. *Sleep*. 2010;33:97-106.
81. Bhattacharjee Y. Psychiatric research. Is internal timing key to mental health? *Science*. 2007;317:1488-1490.
82. Berger M, Vollmann J, Hohagen F, et al. Sleep deprivation combined with consecutive sleep phase advance as a fast-acting therapy in depression: an open pilot trial in medicated and unmedicated patients. *Am J Psychiatry*. 1997;154:870-872.
83. Benedetti F, Barbini B, Campori E, Fulgosi MC, Pontiggia A, Colombo C. Sleep phase advance and lithium to sustain the antidepressant effect of total sleep deprivation in bipolar depression: new findings supporting the internal coincidence model? *J Psychiatr Res*. 2001;35:323-329.
84. Voderholzer U, Valerius G, Schaerer L, et al. Is the antidepressive effect of sleep deprivation stabilized by a three day phase advance of the sleep period? A pilot study. *Eur Arch Psychiatry Clin Neurosci*. 2003;253:68-72.
85. Wu JC, Kelsoe JR, Schachat C, et al. Rapid and sustained antidepressant response with sleep deprivation and chronotherapy in bipolar disorder. *Biol Psychiatry*. 2009;66:298-301.
86. Millan MJ. Multi-target strategies for the improved treatment of depressive states: conceptual foundations and neuronal substrates, drug discovery and therapeutic application. *Pharmacol Ther*. 2006;110:135-370.
87. Adrien J. Neurobiological bases for the relation between sleep and depression. *Sleep Med Rev*. 2002;6:341-351.
88. Gardner JP, Fornal CA, Jacobs BL. Effects of sleep deprivation on serotonergic neuronal activity in the dorsal raphe nucleus of the freely moving cat. *Neuropsychopharmacology*. 1997;17:72-81.
89. Lopez-Rodriguez F, Wilson CL, Maidment NT, Poland RE, Engel J. Total sleep deprivation increases extracellular serotonin in the rat hippocampus. *Neuroscience*. 2003;121:523-530.
90. Hery F, Pujol JF, Lopez M, Macon J, Glowinski J. Increased synthesis and utilization of serotonin in the central nervous system of the rat during paradoxical sleep deprivation. *Brain Res*. 1970;21:391-403.
91. Cramer H, Tagliamonte A, Tagliamonte P, Perez-Cruet J, Gessa GL. Stimulation of brain serotonin turnover by paradoxical sleep deprivation in intact and hypophysectomized rats. *Brain Res*. 1973;54:372-375.
92. Asikainen M, Deboer T, Porkka-Heiskanen T, Stenberg D, Tobler I. Sleep deprivation increases brain serotonin turnover in the Djungarian hamster. *Neurosci Lett*. 1995;198:21-24.
93. Maudhuit C, Jolas T, Chastanet M, Hamon M, Adrien J. Reduced inhibitory potency of serotonin reuptake blockers on central serotonergic neurons in rats selectively deprived of rapid eye movement sleep. *Biol Psychiatry*. 1996;40:1000-1007.
94. Santos R, Carlini EA. Serotonin receptor activation in rats previously deprived of REM sleep. *Pharmacol Biochem Behav*. 1983;18:501-507.
95. Hipolide DC, Moreira KM, Barlow KB, Wilson AA, Nobrega JN, Tufik S. Distinct effects of sleep deprivation on binding to norepinephrine and serotonin transporters in rat brain. *Prog Neuropsychopharmacol Biol Psychiatry*. 2005;29:297-303.

# Clinical research

96. Basheer R, Magner M, McCarley RW, Shiromani PJ. REM sleep deprivation increases the levels of tyrosine hydroxylase and norepinephrine transporter mRNA in the locus coeruleus. *Brain Res Mol Brain Res*. 1998;57:235-240.
97. Tufik S, Lindsey CJ, Carlini EA. Does REM sleep deprivation induce a supersensitivity of dopaminergic receptors in the rat brain? *Pharmacology*. 1978;16:98-105.
98. Mogilnicka E. REM sleep deprivation changes behavioral response to catecholaminergic and serotonergic receptor activation in rats. *Pharmacol Biochem Behav*. 1981;15:149-151.
99. Wirz-Justice A, Tobler I, Kafka MS, et al. Sleep deprivation: effects on circadian rhythms of rat brain neurotransmitter receptors. *Psychiatry Res*. 1981;5:67-76.
