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*Published in:*  
Bipolar Disorders

*DOI:*  
[10.1111/bdi.12847](https://doi.org/10.1111/bdi.12847)

**IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.**

*Document Version*  
Publisher's PDF, also known as Version of record

*Publication date:*  
2019

[Link to publication in University of Groningen/UMCG research database](#)

### *Citation for published version (APA):*

Gottlieb, J. F., Benedetti, F., Geoffroy, P. A., Henriksen, T. E. G., Lam, R. W., Murray, G., Phelps, J., Sit, D., Swartz, H. A., Crowe, M., Etain, B., Frank, E., Goel, N., Haarman, B. C. M., Inder, M., Kallestad, H., Jae Kim, S., Martiny, K., Meesters, Y., ... Chen, S. (2019). The chronotherapeutic treatment of bipolar disorders: A systematic review and practice recommendations from the ISBD task force on chronotherapy and chronobiology. *Bipolar Disorders*, 21(8), 741-773. <https://doi.org/10.1111/bdi.12847>

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# The chronotherapeutic treatment of bipolar disorders: A systematic review and practice recommendations from the ISBD task force on chronotherapy and chronobiology

John F. Gottlieb<sup>1,2</sup>  | Francesco Benedetti<sup>3</sup>  | Pierre A. Geoffroy<sup>4,5</sup>  |  
Tone E. G. Henriksen<sup>6,7,8</sup> | Raymond W. Lam<sup>9</sup> | Greg Murray<sup>10</sup>  | James Phelps<sup>11</sup> |  
Dorothy Sit<sup>12</sup> | Holly A. Swartz<sup>13</sup> | Marie Crowe<sup>14</sup>  | Bruno Etain<sup>15</sup>  |  
Ellen Frank<sup>13,16</sup> | Namni Goel<sup>17</sup> | Bartholomeus C. M. Haarman<sup>18</sup>  | Maree Inder<sup>14</sup>  |  
Håvard Kallestad<sup>19,20</sup> | Seong Jae Kim<sup>21</sup> | Klaus Martiny<sup>22</sup> | Ybe Meesters<sup>18</sup> |  
Richard Porter<sup>14,23</sup>  | Rixt F. Riemersma-van der Lek<sup>18</sup> | Philipp S. Ritter<sup>24</sup> |  
Peter F. J. Schulte<sup>25</sup> | Jan Scott<sup>26</sup>  | Joseph C. Wu<sup>27</sup> | Xin Yu<sup>28</sup> | Shenghao Chen<sup>1</sup> 

<sup>1</sup>Department of Psychiatry and Behavioral Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

<sup>2</sup>Chicago Psychiatry Associates, Chicago, IL, USA

<sup>3</sup>Division of Neuroscience, Scientific Institute San Raffaele, Milano, Italy

<sup>4</sup>Department of Psychiatry and Addictive Medicine, University Hospital Bichat-Claude Bernard, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France

<sup>5</sup>Paris Diderot University - Paris VII, Paris, France

<sup>6</sup>Faculty of Medicine, Section for Psychiatry, Department of Clinical Medicine, University of Bergen, Bergen, Norway

<sup>7</sup>Faculty of Psychology, Bergen Stress and Sleep Group, University of Bergen, Bergen, Norway

<sup>8</sup>Valen Hospital, Fonna Health Authority, Division of Mental Health Care, Valen, Norway

<sup>9</sup>Department of Psychiatry, The University of British Columbia, Vancouver, BC, Canada

<sup>10</sup>Swinburne University of Technology, Hawthorn, VIC, Australia

<sup>11</sup>Samaritan Mental Health, Corvallis, OR, USA

<sup>12</sup>Asher Center for the Study and Treatment of Depressive Disorders, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

<sup>13</sup>Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA, USA

<sup>14</sup>Department of Psychological Medicine, University of Otago Christchurch, Christchurch, New Zealand

<sup>15</sup>Department of Psychological Medicine, Université Paris Diderot UFR de Médecine, Paris, France

<sup>16</sup>Department of Psychology, University of Pittsburgh, Pittsburgh, PA, USA

<sup>17</sup>Department of Psychiatry Philadelphia, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA

<sup>18</sup>Department of Psychiatry Groningen, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

<sup>19</sup>Faculty of Medicine and Health Sciences, Department of Mental Health, Norwegian University of Science and Technology, Trondheim, Norway

<sup>20</sup>Division of Psychiatry, Department of Research and Development, St. Olavs University Hospital, Trondheim, Norway

<sup>21</sup>Department of Psychiatry, Doeun Hospital, Jincheon, Korea

<sup>22</sup>Department of Clinical Medicine, University of Copenhagen, Kobenhavns, Denmark

<sup>23</sup>Canterbury District Health Board, Christchurch, New Zealand

<sup>24</sup>Klinik und Poliklinik für Psychiatrie und Psychotherapie, Universitätsklinikum Carl Gustav Carus, Dresden, Germany

<sup>25</sup>Mental Health Services Noord-Holland-Noord, Alkmaar, Netherlands

<sup>26</sup>Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, UK

<sup>27</sup>Department of Psychiatry & Human Behavior, University of California Irvine School of Medicine, Irvine, CA, USA

<sup>28</sup>Department of Public Mental Health, Peking University Institute of Mental Health, Beijing, China

**Correspondence**

John F. Gottlieb, 25 E. Washington St. Suite  
1805. Chicago, Illinois 60602, U.S.A.  
Email: jgottlieb@northwestern.edu

**Abstract**

**Aims:** To systematically review the literature on the efficacy and tolerability of the major chronotherapeutic treatments of bipolar disorders (BD)—bright light therapy (LT), dark therapy (DT), treatments utilizing sleep deprivation (SD), melatonergic agonists (MA), interpersonal social rhythm therapy (IPSRT), and cognitive behavioral therapy adapted for BD (CBTI-BP)—and propose treatment recommendations based on a synthesis of the evidence.

**Methods:** PRISMA-based systematic review of the literature.

**Results:** The acute antidepressant (AD) efficacy of LT was supported by several open-label studies, three randomized controlled trials (RCTs), and one pseudorandomized controlled trial. SD showed rapid, acute AD response rates of 43.9%, 59.3%, and 59.4% in eight case series, 11 uncontrolled, studies, and one RCT, respectively. Adjunctive DT obtained significant, rapid anti-manic results in one RCT and one controlled study. The seven studies on MA yielded very limited data on acute antidepressant activity, conflicting evidence of both antimanic and maintenance efficacy, and support from two case series of improved sleep in both acute and euthymic states. IPSRT monotherapy for bipolar II depression had acute response rates of 41%, 67%, and 67.4% in two open studies and one RCT, respectively; as adjunctive therapy for bipolar depression in one RCT, and efficacy in reducing relapse in two RCTs. Among euthymic BD subjects with insomnia, a single RCT found CBTI-BP effective in delaying manic relapse and improving sleep. Chronotherapies were generally safe and well-tolerated.

**Conclusions:** The outcome literature on the adjunctive use of chronotherapeutic treatments for BP is variable, with evidence bases that differ in size, study quality, level of evidence, and non-standardized treatment protocols. Evidence-informed practice recommendations are offered.

**KEYWORDS**

bipolar, Chronotherapy, circadian, cognitive behavioral therapy for insomnia adapted for bipolar disorder, dark therapy, interpersonal social rhythm therapy, light therapy, melatonergic agonist, melatonin, sleep deprivation

**1 | INTRODUCTION**

Bipolar disorder (BD) is a major mood disorder that is characterized by manic and depressive symptoms which fluctuate in severity and over time. The affective burden of the illness is compounded by cognitive, psychosocial, and occupational dysfunction, along with increased rates of suicide, medical comorbidity, and premature mortality.<sup>1-7</sup>

Current guidelines for the management of BD include treatments that are limited by suboptimal efficacy rates, medication intolerance, delayed onset of action, iatrogenic mood switches, and variable patient acceptability. There is a pressing public health need for measures to combat these shortcomings. The fields of chronobiology and chronotherapy offer alternative treatment strategies which may address these limitations. The

primary aim of this project was to systematically review efficacy and tolerability evidence of the major chronotherapies for BD and propose practice recommendations based on this review. This commences with a brief introduction to chronobiology to provide a rudimentary overview of the basic science which underlies this field of treatment.

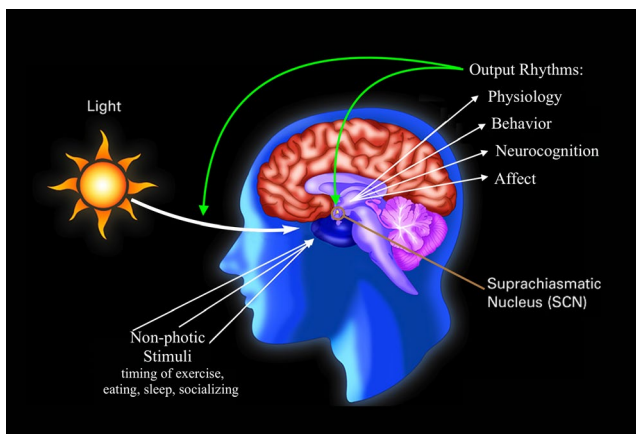
**1.1 | Introduction to the circadian system**

The basic science of chronobiology is the study of biological rhythms, biological timekeeping systems, and their effects on human health and disease.<sup>8</sup> The human time-keeping system is a strongly conserved, phylogenetically ancient, hierarchically organized, and open neurobiological network. It evolved to enable organisms to anticipate and coordinate their internal physiology

and behavior with other organisms and with the 24-hour geophysical cycle of light and darkness.<sup>9</sup> In its most basic form, it consists of input stimuli, the master clock located in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus, and physiologic and behavioral output rhythms (Figure 1). The master clock is constituted by cells which rhythmically oscillate, individually and as an ensemble. This oscillation is driven by a set of transcription factors, CLOCK and BMAL, that promote the read-out of the core CLOCK genes, *Per1*, *Per2*, *Cry1*, and *Cry2*, whose protein products exert negative feedback control on the transcription process (Figure 2). This autoregulatory transcription-translation feedback loop, which is governed by dozens of CLOCK genes, endogenously repeats over a near-24-hour period thereby providing an internal timekeeping system, a ticking brain clock.<sup>10</sup>

The rhythmic output from the SCN is defined by three major features: frequency (or period), amplitude, and timing (or phase). Temporal information from the SCN is constantly adjusted depending on input stimuli and is then distributed to all other organ systems, including other brain areas, primarily through the autonomic nervous system. The musculature, gut, heart, and other organ systems each have their own internal clocks which receive this centralized timing information and use it to calibrate the peaks and troughs of their own functioning. When all is optimally synchronized, the result is a coordinated symphony of undulating rhythms of physiology and behavior. The former includes core body temperature, melatonin secretion, and cortisol production which are all directly driven by the SCN. In contrast, behavioral oscillations in neurocognition, activity, feeding, mood, and the sleep-wake cycle reflect both a direct circadian component together with personal and social factors.

The input to the circadian system consists of photic and non-photic factors, referred to as zeitgebers or time-givers. These factors adjust the timing (phase) and amplitude of the SCN neuronal oscillations. While light is the strongest zeitgeber in humans, non-photic



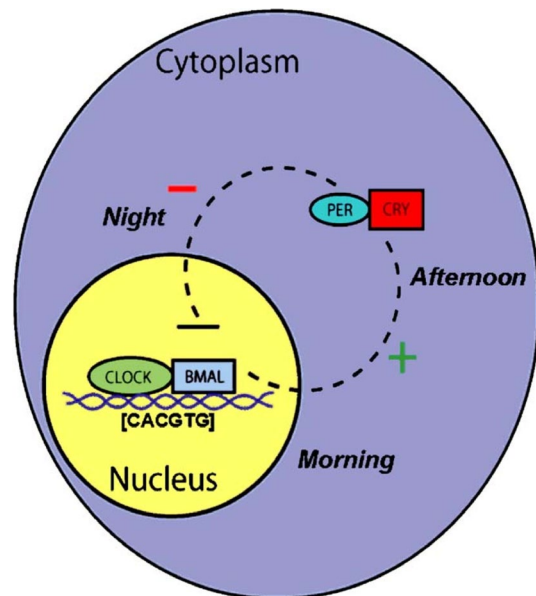
**FIGURE 1** Schematic model of the human circadian system. Adapted from *Circadian Rhythms*, by National Institute of General Medical Sciences, 2017, retrieved from [https://www.nigms.nih.gov/education/pages/factsheet\\_circadianrhythms.aspx](https://www.nigms.nih.gov/education/pages/factsheet_circadianrhythms.aspx). Copyright [2017] by the National Institute of General Medical Sciences [Colour figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]

elements such as the timing of exercise, eating, social interaction, work, and sleep also modulate SCN activity<sup>11,12</sup> (Figure 3). The combined effect of these zeitgebers is to constantly adjust the timing (ie, to shift the phase or phase-shift) of the near-24-hour human circadian period to more precisely conform to the exact 24-hour period of the geophysical day. The chronobiologic model of health is based on optimal entrainment between our internal timing and the external light-darkness cycle, and the degree of alignment between the master pacemaker in the SCN and peripheral clocks in other brain areas and organ systems. Disruption of these temporal coordinations, by factors such as insufficient zeitgebers, altered sleep periods, shift-work, jet lag, seasonal changes, or daylight savings schedules, is increasingly recognized to be associated with significant psychiatric and medical morbidity.<sup>13,14</sup> Specifically, there is a growing literature on circadian disruption in BD which documents phase advances in mania, delays in depression, and trait-related reductions in amplitude.<sup>15-17</sup>

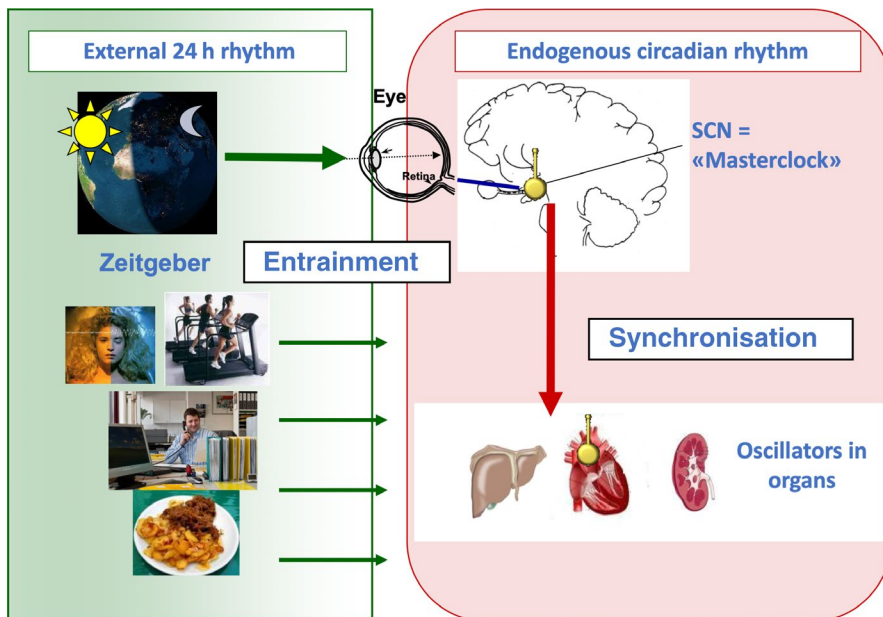
Clinical applications of the basic science of chronobiology has contributed to the field of chronotherapy which refers to treatments which are thought to act on the central biological clock. Though its use has been investigated and established in several areas of medicine, research on psychiatric chronotherapy has predominantly focused on the treatment of mood disorders.<sup>18,19</sup>

## 1.2 | Chronotherapeutics in psychiatry

The origin and development of treatments for mood disorders which act on the biological clock, or affective chronotherapeutics, is a



**FIGURE 2** A simplified model of the intracellular mechanisms responsible for mammalian circadian rhythm generation. Adapted from *The Regulation of Neuroendocrine Function: Timing Is Everything*, by L. H. Kriegsfeld, and R. Silver, 2006, May, *Hormones and Behavior*, 49(5), p. 557-574. Copyright 2006 by Hormones and Behavior. Adapted with permission [Colour figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]



**FIGURE 3** Zeitgebers, Entrainment and Internal Synchronization. Adapted from *External Zeitgebers and Internal Clocks*, by C. Cajochen, and V. Bromundt. Copyright by C. Cajochen and V. Bromundt. Adapted with permission [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

story of translational neuroscience, serendipity, careful clinical observation, seminal case studies, and progressive clinical trials.<sup>20-27</sup> Using these building blocks, five major chronotherapeutic classes have emerged over the past 50 years: bright light therapy (LT), sleep deprivation or wake therapy-based treatments (SD), dark therapy (DT), melatonergic agonists (MA), and behavioral interventions (subsuming interpersonal and social rhythm therapy, IPSRT, and cognitive behavioral therapy for insomnia adapted to bipolar disorders, CBTI-BP). Each of these strategies began with a mixture of chronobiologic discovery or new clinical insight followed by early applied science efforts and later technical refinement with validating clinical trials. The collective result of this work is the growing subdiscipline of affective chronotherapeutics.

What is the evidence that these therapeutics are truly chronotherapeutic in nature, that is, that they exert their effects on, or through, the biological timekeeping system? The substantial data of circadian disruption in BD itself confer a face validity to treatments which target the timekeeping system.<sup>16,17,28-30</sup> This argument is complemented by research demonstrating that effective pharmacotherapies for BD have significant effects on the timing and amplitude of circadian rhythms.<sup>31-35</sup> Additional circumstantial data are provided by animal and basic science studies which document that changes in various zeitgebers can and do alter rhythmic functioning.<sup>36-40</sup> Last, chronotype has been shown to influence the expression and treatment responsiveness of affective illness.<sup>41-46</sup> More direct evidence requires the measurement of a circadian output variable (such as the timing or amplitude of the rest-activity cycle, melatonin secretion, core body temperature, or levels of clock genes or their transcripts) before and after the treatment, finding a regular change in the variable after treatment and establishing that the circadian changes are necessary for the treatment response. Chronobiologic research has taken the initial steps in this process with several studies of LT and SD, showing that phase advances correlate with antidepressant

treatment response.<sup>47-49</sup> Apart from these few correlational studies, the remainder of evidence for a circadian mechanism of action of chronotherapies is circumstantial. Similar to other psychiatric treatments, at the present time it is the surface characteristics and intent that define these interventions as chronotherapeutic.

A comprehensive examination of this literature is warranted for the following reasons: First, there are no recent reviews that address all five major classes of chronotherapeutic modalities currently in use. Second, the literature on this topic has expanded exponentially over the past several decades. Third, while early work in this field initially focused on seasonal, and then non-seasonal, depressions, the application of chronotherapeutic interventions to bipolar depressions, manic states and rapid cycling is more recent and has not been summarized. Fourth, the increasing recognition of circadian dysfunction as a core component of BDs highlights the importance of interventions that directly or indirectly target this pathophysiology. Last, the maturation of outcome research in this area now allows for its juxtaposition with evidence-based pharmacotherapeutic and psychotherapeutic interventions for BD. Such comparisons will enable research that includes and ranks chronotherapeutic treatments within management guidelines for BDs.

The first project of the International Society of Bipolar Disorders (ISBD) task force on chronobiology and chronotherapy was to address the need for such an update through a systematic review of the treatment literature on the five classes of chronotherapy used in BD. This paper describes the outcome of that effort. Each modality will be introduced with a brief review of its historical development. The results of each literature review will then be summarized with a flowchart detailing the search process and a data table listing each study which met the review's inclusion criteria. Each study will be described by its experimental design, outcome measures, main results and multiple tolerability ratings. Scores of study quality, bias,

and level of evidence are included. The results of this review are then used to generate treatment recommendations for each chronotherapy in the acute and maintenance phases of this illness.

## 2 | METHODS

A panel of international experts was convened under the auspices of the International Society of Bipolar Disorders (ISBD). The lead author was appointed to chair the project by the executive committee of ISBD. Members were selected for participation based on research, clinical, or educational expertise in the field of affective chronotherapeutics. Invitations were extended to 45 individuals from 15 countries; 40 agreed to participate on the task force, of whom 25 participated on this review.

The purpose of this project was to critically review and summarize the outcome literature on the chronotherapeutic treatment of BDs. A second objective, based on this review, was to highlight the current status of this subdiscipline and promote its empirically based dissemination into clinical practice. The chronotherapeutic treatment literature can be divided into four classes, based on intervention type: bright light therapy (LT), sleep deprivation or wake therapy-based treatments (SD), dark therapy (DT), melatonergic agonists (MA). A fifth class of behavioral interventions was added that includes interpersonal and social rhythm therapy (IPSRT) and cognitive behavioral therapy for insomnia, adapted to bipolar disorders (CBTI-BP), due to the proposed circadian target of these interventions. While other treatments also modify daily activity, sleep and wake schedules, IPSRT, and CBTI-BP were chosen as the current, best exemplars of behavioral therapies that might act through impact on the biological clock. Because chronotherapies are almost always used in conjunction with primary mood stabilizing pharmacotherapy, unless otherwise specified, this paper examined the *adjunctive* use of each of these treatments. A chair or co-chairs were chosen for each of these sections.

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for systematic reviews and meta-analyses.<sup>50</sup>

### 2.1 | Eligibility criteria

Article inclusion criteria were: peer-reviewed, English-language publication, using adult subjects, 18 years or older, with a diagnosis of any form of BD, who were treated with one of the six chronotherapeutic methods under study, where symptoms and treatment response were tracked objectively (including clinical observation and longitudinal documentation). Animal research, single case studies, abstracts, duplicates, studies with over-lapping samples, or those with mixed diagnostic cohorts where the response and analysis of the bipolar subgroup could not be separately determined were excluded.

### 2.2 | Search strategy

The following databases were used: MEDLINE, Embase, CENTRAL (Cochrane), and PsycINFO. Each section used their own search strategy and key words, the latter of which generally included two categories: bipolar, manic, mania, affective illness, and affective disorder along with words and terms related to the particular modality being investigated (LT, SD, DT, MA, CBTI-BP, and IPSRT). Boolean operators and truncation were used to extend the above search terms. The databases were searched from their inception until end dates which varied between June and August of 2018 (see appendix for exact dates and search strategies). Some section chairs then cross-checked these results with the references found in large literature reviews to further verify the quality of the search process.

### 2.3 | Study selection

All articles generated by searches were screened for eligibility by the section chair(s) based on their title and abstract. The articles that passed this screening were then independently evaluated by two members of each study section to more formally evaluate eligibility. Discrepancies between reviewers were resolved by the section chair or the lead author.

### 2.4 | Data extraction and collection

Data tables were used to collect pre-defined descriptive and statistical measures for each article. When possible, NNT, effect sizes, odds ratio, and NNH were calculated. Uncertainties about article study design or statistics were addressed and resolved, when possible, through e-mail communication with the original author.

### 2.5 | Study quality

A modified Jadad scale was used to assess and grade study quality.<sup>51</sup> The scale was modified to include two additional questions about allocation concealment bias due to past criticism of this shortcoming.<sup>52</sup> The modified scale thus rated study quality from 0 (poorly designed with high risk for bias) to 7 (well-designed with low risk for bias).