100. Zwicker AP, Calil HM. The effects of REM sleep deprivation on striatal dopamine receptor sites. *Pharmacol Biochem Behav*. 1986;24:809-812.
101. Salomon RM, Delgado PL, Licinio J, Krystal JH, Heninger GR, Charney DS. Effects of sleep deprivation on serotonin function in depression. *Biol Psychiatry*. 1994;36:840-846.
102. Kasper S, Sack DA, Wehr TA, Kick H, Voll G, Vieira A. Nocturnal TSH and prolactin secretion during sleep deprivation and prediction of antidepressant response in patients with major depression. *Biol Psychiatry*. 1988;24:631-641.
103. Baumgartner A, Riemann D, Berger M. Neuroendocrinological investigations during sleep deprivation in depression. II. Longitudinal measurement of thyrotropin, TH, cortisol, prolactin, GH, and LH during sleep and sleep deprivation. *Biol Psychiatry*. 1990;28:569-587.
104. Ebert D, Feistel H, Kaschka W, Barocka A, Pirner A. Single photon emission computerized tomography assessment of cerebral dopamine D2 receptor blockade in depression before and after sleep deprivation—preliminary results. *Biol Psychiatry*. 1994;35:880-885.
105. Gerner RH, Post RM, Gillin JC, Bunney WE Jr. Biological and behavioral effects of one night's sleep deprivation in depressed patients and normals. *J Psychiatr Res*. 1979;15:21-40.
106. Ebert D, Albert R, Hammon G, Strasser B, May A, Merz A. Eye-blink rates and depression. Is the antidepressant effect of sleep deprivation mediated by the dopamine system? *Neuropsychopharmacology*. 1996;15:332-339.
107. Muller HU, Riemann D, Berger M, Muller WE. The influence of total sleep deprivation on urinary excretion of catecholamine metabolites in major depression. *Acta Psychiatr Scand*. 1993;88:16-20.
108. Amin MM, Khalid R, Khan P. Relationship between sleep deprivation and urinary MHPG levels. *Int Pharmacopsychiatry*. 1980;15:81-85.
109. Matussek N, Romisch P, Ackenheil M. MHPG excretion during sleep deprivation in endogenous depression. *Neuropsychobiology*. 1977;3:23-29.
110. Benedetti F, Serretti A, Colombo C, et al. Influence of a functional polymorphism within the promoter of the serotonin transporter gene on the effects of total sleep deprivation in bipolar depression. *Am J Psychiatry*. 1999;156:1450-1452.
111. Benedetti F, Barbini B, Bernasconi A, et al. Lithium overcomes the influence of 5-HTTLPR gene polymorphism on antidepressant response to sleep deprivation. *J Clin Psychopharmacol*. 2008;28:249-251.
112. Benedetti F, Colombo C, Serretti A, et al. Antidepressant effects of light therapy combined with sleep deprivation are influenced by a functional polymorphism within the promoter of the serotonin transporter gene. *Biol Psychiatry*. 2003;54:687-692.
113. Benedetti F, Barbini B, Bernasconi A, et al. Serotonin 5-HT(2A) receptor gene variants influence antidepressant response to repeated total sleep deprivation in bipolar depression. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008;32:1863-1866.
114. Benedetti F, Barbini B, Bernasconi A, et al. Acute antidepressant response to sleep deprivation combined with light therapy is influenced by the catechol-O-methyltransferase Val(108/158)Met polymorphism. *J Affect Disord*. 2010;121:68-72.
115. Benedetti F, Colombo C, Pirovano A, Marino E, Smeraldi E. The catechol-O-methyltransferase Val(108/158)Met polymorphism affects antidepressant response to paroxetine in a naturalistic setting. *Psychopharmacology (Berl)*. 2009;203:155-160.
116. Benedetti F, Dallaspezia S, Colombo C, Lorenzi C, Pirovano A, Smeraldi E. Effect of catechol-O-methyltransferase Val(108/158)Met polymorphism on antidepressant efficacy of fluvoxamine. *Eur Psychiatry*. 2010;25:476-478.
117. Serretti A, Benedetti F, Zanardi R, Smeraldi E. The influence of Serotonin Transporter Promoter Polymorphism (SERTPR) and other polymorphisms of the serotonin pathway on the efficacy of antidepressant treatments. *Prog Neuro-Psychopharmacol Biol Psychiatry*. 2005;29:1074-1084.