### 2.6 | Level of evidence

The level of evidence was determined per the 2009 National Health and Medical Research Council (NHMRC) of Australia guidelines (see Appendix I).<sup>53</sup>

### 2.7 | Practice recommendations

Practice recommendations were derived from a synthesis of the efficacy and tolerability data extracted from the eligible review articles. Treatments were categorized as either "Recommended," "No Recommendation," or "Not Recommended." The former categories



were selected based on the presence or absence of evidence of efficacy and tolerability. The latter category was used if there was sufficient evidence that the treatment *lacked* efficacy or if the treatment was judged to pose significant risk and be contraindicated. The authors incorporated relevant preclinical, animal, and epidemiologic research to make and strengthen these latter contraindication determinations. All recommendations were generated through iterative deliberations among the section chairs and members, together with the lead author. An outcome of consensus was required in order to support these practice designations.

### 3 | INDIVIDUAL MODALITIES OF CHRONOTHERAPY

#### 3.1 | Bright light therapy

##### 3.1.1 | Introduction

The impact of light on mood has been appreciated for centuries.<sup>54</sup> The systematic investigation of bright light therapy (LT) in the treatment of depressive disorders did not begin, however, until the 1980's. Two landmark, chronobiologic studies conducted at that time spurred this clinical research. The first suggested that phase shifts of circadian rhythms could have an antidepressant effect.<sup>55</sup> The second established that bright light suppressed melatonin production and cued circadian rhythm timing in humans.<sup>20</sup> Prior to that study, circadian rhythms in humans were thought to be primarily entrained by social zeitgebers.<sup>56</sup> The establishment that light was a zeitgeber in humans, like all other mammals, was a paradigm-shifting advance for the field of circadian neurobiology. These discoveries led two clinical researchers to explore whether bright light could provide antidepressant action by correcting biological rhythm disturbances associated with depression. Kripke<sup>57</sup> working with unipolar depression, and Lewy et al<sup>21</sup> addressing winter depressions, each then conducted the first proof of concept, chronobiologically-informed tests of LT for these different depressive subtypes.

Following these two proof of concept reports, the initial investigations of light therapy focused on the treatment of seasonal affective disorder (SAD). SAD is defined as recurrent major depression that onsets every autumn or winter and spontaneously resolves by springtime. LT was found to induce a robust antidepressant response within 3-4 days that quickly dissipated after withdrawal of the bright light or crossover to the non-active comparator device.<sup>58,59</sup> Three influential clinical trials on SAD found superior efficacy from fluorescent bright white light over plausible placebos<sup>60,61</sup> and equivalent effects from monotherapy light or light combined with fluoxetine.<sup>62</sup> Research then moved to explore light therapy for non-seasonal depression. In this population, studies with larger samples and proper placebos demonstrated the efficacy of LT as monotherapy or as add-on treatment with antidepressants.<sup>26,63-65</sup> Most recently, light therapy has been actively examined as a treatment for bipolar depression.

In parallel with these successive waves of efficacy studies on different depressive subtypes, the technical aspects of light administration have been investigated and progressively refined. The intensity,<sup>66,67</sup> duration,<sup>66</sup> timing,<sup>68,69</sup> and wavelength or color<sup>66,70,71</sup> have been found to be key determinants of the efficacy, tolerability and safety of bright LT. Providing a sufficient level of illumination from a broad visual field (typical light devices measure 12 inches by 14 inches or 30 to 35cm) and lighting from above to avoid glare and target inferior retinal photoreceptors<sup>72</sup> are important features of the light source. Light devices typically provide 7,000 to 10,000 lux (a measure of illumination intensity that is dependent on the distance to light source) at eye level and within a distance of 12-13 inches or 30 to 33 cm.<sup>66</sup> The circadian pathway is most responsive to short wavelength, blue light.<sup>73</sup> However, single wavelength blue light devices still lack long-term clinical and safety outcomes data; hence, UV-filtered bright white light is still recommended in clinical guidelines.<sup>74</sup>

The outcome literature on light therapy for BD depression was initially summarized in a meta-analysis done in 2016.<sup>75</sup> Since that time four controlled trials have been conducted. This current review is warranted in light of this additional research.

##### 3.1.2 | Results

###### Summary

Figure A1 in Appendix II details the search process and exclusion reasons. 13 articles met inclusion criteria for review (Table 1). Six of these enrolled subjects with non-seasonal episodes, five did not characterize seasonality (but likely included subjects with both seasonal and non-seasonal episodes), and two included subjects with seasonal bipolar depression. There are no studies that have examined LT in the treatment of manic states.

From the 13 included articles, 12 examined the outcomes from bright white light and one examined the effects of green light. The studies with positive effects of LT implemented a range of light parameters, from 2500 lux of white light for 2 hours/day, individually titrated doses of 7000 lux broad spectrum light, blue-enriched white light for 30-60 minutes daily, to as high as 10 000 lux of bright white light for 45-60 minutes twice daily. Bright light presented at different times of day (morning, midday or evening) also imparted robust antidepressant effects using a standard dose or a dose titration schedule. Only four studies reported outcomes from placebo-controlled, randomized controlled trials (RCTs). Of the RCTs, one study examined the effects of midday treatment with bright white light compared to dim red placebo light and three examined morning bright white light compared to dim red light or an inactive ionizing unit. The duration of the clinical trials ranged from 8 weeks (2 reports), 6 weeks (3 reports), 2 or 3 weeks (6 reports), and even 1 week (1 report).

Only four articles provided sufficient data to estimate treatment effect or an effect size (Cohen's d, odds ratio or number needed to treat-NNT). The estimates of treatment effect suggested robust effects from morning or midday bright light; the NNT for remission

ranged from 2.17 to 3.17 and for response ranged from 1.61 to 2.86. With seasonal bipolar depression, bright light produced a large treatment effect (Cohen's  $d = 1.485$ ).

Treatment with bright light was well tolerated and none of the articles reported any serious adverse effects. In the case series report of nine women, three reported problems with dysfunctional uterine bleeding. Another study of 32 patients reported headaches in 12.5% who received white light and 6.25% who received dim red light. One of the RCTs on morning light exposure reported headaches in 16% and irritability in 17% of patients who were randomized to bright white light. To mitigate the risk for a mood polarity switch, some studies (but not all) enrolled patients who received stable-dosed antimanic (mood stabilizer) drug therapy and excluded patients with current or recent hypomania, mania, mixed symptoms, and rapid cycling illness. Even so, the rate of mood polarity switch from morning light was high (>10%) in four studies, moderate (5 to 10%) in one study, low (<5%) in four studies, and not reported in four of the 13 studies. Often the treatment-emergent hypomanic symptoms responded to reducing the number of minutes of daily light exposure. Two studies with exposure to bright light at midday reported no mood switches. The quality of the studies was highly variable; the modified JADAD scores ranged from as high as 7 to as low as zero and the corresponding level of evidence to support the scoring ranged from II to IV.

### 3.1.3 | Discussion

An earlier systematic review of studies prior to October, 2015 found some evidence for efficacy of bright light in BD,<sup>75</sup> but the nine included studies were primarily open-label and/or used LT combined with sleep deprivation (SD), and the quantitative meta-analysis examined only pre-post effect sizes. Our updated review identified 13 studies including newer placebo-controlled RCTs and provides further support for efficacy of LT for bipolar depression. Most of the open-label studies found good responses for LT, but one study reported better responses in unipolar depressed patients than the bipolar patients. The four placebo-controlled RCTs showed mixed results, with two studies showing superior effects for active LT versus low-light control conditions in primary outcomes<sup>27,76</sup> whereas the other two studies reported no significant differences in change scores between active light and control conditions (low-density negative ions<sup>77</sup> and sham negative ions.<sup>64</sup> However, one of the negative RCTs (a subgroup analysis of bipolar patients in a mixed-sample RCT) showed significantly higher response and remission rates with active LT.<sup>64</sup> Another pseudorandomized trial (randomized according to admission order) also showed superiority of active LT compared to dim light.<sup>78</sup> Overall, this evidence supports the efficacy of bright LT, with a variety of light parameters, for treatment of bipolar depression. Bright LT also appears well tolerated in bipolar patients with a relatively benign adverse event profile. As for potential for hypomanic switch with bright light, the best-quality data come from the RCTs. In four of the RCTs, no switches were reported with bright LT (338 patient-weeks of exposure) or control treatment, whereas

the other RCT reported hypomanic switches in 4 of 18 patients (144 patient-weeks exposure) treated with bright light compared to 2 of 20 patients (160 patient-weeks exposure) with sham treatment.<sup>78</sup> This suggests a low switch rate with LT in patients with BD. Nonetheless, this documented antidepressant switch potential, together with other clinical, animal, and epidemiologic data identifying associations between light exposure and mania, provide support for designating LT as contraindicated in the acute treatment of manic or mixed states.<sup>79-85</sup>

Limitations of this evidence base must be considered, including the small number of RCTs and small sample sizes in each, with none of the studies including more than 35 patients in each condition. The duration of trials was also short, with many of the study durations 3 weeks or less. Many different LT parameters were used, with variable intensities, wavelengths, and daily timing. Most studies included a mix of bipolar I and bipolar II patients, with several studies not reporting the ratio. Many of these patients were also taking mood stabilizing and other medications.

Given these limitations, a cautious conclusion is that bright LT appears to be effective for patients with bipolar depression. The parameters of effective LT in BD are similar to LT for patients with seasonal and non-seasonal unipolar major depressive disorder, but larger and longer trials are needed to determine optimal treatment parameters. Adjunctive bright LT can be given during the morning or midday, but informed by the evidence from the higher quality published reports (and analogous with other antidepressant treatments in BD), patients should be pre-treated with a mood stabilizer (anti-manic agent) and monitored closely for hypomanic switches. Titrating the daily exposure time (eg, starting with 15 minutes and increasing to 30 minutes or more, depending on response and tolerability) may reduce mood switching with LT. Treatment-emergent hypomanic symptoms may also resolve with reducing the daily exposure time.

## 3.2 | Treatments using sleep deprivation

### 3.2.1 | Introduction

*"But I also know a teacher with severe melancholy phases who explained that the following days would be most unbearable if she had slept quite well. This is precisely the reason for the upset. If she manages to keep up all night, she may feel tired the next morning, but the condition is more bearable. The (more) sleepless the night, the better the following day!"<sup>86</sup>*

The therapeutic potential of sleep deprivation (SD) was discovered by German psychiatrists. Johann Christian August Heinroth was the first physician to recognize, use, and write about the relationship between melancholia and sleep restriction in the early 19th century.<sup>87</sup> After a gap of almost 150 years, the finding was rediscovered by Walter Schulte who published the remarkable observation above in the first modern report on the process in 1966.<sup>86</sup> This report spurred the first clinical study of SD by Pflug and Tolle in 1971.<sup>88</sup>

After this rediscovery, a 20-year period of clinical study ensued in which the basic features of SD, also known as wake therapy, were explicated. These early case reports and case series characterized