118. Shelton RC, Loosen PT. Sleep deprivation accelerates the response to nortriptyline. *Prog Neuropsychopharmacol Biol Psychiatry*. 1993;17:113-123.
119. Gessa GL, Pani L, Fadda P, Fratta W. Sleep deprivation in the rat: an animal model of mania. *Eur Neuropsychopharmacol*. 1995;5(suppl):89-93.
120. Holsboer-Trachsler E, Hemmeter U, Hatzinger M, Seifritz E, Gerhard U, Hobi V. Sleep deprivation and bright light as potential augmenters of antidepressant drug treatment—neurobiological and psychometric assessment of course. *J Psychiatr Res*. 1994;28:381-399.
121. aan het Rot M, Benkelfat C, Boivin DB, Young SN. Bright light exposure during acute tryptophan depletion prevents a lowering of mood in mildly seasonal women. *Eur Neuropsychopharmacol*. 2008;18:14-23.
122. Diazgranados N, Ibrahim L, Brutsche NE, et al. A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. *Arch Gen Psychiatry*. 2010;67:793-802.
123. Zarate CA Jr, Quiroz JA, Singh JB, et al. An open-label trial of the glutamate-modulating agent riluzole in combination with lithium for the treatment of bipolar depression. *Biol Psychiatry*. 2005;57:430-432.
124. Dash MB, Douglas CL, Vyazovskiy VV, Cirelli C, Tononi G. Long-term homeostasis of extracellular glutamate in the rat cerebral cortex across sleep and waking states. *J Neurosci*. 2009;29:620-629.
125. Benedetti F, Calabrese G, Bernasconi A, et al. Spectroscopic correlates of antidepressant response to sleep deprivation and light therapy: a 3.0 Tesla study of bipolar depression. *Psychiatry Res Neuroimaging*. 2009;173:238-242.
126. Elliott R, Rubinsztein JS, Sahakian BJ, Dolan RJ. The neural basis of mood-congruent processing biases in depression. *Arch Gen Psychiatry*. 2002;59:597-604.
127. Wu JC, Buchsbaum M, Bunney WE Jr. Clinical neurochemical implications of sleep deprivation's effects on the anterior cingulate of depressed responders. *Neuropsychopharmacology*. 2001;25(suppl 5):S74-S78.
128. Gillin JC, Buchsbaum M, Wu J, Clark C, Bunney W Jr. Sleep deprivation as a model experimental antidepressant treatment: findings from functional brain imaging. *Depress Anxiety*. 2001;14:37-49.
129. Schulz P. Biological clocks and the practice of psychiatry. *Dialogues Clin Neurosci*. 2007;9:237-255.
130. Wirz-Justice A. Biological rhythm disturbances in mood disorders. *Int Clin Psychopharmacol*. 2006;21(suppl 1):S11-S15.
131. Schibler U. The daily timing of gene expression and physiology in mammals. *Dialogues Clin Neurosci*. 2007;9:257-272.
132. Benca R, Duncan MJ, Frank E, McClung C, Nelson RJ, Vicentic A. Biological rhythms, higher brain function, and behavior: gaps, opportunities, and challenges. *Brain Res Rev*. 2009;62:57-70.
133. Benedetti F. The molecular clock as a target in the treatment of bipolar disorder. *Neuropsychopharmacology*. 2005;30:S63-S64.
134. Sproue J. Pharmacological modulation of circadian rhythms: a new drug target in psychotherapeutics. *Expert Opin Ther Targets*. 2004;8:25-38.
135. Ciarleglio CM, Resuehr HE, McMahon DG. Interactions of the serotonin and circadian systems: nature and nurture in rhythms and blues. *Neuroscience*. 2011;197:8-16.
136. Lambert GW, Reid C, Kaye DM, Jennings GL, Esler MD. Effect of sunlight and season on serotonin turnover in the brain. *Lancet*. 2002;360:1840-1842.
137. Roybal K, Theobald D, Graham A, et al. Mania-like behavior induced by disruption of CLOCK. *Proc Natl Acad Sci U S A*. 2007;104:6406-6411.
138. McClung CA, Sidiropoulou K, Vitaterna M, et al. Regulation of dopaminergic transmission and cocaine reward by the Clock gene. *Proc Natl Acad Sci U S A*. 2005;102:9377-9381.