**TABLE 1** Data Table for Systematic Review of Bright Light Therapy Studies

Study	Design <sup>a</sup>	Groups (N) <sup>b</sup>	Interventions	Duration of Intervention	Outcome Measures
Bauer <sup>174</sup>	Case series	N = 3, BP depression	LT: 2hr/d between 6 AM and 8 AM	6 wks	HDRS-17 at baseline, wks 1, 2, 3 and final visit
Benedetti et al <sup>175</sup>	RCT <sup>d</sup>	N = 9, inpatients with BP depression	40 mg/d citalopram + green Light, 30 min/d (n = 6) vs. 40 mg/d citalopram + deactivated negative ion generator (n = 3)	2 wks	HAM-D, SDS, VAS
Camardese et al <sup>176</sup>	Case series	N = 15, BP depression	LT: 30 min/d between 5:45 and 8:15 AM. If none or partial response after wk 1 increase to 45 min/d	3 wks	HDRS; Wks 1, 3, 4 and 8
Chojnacka et al <sup>64</sup>	RCT <sup>e</sup>	N = 50, BP depression	LT, 30 min/d (n = 29) vs. Sham (n = 21)	2 wks	HDRS-21, MADRS, BDI, CGI, PGI
Dauphinais et al <sup>77</sup>	RCT	N = 38, BP depression	LT, adjusted up to max dose of 45 min/d (n = 18) vs. Low density ions (n = 20)	8 wks	SIGH-ADS; YMRS and SAFTEE (adverse events)
Franchini et al <sup>177</sup>	RCT	N = 26, inpatient with BP depression	LT, 30 min/d + fluvoxamine (n = 16) vs. Fluvoxamine (n = 10)	6 wks	HDRS
Kupeli et al <sup>78</sup>	Pseudo-RCT	N = 32, BP depression	LT (n = 16) vs. Dim red light (n = 16) 30 min/d for 2 wks	2 wks	MADRS, HAM-D weekly
Papatheodorou & Kutcher <sup>178</sup>	Case series	N = 12 BP depression	LT: 45-60 min/day between 0700 and 0900 and between 1900 and 2100	1 wk in the hospital and take home light box prn.	BDI, SCL-58; Ratings at baseline, d 1 and 7
Rosenthal et al <sup>58</sup>	Comp. study w/ concurrent controls	N = 11, BP depression	9/11 received LT and were crossed over to control, dim light; 2 received LT only LT first (n = 4); Dim yellow light first (n = 5)	2 wks	HRS, Sleep EEG, Neuroendocrine studies
Sit et al, 2007	Case series	N = 9, females with BP depression	Morning LT (n = 4) vs. Midday LT (n = 5) Target dose of 45 min/d	8 wks acute, 16 wks continuation phase	SIGH-ADS and MRS Biweekly for 8 wks

Main Results	Effect Size, NNT, or Odds Ratio	Tolerability/ NNH	Serious Adverse Event	Mood Switch Potential	Speed of Response <sup>c</sup>		Modified Jadad Scale	Level of Evidence
					Score A	Score B		
In all 3 pts, response ( $\geq 50\%$ reduction in HDRS-17) and remission ( $\text{HDRS} \leq 7$ ) onset wk 3 and sustained until wk 6	NA	NA	None	High	8-28 d	8-28 d	1	IV
Response ( $\geq 50\%$ reduction HAM-D) rate: green light vs. PBO, 77.8% vs 41.7%, $P = .04$	NA	None	None	Low	8-28 d	8-28 d	2	IV
Response ( $\geq 50\%$ HDRS reduction) rate = 6.7%	NA	None	None	Low	>28 d	>28 d	1	IV
LT vs sham: response ( $\geq 50\%$ reduction in HDRS-21) rates were 55.20% vs. 23.80%, $P = .026$ ; remission rates ( $\text{HDRS-21} \leq 8$ ) were 34.50% vs. 9.50%, $P = .041$ Both groups improved on HDRS-21 but no sig. differences in the change in scores	Response NNT = 3.09, OR = 3.94; Remission NNT = 4.01, OR = 5.00;	None	None	NA	8-28 d	8-28 d	2	III-1
LT vs. Low density ions No sig. differences in response or remission rate ( $\geq 50\%$ reduction SIGH-ADS or $\text{SIGH-ADS} \leq 8$ at the endpoint., 50% vs 55.6%) and in % reduction in SIGH-ADS (52% vs 47%)	NA	LT: Headaches 61%, Irritability 17%	None	Wk3, 4: briefly high; Wk8: low	>28 d	>28 d	5	II
80% remission ( $\text{HDRS} < 8$ ) rate in both groups	Remission OR = 1.0	None	None	Moderate	8-28 d	NA	2	III-1
LT vs red light: MADRS response ( $\geq 50\%$ reduction) rates: 81% vs 19%, $P < .0001$ ; HAM-D response ( $\geq 50\%$ reduction) rate: 69% vs 12.5%, $P < .001$ ; MADRS (<9) Remission rates: 44% vs 12.5%, $P = .05$ ; HAM-D (<7) Remission rates: 44% vs 6%, $P = .05$	Response NNT = 1.61, OR = 18.8; Remission NNT = 3.17, OR = 5.44	LT: headaches 12.5% vs Red Light: 6.25%	None	NA	8-28 d	8-28 d	1	III-1
3 marked response(70% decrease in baseline depression scores); 2 moderate response (40 to 74% decrease); 2 mild or no response Mean BDI scores pre vs. post LT ( $21.2 \pm 10.0$ vs. $11.1 \pm 8.8$ , $sd = 8.8$ , $P < .005$ )	NA	None	None	NA	4-7 d	4-7 d	0	IV
LT: HRS pre vs. post ( $n = 11$ , $18.8 \pm 4.3$ vs. $7.7 \pm 5.5$ , $P < .001$ ; $n = 9$ , $17.7 \pm 3.7$ vs. $6.7 \pm 5.1$ , $P < .001$ ).Relapse with 3-4 d of withdrawing LT. Only 1 experienced sustained effect after withdrawal. Dim yellow light: HRS pre vs. post ( $15.1 \pm 4.6$ vs. $13.2 \pm 7.1$ , n.s.)	HRS Baseline vs post-treatment (all N): Cohen's d ES = 1.485 (large)	None	None	Moderate	8-28 d	8-28 d	1	III-2
Morning LT: 1 of 4 full sustained response ( $\text{SIGH-ADS} \geq 50\%$ reduction and $\text{MRS} < 4$ ) with 30 min/d LT; 3 of 4 induction of mixed states within 2 wks of LT for 15 min/d, Midday LT: 3 of 5, full response with 30-60 min/d midday LT; 1 partial response with midday light and eventual full response	NA	3/9 (33%) with dysfunctional uterine bleeding	None	Morning LT: High; Midday LT: Low	>28 d	NA	1	IV

(Continued)

TABLE 1 (Continued)

Study	Design <sup>a</sup>	Groups (N) <sup>b</sup>	Interventions	Duration of Intervention	Outcome Measures
Sit et al, 2017	RCT	N = 46, BP depression	LT (n = 23) vs. Dim red light (n = 23) Target dose of 60 min/d	6 wks	SIGH-ADS and MRS weekly
Yamada et al <sup>179</sup>	Case series	N = 7, inpatients with BP depression	LT morning exposure (n = 3) 06:00-08:00 vs. LT evening exposure (n = 4) 18:00-20:00	1 wk	HRSD
Zhou et al <sup>768</sup>	RCT	N = 63, BP depression	LT (n = 33) vs. Dim red light (n = 30) 1 hr every morning for 2 wks	2 wks	HAMD-17, QIDS-SR16; weekly YMRS and SERS

Note: See Table A2 for legend of all abbreviations used in this table.

See Table S1 for details of light therapy protocols used in these studies.

<sup>a</sup>Corresponds to the NHMRC study designs

<sup>b</sup>All groups contain male and female, BDI and II outpatients, unless otherwise specified. N refers to the total number of BD subjects.

<sup>c</sup>Score A is the first time point of statistically significant separation from comparator; Score B is the time to reach  $\geq 50\%$  reduction in primary outcome measure

<sup>d</sup>Subgroup analysis of RCT, with small N

<sup>e</sup>Subgroup, secondary analyses

the antidepressant effects of SD as rapid, typically occurring over 24 to 36 hours, broadly effective, yielding response rates of approximately 60% across a wide range of unipolar and bipolar depressive states, and transient, with relapse rates of 83% after recovery sleep or even brief naps.<sup>89</sup> A literature review by Wu and Bunney in 1990 summarized these early findings from over 60 studies and 1700 subjects.<sup>90</sup> For most psychiatrists this is where the story began and ended: an unusual procedure with dramatic but typically fleeting clinical value.

Following these initial investigations, a second wave of more systematic research ensued that sought to determine how to sustain the early antidepressant response associated with SD, optimize technical aspects of the procedure, identify clinical predictor variables of response and evaluate safety. This second phase showed that adjunctive treatment with lithium, bright light therapy (LT), sleep phase advance, or pindolol could each prolong the rapid but ephemeral mood elevation for weeks to months.<sup>91-96</sup> As a result, when used in current clinical practice, it is standard to combine wake therapy with other chronotherapeutic and/or pharmacologic treatments.

The format and dosing of SD was investigated. Originally, a complete night of SD was employed resulting in a 36-hour period of wakefulness (total sleep deprivation, TSD). Later studies explored the use of partial sleep deprivation (PSD) where subjects are allowed to sleep for 4 to 5 hours, either in the first half of the night, from 10PM to 2 or 3AM (and are thus deprived of sleep in the latter half of the night, hence PSD-Late), or the latter half of the night, from

3AM to 8AM (PSD-early). Though more commonly used, PSD-late has not shown consistent superiority over PSD-early and is roughly comparable in efficacy to TSD.<sup>97-100</sup>

Two formats of SD emerged: a week-long protocol consisting of three nights of TSD each followed by a night of full recovery sleep, and an approximately 4-day procedure, termed triple chronotherapy, that uses one night of TSD accompanied by LT and sleep phase advance. Despite their common usage, there are no studies comparing these two formats. Some reports find that response can be increased with more cycles of SD whereas others show no such dose response relationship.<sup>101</sup> There is some evidence that the presence of diurnal variation in mood and bipolarity predicts positive response.<sup>102-105</sup> Last, few adverse effects have been noted. When used with lithium, initial reports found switch rates of approximately 9% into hypo/mania among bipolar depressives<sup>106</sup>; more recent studies document substantially lower rates of 1.4%.<sup>107</sup>

In the last two decades, clinical trials of SD have continued. These later studies have provided additional support for its efficacy in the acute treatment of bipolar depression, suggested a role in treatment resistant depressions, and identified a mood-independent, suicide-reducing impact of the process.<sup>107-110</sup> Its rapid onset of action has also allowed it to serve as a convenient, experimental vehicle to explore the molecular, genetic, circadian, and neurobiological correlates of antidepressant response and remission.<sup>111</sup> While a meta-analysis was recently conducted on the efficacy of SD across all depressive subtypes, it excluded the type of combined, chronotherapeutic protocols in which SD is typically

Main Results	Effect Size, NNT, or Odds Ratio	Tolerability/ NNH	Serious Adverse Event	Mood Switch Potential	Speed of Response <sup>c</sup>		Modified Jadad Scale	Level of Evidence
					Score A	Score B		
LT group showed significantly higher remission rate (SIGH-ADS $\leq 8$ , 68.2% vs 22.2%) and lower mean depression score at the endpoint visit (SIGH-ADS $9.18 \pm 6.57$ vs. $14.94 \pm 9.16$ , adjusted $P = .023$ )	LT vs dim red light Remission Rate: OR = 7.50, 95% CI = 1.78, 31.28, $P = .003$ ; NNT(remission) = 2.17	None	None	Low	>28 d	NA	7	II
Morning LT: mean reduction for HRSD score = 4.0; Evening LT: mean HRSD score reduction = 9.0	NA	NA	None	NA	4-7 d	NA	1	IV
Morning LT vs dim red light: response ( $\geq 50\%$ reduction HAMD-17) rates of 78.2% vs 43.3% and HAMD endpoint scores of $8.6 \pm 3.4$ vs $10.5 \pm 3.2$ ( $P = .03$ ) after 2 wks	Response NNT = 2.86, Cohen's d = 0.58	None	None	Low	4-7 d	4-7 d	5	II

administered.<sup>112</sup> This review was designed to address this shortcoming by assessing the efficacy and safety of standard wake therapy-utilizing combination interventions for the acute treatment of bipolar depression.

### 3.2.2 | Results

#### Summary

Figure A2 in Appendix II details the search process and exclusion reasons. The 21 articles left for review included eight case series, 11 comparative studies without concurrent controls, one pseudorandomized trial, and one randomized control study (Table 2). Seven of these articles were published in the past 20 years. Each of these more recent studies used SD in conjunction with either pharmacotherapy or other chronotherapeutic interventions and all but one used either the Hamilton Rating Scale for Depression or the MADRS to measure outcome. All studies examined the acute, antidepressant effects of SD; one study conducted a 9-month prospective follow-up after initial administration. There were no studies of SD for manic states or their prophylaxis.