139. Mukherjee S, Coque L, Cao JL, et al. Knockdown of Clock in the ventral tegmental area through RNA interference results in a mixed state of mania and depression-like behavior. *Biol Psychiatry*. 2010;68:503-511.
140. Benedetti F, Radaelli D, Bernasconi A, et al. Clock genes beyond the clock: CLOCK genotype biases neural correlates of moral valence decision in depressed patients. *Genes Brain Behav*. 2008;7:20-25.

141. Benedetti F, Dallaspezia S, Fulgosi MC, et al. Actimetric evidence that CLOCK 3111 T/C SNP influences sleep and activity patterns in patients affected by bipolar depression. *Am J Med Genet B Neuropsychiatr Genet.* 2007;144B:631-635.
142. Siegel JM, Rogawski MA. A function for REM sleep: regulation of noradrenergic receptor sensitivity. *Brain Res.* 1988;472:213-233.
143. Payne JL, Quiroz JA, Zarate CA Jr, Manji HK. Timing is everything: does the robust upregulation of noradrenergically regulated plasticity genes underlie the rapid antidepressant effects of sleep deprivation? *Biol Psychiatry.* 2002;52:921-926.
144. Lee B, Li A, Hansen KF, Cao R, Yoon JH, Obrietan K. CREB influences timing and entrainment of the SCN circadian clock. *J Biol Rhythms.* 2010;25:410-420.
145. St Hilaire MA, Gooley JJ, Khalsa SB, Kronauer RE, Czeisler CA, Lockley SW. Human phase response curve (PRC) to a 1-hour pulse of bright white light. *J Physiol.* In press.
146. Khalsa SB, Jewett ME, Cajochen C, Czeisler CA. A phase response curve to single bright light pulses in human subjects. *J Physiol.* 2003;549:945-952.
147. Deboer T, Vansteensel MJ, Detari L, Meijer JH. Sleep states alter activity of suprachiasmatic nucleus neurons. *Nat Neurosci.* 2003;6:1086-1090.
148. Mongrain V, La Spada F, Curie T, Franken P. Sleep loss reduces the DNA-binding of BMAL1, CLOCK, and NPAS2 to specific clock genes in the mouse cerebral cortex. *PLoS One.* 2011;6:e26622.
149. Benedetti F, Barbini B, Fulgosi MC, et al. Combined total sleep deprivation and light therapy in the treatment of drug-resistant bipolar depression: Acute response and long-term remission rates. *J Clin Psychiatry.* 2005;66:1535-1540.
150. Sprouse J, Braselton J, Reynolds L. Fluoxetine modulates the circadian biological clock via phase advances of suprachiasmatic nucleus neuronal firing. *Biol Psychiatry.* 2006;60:896-899.
151. Krauchi K, Cajochen C, Mori D, Graw P, Wirz-Justice A. Early evening melatonin and S-20098 advance circadian phase and nocturnal regulation of core body temperature. *Am J Physiol.* 1997;272:R1178-R1188.
152. Wehr TA, Duncan WC Jr, Sher L, et al. A circadian signal of change of season in patients with seasonal affective disorder. *Arch Gen Psychiatry.* 2001;58:1108-1114.
153. Masubuchi S, Kataoka N, Sassone-Corsi P, Okamura H. Mouse Period1 (mPER1) acts as a circadian adaptor to entrain the oscillator to environmental light/dark cycles by regulating mPER2 protein. *J Neurosci.* 2005;25:4719-4724.
154. Abe H, Honma S, Namihira M, et al. Clock gene expressions in the suprachiasmatic nucleus and other areas of the brain during rhythm splitting in CS mice. *Brain Res Mol Brain Res.* 2001;87:92-99.
155. Benedetti F, Radaelli D, Bernasconi A, et al. Clock genes beyond the clock: CLOCK genotype biases neural correlates of moral valence decision in depressed patients. *Genes Brain Behav.* 2008;7:20-25.
156. Kondratov RV, Shamanna RK, Kondratova AA, Gorbacheva VY, Antoch MP. Dual role of the CLOCK/BMAL1 circadian complex in transcriptional regulation. *FASEB J.* 2006;20:530-532.
157. Benedetti F, Dallaspezia S, Colombo C, Pirovano A, Marino E, Smeraldi E. A length polymorphism in the circadian clock gene Per3 influences age at onset of bipolar disorder. *Neurosci Lett.* 2008;445:184-187.
158. Benedetti F, Serretti A, Colombo C, et al. Influence of CLOCK gene polymorphism on circadian mood fluctuation and illness recurrence in bipolar depression. *Am J Med Genet B Neuropsychiatr Genet.* 2003;123B:23-26.
159. Dallaspezia S, Lorenzi C, Pirovano A, Colombo C, Smeraldi E, Benedetti F. Circadian clock gene Per3 variants influence the postpartum onset of bipolar disorder. *Eur Psychiatry.* 2011;26:138-140.
160. Iitaka C, Miyazaki K, Akaike T, Ishida N. A role for glycogen synthase kinase-3beta in the mammalian circadian clock. *J Biol Chem.* 2005;280:29397-29402.
161. Grimes CA, Jope RS. The multifaceted roles of glycogen synthase kinase 3beta in cellular signaling. *Prog Neurobiol.* 2001;65:391-426.
162. Kockeritz L, Doble B, Patel S, Woodgett JR. Glycogen synthase kinase-3—an overview of an over-achieving protein kinase. *Curr Drug Targets.* 2006;7:1377-1388.
163. Forde JE, Dale TC. Glycogen synthase kinase 3: a key regulator of cellular fate. *Cell Mol Life Sci.* 2007;64:1930-1944.
164. Manji HK, Moore GJ, Rajkowska G, Chen G. Neuroplasticity and cellular resilience in mood disorders. *Mol Psychiatry.* 2000;5:578-593.
165. Gould TD, Manji HK. Glycogen synthase kinase-3: a putative molecular target for lithium mimetic drugs. *Neuropsychopharmacology.* 2005;30:1223-1237.
166. Beaulieu JM, Zhang X, Rodriguiz RM, et al. Role of GSK3 beta in behavioral abnormalities induced by serotonin deficiency. *Proc Natl Acad Sci U S A.* 2008;105:1333-1338.
167. Beaulieu JM, Gainetdinov RR, Caron MG. Akt/GSK3 signaling in the action of psychotropic drugs. *Annu Rev Pharmacol Toxicol.* 2009;49:327-347.
168. Benedetti F, Bernasconi A, Lorenzi C, et al. A single nucleotide polymorphism in glycogen synthase kinase 3-beta promoter gene influences onset of illness in patients affected by bipolar disorder. *Neurosci Lett.* 2004;355:37-40.
169. Benedetti F, Serretti A, Pontiggia A, et al. Long-term response to lithium salts in bipolar illness is influenced by the glycogen synthase kinase 3-beta -50 T/C SNP. *Neurosci Lett.* 2005;376:51-55.
170. Adli M, Hollinde DL, Stamm T, et al. Response to lithium augmentation in depression is associated with the glycogen synthase kinase 3-beta -50T/C single nucleotide polymorphism. *Biol Psychiatry.* 2007;62:1295-1302.
171. Benedetti F, Serretti A, Colombo C, Lorenzi C, Tubazio V, Smeraldi E. A glycogen synthase kinase 3-beta promoter gene single nucleotide polymorphism is associated with age at onset and response to total sleep deprivation in bipolar depression. *Neurosci Lett.* 2004;368:123-126.
172. Benedetti F, Dallaspezia S, Lorenzi C, et al. Gene-gene interaction of glycogen synthase kinase 3-beta and serotonin transporter on human antidepressant response to sleep deprivation. *J Affect Disord.* 2012;136:514-519.
173. Schloesser RJ, Martinowich K, Manji HK. Mood-stabilizing drugs: mechanisms of action. *Trends Neurosci.* 2012;35:36-46.
174. Tononi G, Cirelli C. Sleep function and synaptic homeostasis. *Sleep Med Rev.* 2006;10:49-62.
175. Massimini M, Ferrarelli F, Huber R, Esser SK, Singh H, Tononi G. Breakdown of cortical effective connectivity during sleep. *Science.* 2005;309:2228-2232.
176. Tononi G, Cirelli C. Sleep and synaptic homeostasis: a hypothesis. *Brain Res Bull.* 2003;62:143-150.
177. Huber R, Maki H, Rosanova M, et al. Human cortical excitability increases with time awake. *Cereb Cortex.* Epub ahead of print: February 7, 2012.
178. Vyazovskiy VV, Cirelli C, Pfister-Genskow M, Faraguna U, Tononi G. Molecular and electrophysiological evidence for net synaptic potentiation in wake and depression in sleep. *Nat Neurosci.* 2008;11:200-208.