The experimental design of most studies did not allow for calculation of effect sizes. The average pre-post treatment response rates were 43.9% from the case series, 59.3% from the uncontrolled comparative studies, and 59.4% from the one, RCT. In the two studies that used controls, separation of response from the control condition occurred within 7 days. When speed of response was determined by time to achieve a 50% reduction in baseline depression

score, four studies showed response in 0 to 3 days, three in 3 to 7 days, three in 7 to 28 days, and one in more than 28 days.

Tolerability was not systematically assessed in most of the articles but when it was, side effects rarely surpassed 10% in frequency. The one serious adverse event was associated with adjunctive medication. Treatment emergent affective switch was examined in about one half of the studies and in those, seven noted a frequency of 0 to 5%, two found a frequency of 5 to 10% (one with an N of 3, the other using drug-free rapid-cycling subjects) and two small studies reported a frequency of greater than 10%. In keeping with the predominance of case series and uncontrolled comparative studies, Jadad scores were either 0 or 1, and the level of evidence was class III or IV (with the exception of the one RCT).

### 3.2.3 | Discussion

This is the first literature review to comprehensively examine the outcome research on treatments using SD for subjects with bipolar depression. In contrast to a meta-analysis conducted in 2017,<sup>112</sup> this review was confined to subjects with BD and reviewed SD treatments, as they are commonly employed as part of a combination strategy with other chronotherapeutic interventions. Using these inclusion and exclusion criteria, our search yielded 21 articles published over a 43-year period.

The major findings of this review are as follows: The literature on SD-based treatments is largely based on older research consisting predominantly of case series and uncontrolled comparative

**TABLE 2** Data Table for Systematic Review of Sleep Deprivation Studies

Study	Design <sup>a</sup>	Groups (N) <sup>b</sup>	Interventions	Duration of Intervention	Outcome Measures
Benedetti et al <sup>180</sup>	Comp. study w/o concurrent controls	N = 30 inpatients with BP depression	TSD x 1 + 3 d SPA + continuation/ongoing lithium (n = 16) vs. Drug-free TSD x 1 + 3 d SPA (n = 14)	6 d	HRSD-NOW, daily, day 1 to 6; self-administered VAS, daily, day 1 to 6
Barbini et al <sup>102</sup>	Comp. study w/o concurrent controls	N = 25 drug-free inpatients with BP I and BPII depression	TSD x 3	7 d	HRSD-NOW on d 1,2 and 7; self-perceived VAS on d 1-3 and 7.
Benedetti <sup>181</sup>	Pseudo-RCT <sup>d</sup>	N = 10 inpatients with BP depression	TSD x 3 plus fixed dose fluoxetine (n = 5) vs. Fixed dose fluoxetine alone (n = 5)	4 wks	weekly HRSD scores
Benedetti et al <sup>91</sup>	Comp. study w/o concurrent controls	N = 40 inpatients with BP I depression	TSD x 3 plus lithium (n = 20) vs. TSD x 3 no lithium (n = 20)	3 to 7 d	3 x day mood self ratings using a VAS during TSD treatment. HAM-D scores on day 0 and 10
Benedetti et al <sup>180</sup>	Comp. study w/o concurrent controls	N = 28 inpatients with BP depression	TSD x 3 with PBO (n = 14) vs. TSD x 3 with amineptine (dopaminergic AD, n = 14)	9 d	MADRS on d 1, 2 and 7; VAS on d 1 through 7
Benedetti et al <sup>182</sup>	Comp. study w/o concurrent controls	N = 60 inpatients with BP I depression, 27 with stage I or II drug resistance	1 wk with TSD x 3 and LT (400 lux green light x 30 min at 3 AM on TSD night and between 8 to 9 AM after recovery sleep) + antidepressants and lithium salts	7 d	HDRS, VAS
Benedetti et al <sup>107</sup>	Comp. study w/o concurrent controls	N = 143 inpatients with BP depression, 83% with positive history of drug resistance	TSD x 3. 30' LT at 3AM during each of 3 TSD nights and in the morning during, and for 2 wks after, the wk of TSD. All subjects either started on or continued on lithium during TSD and LT.	7 d	HRSD-NOW, BDI, HRSD item 3 to rate suicidality
Cole et al <sup>183</sup>	Case series	N = 3 inpatients with BP depression	TSD, unknown number of cycles	Vary	HDRS or clinical observation.
Colombo et al, <sup>184</sup>	Comp. study w/o concurrent controls	N = 108 inpatients with BP depression	TSD x 3 over 1 wk + (1) lithium alone (n = 15) (2) lithium + dim light (n = 14) (3) lithium + LT (n = 17) (4) drug free + no light (n = 20) (5) drug free + dim light (n = 19) (6) drug free + LT (n = 23)	6 d	3 x day self rating of Mood using VAS; Sleepiness hourly assessed by SSS on night of TSD
Fähndrich <sup>185</sup>	Case series	N = 22 BP depression	TSD x 1	3 d	"Befindlichkeits" scale, VAMS, and HDRS
Gill et al <sup>186</sup>	Case series	N = 3 BP rapid-cycling	TSD x (1 to 8)	Vary	BHDR, BHMR



Main Results	Effect Size, NNT, or Odds Ratio	Tolerability/ NNH	Serious Adverse Event	Mood Switch Potential	Speed of Response <sup>c</sup>		Modified Jadad Scale	Level of Evidence
					Score A	Score B		
Response rate = 43.33% (HDRS score < 8 at day 6)	NA	NA	NA	NA	NA	4-7 d	0	III-3
After TSD, mood levels significantly improved in bipolar I or bipolar II patients	NA	NA	NA	Low	NA	0-3 d	0	III-3
At day 7 and 14 statistically significant faster reduction in HRSD scores in FLX + TSD vs. FLX-alone group, at d 21 and 28 no differences between groups	NA	NA	NA	NA	4-7 d	8-28 d	1	III-1
VAS scores and HAM-D showed an overall improvement: TSD + Lithium: HAM-D 63.9% decrease TSD alone: HAM-D 45.0% decrease	NA	NA	NA	NA	NA	NA	0	III-3
Response rate = 22.22% (MADRAS < 6) Improved greatest at first cycle and decreased with treatment repetition.	NA	None	Amineptine group: one subject developed hepatitis with cholestatic jaundice	Low	NA	0-3 d	1	III-3
Response rate = 58.3% (>= 50% reduction in HDRS)	NA	None	None	NA	NA	4-7 d	0	III-3
Response rate = 70.1% (≥50% reduction in HRSD after one wk); response maintained in 55.3% of subjects at one month. TSD and light treatment with lithium can rapidly reduce suicidality and depression in drug resistant major depression in bipolar disorder patients	NA	NA	NA	Low	NA	4-7 d	0	III-1
Response rate = 33.3% "marked improvement" lasting at least 12 hours following 1 or 2 treatments	NA	None	None	High	NA	NA	0	IV
VAS scores showed an overall change across all conditions.	NA	NA	NA	Mod	NA	NA	1	III-3
Significant decline in Bf-S and VAMS but not HDRS after 1 TSD	NA	NA	NA	NA	NA	NA	0	IV
Little response to TSD early vs. robust responses late in depressive episode	NA	None	None	Low	NA	NA	0	IV

(Continues)

TABLE 2 (Continued)

Study	Design <sup>a</sup>	Groups (N) <sup>b</sup>	Interventions	Duration of Intervention	Outcome Measures
Larsen et al <sup>187</sup>	Case series	N = 3 drug-free inpatients BP depression	TSD x 1	3 d	Bjorum and Lindberg Scale
Leibenluft et al <sup>188</sup>	Case series	N = 4 BP depression	Late PSD x 4 over two wks vs. Early PSD (control)	33 d	modified SIGH-SAD, a rating hypomanic and manic symptoms, BDI, POMS
Papadimitriou <sup>189</sup>	Comp. study w/o concurrent controls	N = 7 drug-free BP depression	TSD x 2 per wk for 4 wks	4 wks	weekly HRSD scores
Pflug <sup>190</sup>	Case series	N = 12 BP depression	TSD x (1 to > 4)	Vary	Bojunovsky and Chloupkova
Smeraldi et al <sup>92</sup>	Comp. study w/o concurrent controls	N = 40 inpatients with BP I depression	TSD x 3 with PBO (n = 20) vs. TSD x 3 with pindolol (n = 20)	9 d	HDRS and VAS, at baseline and
Souetre et al <sup>95</sup>	Comp. study w/o concurrent controls	N = 5 drug-free inpatients with BP depression	Late PSD x1 (sleep from 11PM to 2AM) plus 13d sleep phase advance (SPA)	2 wks	HDRS, daily during baseline and during SPA
Vovin et al <sup>191</sup>	Case series	N = 19 with "manic-depressive psychosis"	TSD, 2-3x wk one, and 1x/week thereafter, with ongoing pharmacotherapy	Vary	clinical observation
Wehr et al <sup>192</sup>	Case series	N = 4 drug-free BP depression	TSD plus LT (48 x 40 watt fluorescent bulbs, 3000 lux) and TSD plus dim light (single 15 watt incandescent bulb, 1 lux)	3 d	Bunney-Hamburg scale, VAS
Wehr, et al <sup>22</sup>	Comp. study w/o concurrent controls	N = 9 drug-free rapidly cycling subjects	TSD x 1	3 d	Modified Bunney Hamburg scale
Wu et al <sup>108</sup>	RCT	N = 49 BP depression	TSD x 1 + LT (3 d, 2 h 5000 lux) and SPA (3 nights) and medication treatment as usual (TAU, n = 32) vs. TAU only (n = 17)	7 d	HRSD-19

Note: See Table A2 for legend of all abbreviations used in this table.

<sup>a</sup>Corresponds to the NHMRC study designs

<sup>b</sup>All groups contain male and female, BDI and II outpatients, unless otherwise specified. N refers to the total number of BD subjects.

<sup>c</sup>Score A is the first time point of statistically significant separation from comparator; Score B is the time to reach >= 50% reduction in primary outcome measure

<sup>d</sup>Randomization method not described

Main Results	Effect Size, NNT, or Odds Ratio	Tolerability/ NNH	Serious Adverse Event	Mood Switch Potential	Speed of Response <sup>c</sup>		Modified Jadad Scale	Level of Evidence
					Score A	Score B		
Response rate = 66.6% (>= 3 point divergence in pre vs. post Tx score on Bjorun Lindberg scale)	NA	NA	NA	NA	NA	0-3 d	0	IV
Response rate = 25% (≥ 30% decrease in SIGH-SAD)	NA	NA	NA	NA	NA	NA	0	IV
2/7 improved >=50% on HRSD; 1/7 improved 30% on HRSD "Prophylactic treatment": 1x/wk without prior acute treatment, 3/5 reacted positively; 1x/wk following acute treatment, 4/6 responded very positively	NA	None	None	NA	NA	8-28 d	0	III-3
42.15 average reduction on the Bojunovsky and Chloupkova Rating Scale across the 39 TSD in 12 subjects	NA	NA	NA	NA	NA	NA	0	IV
TSD + pindolol: response rate (HDRS <= 8 at day 10) at end of treatment = 75%; TSD + PBO: response rate = 15%	NA	Pindolol: 30% hypotension, 10% headache, 40% "scarcely restorative sleep" during recover sleep; PBO: 10% - headache; 10% scarcely restorative sleep during recovery night	None	Low	NA	8-28 d	1	III-3
All improved with PSD and 4/5 showed continuing remission during SPA	NA	None	None	NA	NA	NA	0	III-3
7 "cured" at end, 11 temporary improvement with relapses	NA	10% worsening premorbid depression and anxiety;	None	Low	NA	>28 d	1	IV
Post- vs. pre-treatment mood and depression ratings significantly improved regardless of light conditions	NA	NA	NA	Low	NA	0-3 d	0	IV
8/ 9 subjects switched out of the depressive phase on at least one occasion after TSD: 4 into mania, 3 into hypomania	NA	NA	NA	High	NA	NA	0	III-3
Significant differences in HRSD scores seen within 48 h after TSD between chrono plus med vs. med only groups, which were sustained for at least 7 wks	NA	None	None	Mod	0-3 d	NA	3	II

studies. This literature is characterized by significant variability in administration protocols, length of follow-up, and outcome criteria used. Within the scope of these limitations, the acute, antidepressant response rates from the better Level III and one Level II studies were approximately 60%, the figure typically cited in past reviews for all depressive subtypes. Tolerability, treatment emergent affective switches and speed of response were not commonly assessed systematically. When these parameters were tracked, SD-based treatments were generally safe, had low rates of manic symptom induction (0 to 5% in over 60% of treated subjects), and were rapid, most yielding response within 7 days.

The above summary provides a low level of evidentiary support, from a research literature consisting primarily of uncontrolled studies, for the use of SD-based treatments in the acute management of bipolar depression. The clinical application of this efficacy data is bolstered by a generally benign tolerability profile and a rapid response speed. When combined with the relative paucity of effective, safe alternatives, treatments that use SD may be considered after more established options fail, when they are not tolerated, or when rapid antidepressant response is required.

There are no studies that examined SD for manic states. The potential, albeit low, for inducing manic symptoms found in this review, combined with clinical data documenting the role of sleep loss in precipitating mania and sleep deprivation-based models of mania in animals coalesces to contraindicate the use of this intervention for the acute treatment of manic or mixed states.<sup>113-117</sup>

This review identifies several challenges to research on SD for bipolar depression. The low level of evidence for most of the obtained studies can be partly attributed to the difficulty in creating an effective control condition for SD: subjects cannot be blinded to their state of wakefulness. Creative strategies to circumvent this challenge—such as those used by Parry et al<sup>118</sup> when comparing PSD-early to PSD-late—would strengthen this literature. Second, none of the reviewed studies attempted to time the SD period based on the subject's chronotype or adjust its duration based on the subject's

habitual sleep length. Personalized adjustments of this kind might enhance response rates and clarify underlying mechanisms. Last, while this review specifically sought to address SD combinations (eg SD, light therapy, and sleep phase advance), these bundled treatments make discernment of individual contributions to response difficult. Future studies that separate these SD combinations into component parts that are compared to each other would advance our understanding of this treatment.

### 3.3 | Dark therapy

#### 3.3.1 | Introduction

If antidepressants can induce mania and light can be an antidepressant, can darkness be anti-manic?<sup>119,120</sup> Can regular periods of darkness act as a mood stabilizer? This idea was introduced in a case report in 1998 in which a patient with severe rapid-cycling bipolar disorder (BD) was treated with 14 hours of enforced darkness, consisting of bedrest in a light-sealed room from 6 PM to 8 AM<sup>23</sup> Rapid reduction in cycling was followed by over a year of stability of sleep, mood, and motor activity. During the dark-therapy regime, antidepressant medication no longer provoked mood cycling.

A second case report of dark therapy (DT) for a patient with a long history of severe BDI replicated the results, with no medications.<sup>121</sup> Six years later, a pseudorandomized trial (randomized according to admission order) of DT followed, as adjunctive treatment for patients hospitalized with mania. Compared to treatment as usual alone, adjunctive DT more quickly reduced manic symptoms, with an effect size of 1.6 after 3 days of treatment in patients with a manic episode lasting shorter than 14 days.<sup>122</sup>

A basic science discovery in 2001 paved the way for a simpler means of delivering darkness in electrically lit environments. A new retinal photoreceptor responsible for mediating the effects of light on the master clock was discovered that responds almost exclusively to wavelengths between 420 and 600 nanometers blue to

**TABLE 3** Data Table for Systematic Review of Dark Therapy Studies

Study	Design <sup>a</sup>	Groups (N) <sup>b</sup>	Interventions	Duration of Intervention	Outcome Measures	Main Results
Barbini et al <sup>122</sup>	Comp. study w/ concurrent controls	N = 32 inpatients with BP I, manic episode	Dark therapy (14 hours from 18:00 to 08:00) plus TAU (n = 16) vs. TAU only (n = 16)	3 d	Daily YMRS, clinical observation of sleep, time in hospital	Rapid reduction in manic symptoms in dark therapy group
Henriksen et al <sup>126</sup>	RCT	N = 23 inpatients with BP I, manic episode,	BB-glasses (n = 12) vs. PBO-glasses (clear, n = 11) 14 hrs from 18:00 to 08:00 + TAU	7 d	Daily YMRS, actigraphy, patient satisfaction self report form	Rapid reduction in manic symptoms on YMRS in BB-glasses group (14.1 [9.7-18.5]) vs. PBD group (1.7 [4.0 -7.4])
Phelps <sup>24</sup>	Case series	N = 21 BP and Comorbid Insomnia	BB-glasses 20:00 to bedtime (all artificial light out)	as needed	CGI, clinical assessment of change in initial insomnia	11 improved, 8 no response, 2 worse (they disliked fell asleep earlier)

Note: See Table A2 for legend of all abbreviations used in this table.

<sup>a</sup>Corresponds to the NHMRC study designs

<sup>b</sup>All groups contain male and female, BDI and II outpatients, unless otherwise specified. N refers to the total number of BD subjects.

<sup>c</sup>Score A is the first time point of statistically significant separation from comparator; Score B is the time to reach  $\geq 50\%$  reduction in primary outcome measure

blue-green light.<sup>70</sup> In mediating the effects of light, the strongest mammalian zeitgeber, this photoreceptor acts as the major driver of circadian rhythms in humans.<sup>82</sup> Thus if blue light is prevented from reaching the retina, the brain experiences "virtual darkness", as confirmed with the demonstrations of normal melatonin secretion when subjects wore amber-tinted blue-blocking glasses while awake all night in a fully illuminated sleep labs.<sup>123,124</sup>

This basic science finding suggested the possibility of using virtual darkness, via blue-blocking lenses at night, for bipolar manic or mixed states.<sup>24</sup> A preliminary trial of amber lenses demonstrated feasibility of outpatient use and possible improvement in sleep quality.<sup>125</sup> This led to a randomized trial by Henriksen and colleagues, replicating the earlier inpatient mania study but this time using blue-blocking lenses to provide adjunctive *virtual* darkness.<sup>126</sup> In this trial, patients using control lenses experienced a slow reduction in mania rating scores over the first week, whereas the blue-blocking lenses were associated with much steeper reduction in scores, effect size 1.86.

### 3.3.2 | Results

#### Summary

Figure A3 in Appendix II details the search process and exclusion reasons. The three articles which met inclusion criteria for review were published between 2005 and 2016 and included one pseudoRCT with 3 days of evening DT for inpatients in a manic episode (Jadad score 1, Level of evidence III-2); one case series utilizing evening blue-blocking glasses for euthymic outpatients (no Jadad score, level of evidence IV); and one randomized placebo-controlled trial (referenced in the previous section) with 1 week of evening blue-blocking glasses for inpatients in a manic episode (Jadad score 4, level of evidence II) (Table 3). For the inpatients in a manic episode, a significant effect on manic symptoms was found within 3 days compared to the control condition. For the euthymic outpatients, 42% experienced a self-report-based large reduction

in insomnia as assessed with the Clinical Global Impression Scale. Tolerability was not reported in two trials and one showed minor side effects. There were no studies of DT for the treatment of bipolar depression .

### 3.3.3 | Discussion

The two controlled trials of adjunctive DT for acute mania each demonstrated a more rapid reduction in manic symptoms, a decrease in the associated use of antipsychotic medication, and, in one, a shorter duration of hospitalization relative to treatment as usual.<sup>122,127</sup> Are current data sufficient to justify adoption of DT as an adjunct to treatment as usual?

For scientists guiding future research, the small sample sizes in the two inpatient trials of DT (literal and virtual using blue-blocking lenses, respectively: Barbini et al, N = 16; Henriksen et al, N = 23) are a concern. A landmark 2005 overview of medical research found that replication of earlier studies was lower with small sample sizes.<sup>128</sup> On the other hand, a large effect size, as found in both these trials, predicts higher replicability. The rapid and uniform clinical response in each of the DT studies is an internal consistency that also suggests further trials will replicate results to date. Furthermore, the  $P = .001$  in the study by Henriksen et al suggests that no efficacy at all is very unlikely.<sup>126</sup>

For clinicians treating patients with mania, risk/benefit ratios are major determinants of the choice between available treatments. Per multiple treatment guidelines including the 2018 ISBD/CANMAT, current treatments for acute mania are full-dose lithium or divalproex plus an antipsychotic.<sup>129</sup> Antipsychotics carry well-known substantial risks, including adverse metabolic changes and weight gain even with short-term use. In the two controlled trials, patients receiving adjunctive DT required *fewer* antipsychotics during their shorter hospital stays<sup>122,126</sup> In comparison, there were no adverse side effects noted in the Barbini study and Henriksen reported that two subjects, 18% of the treatment group, developed depressive

Effect Size, NNT, or Odds Ratio	Tolerability/NNH	Serious Adverse Event	Mood Switch Potential	Speed of Response <sup>c</sup>		Modified Jadad Scale	Level of Evidence
				Score A	Score B		
Cohen's d after 1 night: 0.9, 2 nights: 1.2, 3 nights 1.6	None	None	Low	0-3 d	4-7 d	1	III-2
Cohen's d after 1 night: 0.7, 2 nights: 0.4, 3 nights 0.9, 4 nights 1.5, 5 nights:1.0, 6 nights:1.4, 7 nights 1.9	15% - emerging depressive symptoms	None	Low	0-3 d	4-7 d	4	II
NA	None	None	Low	NA	NA	N/A	IV



symptoms which were relieved within hours by delaying the use of the lenses or discontinuing them. There were no other significant adverse effects (though sensitivity to anti-dopaminergics may increase such that their doses as well as the timing of BB-glasses should be handled dynamically based on day-to-day observation of symptoms<sup>127</sup>).

Usability is another factor impacting treatment selection. While literal darkness is difficult to administer, the feasibility of using BB lenses has been demonstrated in the Henriksen trial and they are now being increasingly used in our own inpatient units for patients admitted with acute mania (JP; TH). Alternatively, a dynamic LED light system can be installed in a hospital unit and be used to create a blue-depleted evening light environment similar to a “virtual darkness.” Indeed, a RCT to test the effectiveness of such an evening blue-depleted light environment is underway in a psychiatric emergency ward.<sup>130</sup>

Extending this logic: is there a role for DT in *maintenance* treatment of BD? Many antimanic treatments are also used as mood stabilizers. A regular rhythm of adequate sleep appears to be a mood stabilizer, per this ISBD review. Regular darkness may promote such a regular rhythm, per the case data: note the continued stable mood experienced by the NIMH patient whose severe rapid cycling remitted and remained stable for over a year on no medications, just DT alone.<sup>23,121</sup> Just as lithium appears to enhance the amplitude of certain circadian rhythms, so too does exposure to a regular cycle of light and darkness increase the amplitude of the circadian signal.<sup>33,131,132</sup> Psychotherapy focusing primarily on a regular pattern of sleep significantly reduced relapse into depression or mania.<sup>133</sup> Future RCT's would help to assess this circumstantial evidence of potential maintenance efficacy of DT in BD.

This review found no studies of DT for the acute treatment of BD depression. Given the animal and epidemiologic data identifying correlations and possible causal links between reduced light exposure and depressive episodes<sup>134-137</sup> the extended light deprivation used in DT is best considered as contraindicated in the acute treatment of BD depression at this time.

Evidence-based medicine calls for “the conscientious, explicit, and judicious use of *current best evidence* in making decisions about the care of individual patients”<sup>138</sup> [emphasis ours]. Note that without pharmaceutical or other major research support, it took 6 years from case reports to a clinical trial, then another eleven years before a replication/extension trial. Given that risks of BB lenses are low, especially compared to current treatments; and given that both clinical trials demonstrated less need for antipsychotics, thus *lowering* the risk of concurrent treatments; we believe that the risk/benefit ratio analysis justifies the hospital-based adoption of DT now.

Voltaire warned in 1770, quoting an Italian proverb, *Le meglio è l'inimico del bene*: “the perfect is the enemy of the good”.<sup>139</sup> Current best evidence supports use of DT as an adjunct in the inpatient treatment of acute mania, and supports urgent investigation of its use in outpatient settings and as an adjunct in maintenance treatment of BD.

## 3.4 | Melatonergic agents

### 3.4.1 | Introduction

Melatonin, N-acetyl-5-méthoxytryptamine, is a natural mammalian hormone first identified in 1958. It is secreted in the brain by the pineal gland, or epiphysis, during the night.<sup>140</sup> Melatonin results from the conversion of serotonin to N-acetyl-serotonin and then to melatonin and its secretion involves two enzymes: the Serotonin-N-Acetyl-Transferase (AANAT) and the Acetyl-Serotonin-Methyl-Transferase (ASMT). Its level of secretion is determined by the length of the photoperiod, which is conveyed via the suprachiasmatic nuclei, and rises in the evening with a peak during the night and is mostly undetectable during the day.<sup>140</sup> Melatonin levels are most commonly measured in blood or saliva.

Melatonin has several functions, including serving as a chemical signal of darkness. Based on SCN input, it conveys photoperiodic information to organ systems and peripheral clocks throughout the body. This chronobiotic property supports phase adjustment and synchronization of internal body clocks and entrainment of this internal timing with the external geophysical day. In addition to its role as a major chronobiotic agent, it also has significant sleep-promoting, antioxidant, antiapoptotic, immune-enhancing, and oncostatic properties.<sup>141</sup>

Melatonergic disturbances in bipolar disorder (BD) have been suggested since the 1980's with findings of later nocturnal peak secretion, reduced secretion amplitude and a higher sensitivity to suppression by light.<sup>142</sup> These findings have prompted therapeutic studies of exogenous melatonin for both the common sleep disturbance and mood instability associated with BDs.<sup>142</sup> The first study was a 1997 case report which described the effects of instant-release melatonin on the sleep, mood and psychotic symptoms of a 10-year-old child with severe treatment-resistant BD.<sup>143</sup> The same year, Leibenluft et al published the first randomized, cross-over trial in rapid-cycling, bipolar adults, which failed to observe differences between melatonin and placebo.<sup>144</sup> After these initial reports, additional randomized trials have been conducted including one which evaluated the melatonin agonist (MA), ramelteon, in 2011.<sup>145</sup> This section will review the current evidence for the safety and efficacy of melatonin and MA's in the treatment of patients with BD. Agomelatine was not included in this review because of its dual action at both melatonergic and serotonergic receptors.

### 3.4.2 | Results

#### Summary

Figure A4 in Appendix II details the search process and exclusion reasons. The seven studies included in this review were heterogeneous in design, treatment objective and study quality (Table 4). Five were RCTs with Jadad scores between 3 and 7 and a class II level of evidence. The remaining two were case series. Melatonin was examined as an adjunctive acute or maintenance treatment, using

an instant release (IR), slow release (SR) or synthetic agonist form (ramelteon), in several different bipolar cohorts including rapid cycling, acute mania, and euthymic periods, with or without sleep disturbances.

An antimanic effect of MA was supported by two small case series, the first<sup>146</sup> in a group of 11 subjects with BPI and treatment-resistant insomnia treated with 3 mg of IR MT at bedtime, and the second in a cohort of 14, euthymic, predominantly BD subjects with insomnia treated with flexible doses of MT at bedtime.<sup>147</sup> These results were opposed by two, larger RCTs the first of which found no difference between 8 mg of ramelteon before bedtime vs. placebo in 21 subjects with BPI<sup>145</sup>; the second was a secondary outcome of a study examining the metabolic effects of 5 mg SR MT vs. placebo added to an atypical antipsychotic in 20 subjects with BPI.<sup>148</sup>

Acute antidepressant action was found in one of two depression measures used in a RCT of subjects with BPI, active manic symptoms and insomnia treated with ramelteon,<sup>145</sup> and in a small case study of 14 euthymic, predominantly BD subjects treated with melatonin at bedtime.<sup>147</sup>

Three additional studies investigated the maintenance efficacy of melatonin or MA's. A small case series of a mixed euthymic BD cohort with insomnia reported reduced depression scores, however, the melatonin dosage was flexible, the time of administration was not fixed, and the follow-up interval was not specified.<sup>147</sup> A second placebo-controlled RCT of ramelteon, 8 mg at HS, in 83 euthymic subjects with BDI determined that relapse was less likely in those receiving active treatment (odds ratio = 0.48,  $P = .024$ ).<sup>149</sup> A final, large, placebo-controlled RCT of 642 euthymic subjects with BDI, using three more physiologic doses of ramelteon (0.1 mg, 0.4 mg, and 0.8 mg), found no difference between active and placebo arms and was stopped prematurely after meeting futility criteria.<sup>150</sup> Of note, only 35% of subjects completed the full 12-month follow-up of this study. Apart from its effect on mood, the two case series in this review each observed increased sleep duration and one also reported enhanced sleep quality associated with melatonin use. Tolerability was not routinely assessed; when it was, somnolence and sedation were the most common side effects. Two reports noted serious adverse events consisting of acute depression and/or suicidality: one subject in the small RCT of rapid cycling women with BD was withdrawn after a suicide attempt (1 of 5 subjects for a TEAS rating of high), and 9 of 477 subjects receiving ramelteon experienced an affective relapse and/or the onset of suicidal ideation (1.9%, TEAS rating of low).

### 3.4.3 | Discussion

This systematic review of the literature identified only a small number of heterogeneous articles which conducted studies of melatonin in adults with BD. While five of these studies were RCTs with moderate Jadad scores and a class II level of evidence, the study design, phase of illness addressed, target symptoms, and the dose, time of administration, and formulation of melatonin used varied

considerably. This is, perhaps, the main conclusion of this review area: the literature on the therapeutic use of melatonin in BD is a small and miscellaneous aggregation of widely disparate studies. This heterogeneity limits and underscores as preliminary the conclusions which are drawn from this current review.

With these qualifications in mind, this review finds little support for the adjunctive use of melatonin or its agonists in the acute treatment of either mania or bipolar depression. The two, well-designed, placebo-controlled RCT's evaluating maintenance efficacy for MA's obtained conflicting results with one showing a significant reduction in relapse and the other, larger study, finding no difference with placebo. This difference might be explained by the significantly higher dose of ramelteon used in the first study, which was 10 to 80 times higher than the dose used in the latter study. At this time, therefore, the maintenance efficacy of melatonin or MA's in BD is unresolved and awaits further dose-finding RCT's. Beyond its impact on mood, the two case series in this review documented a melatonin-related improvement in sleep in both acute and euthymic states of the disorder. This effect on insomnia was not, however, identified in any of the RCT's. Melatonin may also have cardiovascular benefits with one study finding usage was associated with reduced diastolic blood pressure and less weight gain in individuals with BD treated with antipsychotics.<sup>148</sup> Finally, this review found two reports of treatment emergent depression or suicidality, one ranked as high from a small N RCT and the other ranked as low, associated with the use of melatonin or MA. This signal requires further clarification to better understand how, when and with which BD patients melatonin or its agonists may be effectively and safely used.

This review presents a disparity between early basic science reports of altered melatonin kinetics and sensitivity in BD and the limited, current therapeutic utility of melatonergic treatments. This gulf might be explained by the aforementioned heterogeneity among the few clinical studies that met eligibility criteria. In particular, the existing research appears to have focused on the dose-dependent soporific effect<sup>151</sup> of melatonin but has ignored the chronobiotic properties of melatonergic treatments<sup>152</sup> and administered the agonists without regard to timing and the circadian profiles of the individuals. Future investigation in this area would be advanced by inclusion of these parameters, standardization of agonist formulation and dose, and the targeting of illness features that might be most sensitive to melatonergic manipulation. Precision of this kind would enable a more accurate assessment of melatonin's therapeutic potential in this illness. Apart from its circadian-shifting and soporific effects, it is also possible that the oncostatic, antiapoptotic, and antioxidant effects of melatonin may have influence on the course of illness and non-psychiatric comorbidities associated with BD. This could be evaluated through longer term maintenance and relapse prevention studies.

### 3.5 | Introduction of behavioral chronotherapeutics

Zeitgebers modify the timing and amplitude of circadian rhythms. Non-photic zeitgebers include the sleep-wake cycle, daily

**TABLE 4** Data Table for Systematic Review of Melatonin Agonist Studies

Study	Design <sup>a</sup>	Groups (N) <sup>b</sup>	Interventions	Duration of Intervention	Outcome Measures	Main Results
Bersani et al <sup>146</sup>	Case series	N = 11 BP I and treatment resistant insomnia, on stabilized antimanic treatment	3 mg MT IR (add-on) to treat insomnia at 22:30 pm without changing previous antimanic and hypnotic treatments	4 wks	BPRS	Manic symptoms significantly decreased from 22.72 (SD = 4.45) to 14.09 (SD = 4.43).
Leibenluft et al <sup>144</sup>	RCT	N = 5 females with rapid cycling BP	After 1 mo washout, either 10 mg MT IR or PBO, at 10PM, added to standard treatment	12 wks	HDRS, Daily self-rating scale and sleep log, Hypomania interview.	Both melatonin and placebo had mild mood-elevating effects. No differences between the groups.
Livianos et al <sup>147</sup>	Case series	N = 14 euthymic patients with BP and insomnia (6 BP I, 6 BP II, and 2 schizoaffective disorder)	MT "at bedtime", dose "free" between 3-6 mg/day, added to a stable treatment.	Visits spaced from 48.8 to 65.3 d	OSQ, CPI, NES, CGI-BP-M	MT significantly reduced the scores for the measured clinical depression (CPI-Depression, CGI-BP, NES) and mania (CGI-BP) CPI-Depression (29.78 ± 16.25 vs. 23.84 ± 13.16; P = .04); CGI-BP, subscale for depression (2.49 ± 0.82 vs. 1.88 ± 0.85; P = .004) and for mania (1.23 ± 0.3 vs 1.05 ± 0.15; Z=2.375; P = .018); NES scores (42.43 ± 8.77 vs 44.39 ± 5.49)]
Mahableshwarkar et al <sup>150</sup>	RCT	N = 642 remitted BP I	Ramelteon at doses of 0.1 (n = 164), 0.4 (n = 160), or 0.8 mg (n = 154), vs. PBO (n = 164)	12 mos	CGI-S, HAM-A, MADRS, YMRS, Quality of Life Enjoyment and Satisfaction Questionnaire - Short Form (Q-LES-Q-SF), Response Style Questionnaire (RSQ-W)	No significant differences between any dose of ramelteon SL and placebo
McElroy et al <sup>145</sup>	RCT	N = 21 BP I with manic symptoms and insomnia.	8 mg ramelteon, MT Receptor agonist, 30 min before bedtime (n = 10) vs. PBO (n = 11)	8 wks	CGI-BP, HARS, PIRS, PSQI, Q-LES-Q, YMRS, IDS.	A larger decrease for the CGI-BP depression subscale for ramelteon versus placebo (estimate = -0.10; P = .001). No significant group difference for antimanic response.
Norris et al <sup>149</sup>	RCT	N = 83 BP I in remission (MADRS < 12, YMRS < 12) but with current sleep difficulties (PSQI > 5)	Ramelteon (MT receptor agonist, n = 42) or PBO (n = 41) in addition to TAU for up to 24 wks or until manic or depressive relapse.	24 wks	PSQI, YMRS, MADRS, CGI-I.	Participants who received ramelteon (odds ratio 0.48, P = .024) were less likely to relapse; Ramelteon was superior to PBO in terms of median duration until relapse (ramelteon = 188 d, placebo = 84 d; P = .002)
Romo-Nava et al <sup>148</sup>	RCT	N = 20 BP I	5 mg MT SR (20:00 pm, 2 hours before bedtime) added to SGA (n = 10) vs. PBO, given at 20:00pm added to SGA	8 wks	HDRS, YMRS.	no significant difference between MT and PBO on depressive or manic symptoms

Note: See Table A2 for legend of all abbreviations used in this table.

<sup>a</sup>Corresponds to the NHMRC study designs

<sup>b</sup>All groups contain male and female, BDI and II outpatients, unless otherwise specified. N refers to the total number of BD subjects.

<sup>c</sup>Score A is the first time point of statistically significant separation from comparator; Score B is the time to reach ≥ 50% reduction in primary outcome measure

Effect Size, NNT, or Odds Ratio	Tolerability/NNH	Serious Adverse Event	Mood Switch Potential	Speed of Response <sup>c</sup>		Modified Jadad Scale	Level of Evidence
				Score A	Score B		
NA	NA	None	Low	>28 d	NA	0	IV
NA	NA	One withdrawal due to acute depressive mood and suicide attempt. One had unentrained sleep-wake cycle following MT withdrawal	High	NA	NA	3	II
NA	NA	None	Low	8-28 d	NA	0	IV
NA		10 events identified as "serious AE's" out of 477 subjects receiving study drug. Criteria for 'serious AE' unspecified. Of 10 'serious AE', 9 involved worsening of affective illness (relapse, suicidal ideation), 1 involved generalized tonic clonic convulsion.	NA	>28 d	>28 d	7	II
NA	Sedation = 20%, Somnolence = 20%, Diarrhea = 10%, Headache = 10%, Increased appetite = 10%, Upper respiratory infection = 10%	None	Low	NA	NA	7	II
Relapsing in treatment group OR = 0.48		None	Low	8-28 d	>28 d	7	II
NA	NA	None	Low	>28 d	>28 d	4	II

activities, eating schedules, and patterns of exercise and socializing. Manipulation of these parameters constitutes the field of behavioral chronotherapeutics. This review has chosen to include the two best, current exemplars of this field: interpersonal and social rhythm therapy (IPSRT) and cognitive behavioral therapy for insomnia, modified for bipolar disorder (CBTI-BP). While both IPSRT and CBTI-BP share a common objective of enhancing behavioral and biorhythmic stability, IPSRT addresses this through the temporal standardization of key routines throughout the day, whereas CBTI-BP targets the routines, timing, and integrity of the sleep cycle itself.

### 3.6 | Behavioral chronotherapeutics—Interpersonal and social rhythm therapy (IPSRT)

#### 3.6.1 | Introduction

IPSRT is a manualized treatment, developed by Ellen Frank and colleagues, that addresses interpersonal problems and disrupted social rhythms with the intent of stabilizing underlying biologic processes.<sup>153</sup> In IPSRT, therapists utilize the Social Rhythm Metric (SRM)<sup>154</sup> to monitor and improve the regularity of five daily activities over 20 weeks (as an acute intervention) or monthly (as a maintenance treatment): time of out of bed, first contact with another person, start of daily activity, dinner, and time to bed. Patients learn to identify potential sources of rhythm disruption in their lives, both planned and unplanned, and develop strategies to maintain rhythm integrity, despite routine-disrupting events. Although focus on the sleep-wake cycle is an essential component of IPSRT, this intervention takes a more global approach to standardizing daily routines. For instance, patients may be encouraged to seek employment characterized by more fixed hours, seek out a partner to help them stay on track for fixed exercise times, or select classes that meet at times consistent with their chronotype.

#### 3.6.2 | Results

##### Summary

We identified eight trials of IPSRT: four RCTs<sup>25,155-157</sup> three comparative studies without controls,<sup>158</sup> and one case series (Table 5). The case series evaluated group administration of IPSRT for efficacy. Follow-up lasted between 3 months and 3 years. Typically, IPSRT was administered concurrently with pharmacotherapy, but in trials focusing on bipolar II disorder (BDII), it was administered alone.<sup>158-160</sup> The studies examined IPSRT both as an acute and a maintenance treatment most commonly for bipolar depression; two articles addressed maintenance efficacy for both manic and depressive relapse.

Of the eight included articles, three evaluated the acute efficacy of IPSRT monotherapy on BDII depression.<sup>155,158,160</sup> Two of these, each comparative studies without controls, obtained acute antidepressant response rates of 41% and 67% respectively, however, the former was compromised by a high dropout rate of 41%. The third,

an RCT of IPSRT vs quetiapine, found significant and equal declines in YMRS and HRSD scores at 12 weeks.

Three of the RCT's investigated both acute and maintenance efficacy of IPSRT, one for depression in subjects with BDI or BDII disorder,<sup>156</sup> the other two assessed both depressive and manic symptom response. Miklowitz et al<sup>156</sup> compared three active, adjunctive psychotherapies—cognitive behavioral therapy, family focused therapy, and IPSRT—to a lower-dosage, minimally active comparator treatment, collaborative care (CC), for BDI and BDII subjects with depression. Each of the test therapies showed significant and equal superiority over the control treatment (IPSRT vs CC, odds ratio, 1.61; SE = 0.20; 95% CI, 1.09-2.37), resulting in a more rapid remission from depression. When an active psychological control condition was used, Inder et al<sup>157</sup> found that both it and IPSRT resulted in significant and equal improvement on acute and longer term depressive and manic symptom measures. Finally, in another study which evaluated both acute and maintenance efficacy of adjunctive IPSRT compared to intensive clinical management for both poles of the illness in subjects with BDI, Frank et al<sup>25</sup> found no difference in time to remission but demonstrated that acute IPSRT was associated with longer remission at two year follow-up (hazard ratio = 0.34). In this study, increased regularity of daily routines mediated outcomes among those who improved such that more regular routines were associated with a lower risk of recurrence during the follow-up period.

#### 3.6.3 | Discussion

There is evidence from RCTs to support efficacy of IPSRT in hastening recovery from a depressive episode<sup>156</sup> and in increasing time to recurrence over two years of maintenance treatment.<sup>25</sup> Indirect evidence (superiority trials that show similar outcomes for two active treatments) suggests that IPSRT is comparable to active treatments such as quetiapine and specialist care for acute bipolar depression.<sup>157-159</sup> While receiving support from one RCT, the acute anti-manic efficacy of IPSRT requires further evaluation. Overall, these trials indicate that IPSRT is a viable therapy for the acute treatment of bipolar depression and for the prevention of bipolar mood episodes, although more studies are needed to replicate these initial promising findings.

### 3.7 | Behavioral chronotherapeutics—Cognitive behavioral therapy for insomnia adapted for bipolar disorders (CBTI-BP)

#### 3.7.1 | Introduction

Sleep difficulties and disorders are common amongst people with BD, and have multiple interactions with the disorder's core mood symptoms.<sup>30</sup> As part of a program of research into insomnia and psychiatric disorder, Harvey and colleagues postulated that treating comorbid sleep and/or circadian disturbances may ameliorate the mood symptoms of BD.<sup>161</sup> They further proposed that cognitive



behavioral therapy for insomnia (CBT-I)<sup>162</sup> would be an appropriate basis for such treatment, and developed a variant of CBT-I modified for BD<sup>133,1</sup> (CBTI-BP). CBTI-BP aims to improve mood, sleep, and functioning in people with BP, adding to CBT-I elements of motivational interviewing, interpersonal, and social rhythm therapy, and chronotherapy (viz., regularizing sleep and wake times, daily timing of meals and exercise). As delivered in Harvey et al, 2015, CBTI-BP involves 8 weekly sessions of 50-60 minutes; an individualized case formulation is developed in the first session, which determines the weighting given to prescribed elements of behavioral and cognitive modules completed by all participants.<sup>2</sup>

### 3.7.2 | Results

#### Summary

Systematic review identified one outcome study of CBTI-BP (Table 6), a pilot RCT conducted by its developers.<sup>133,3</sup> Key inclusion criteria for the trial were a DSM-IV-TR diagnosis of BD-I, Research Diagnostic Criteria for insomnia disorder, and euthymic mood state. Assessment time points were immediate post-treatment (8 weeks) and 6-month follow-up. Compared to a psychoeducation control condition (PE,  $n = 28$ , differentiated by the absence of behavior change content), intent-to-treat analyses found the CBTI-BP group ( $n = 30$ ) did not differ on mood outcomes during the 8 week treatment phase. However, at follow-up, CBTI-BP was associated with lower hypomania/mania relapse rate ( $P = .036$ , number needed to treat [NNT] = 3.7), and non-significant trends toward lower depression relapse rate ( $P = .391$ ) and overall mood relapse rate (13.6% vs. 42.1%,  $P = .075$ ). At follow-up, the groups also differed on total number of days in a bipolar episode ( $P = .028$ )—paralleling the finding for relapse rates, CBTI-BP benefits on days in episode were attributable primarily to effects on mania/hypomania. CBTI-BP was also associated with higher rates of remission from insomnia at both post-treatment (NNT = 1.7) and follow-up (NNT = 2.4).

### 3.7.3 | Discussion

In summary, the single trial to date found CBTI-BP produced benefits for mood relapse post-acute treatment amongst inter-episode

patients with comorbid insomnia disorder, with the benefit being statistically significant for hypomania/mania relapse and a signal of benefit across either hypomania/mania or depression. Effect sizes were moderate for mood, and moderate-large for insomnia; no significant adverse events or mood switches attributable to the intervention were recorded. In contrast, there is no evidence that CBTI-BP is safe or effective in the management of acute bipolar episodes. More research is needed to investigate the generalizability of CBTI-BP beyond the subset of BD patients diagnosed with insomnia (Table A2).

### 3.7.4 | Discussion of behavioral chronotherapeutics for bipolar disorder

There is some evidence that behavioral therapies targeting sleep and social rhythms have benefits for the maintenance phase of BD, and IPSRT has shown benefits for speed of recovery from a depressive episode. IPSRT has a Level 2 rating for quality of evidence in CANMAT/ISBD guidelines for treating bipolar disorders and is recommended as a third-line intervention for the depressive and maintenance phases of bipolar disorder.<sup>129</sup> CBT-I has less direct evidence of efficacy and is not yet included in evidence-based treatment guidelines. Importantly, neither approach has shown evidence of negative side effects, perhaps explaining why (unlike the other interventions reviewed here), behaviorally based chronotherapeutic strategies have been incorporated in most evidence-based approaches to BD. Specifically, proactive stabilization of sleep/wake and other social rhythms is one of the content elements shared across the evidence-based psychological interventions for the maintenance phase.<sup>163,164</sup> In contrast to this wide acceptance of the principles on which these two therapies are based, and their therapeutic strategies, their scientific foundations are limited in terms of high-quality outcome trials, let alone data on moderators and mediators of outcome (a limitation shared with all psychotherapies).<sup>165</sup>

## 4 | SUMMARY AND PRACTICE RECOMMENDATIONS

This is the first systematic and comprehensive review of the six most commonly used adjunctive chronotherapeutic interventions in the treatment of bipolar disorders (BDs): bright light therapy (LT), dark therapy (DT), treatments using sleep deprivation (SD), melatonin agonists (MA), and the behavioral chronotherapeutics of cognitive behavioral therapy for insomnia, adapted for bipolar disorders (CBTI-BP) and interpersonal social rhythm therapy (IPSRT). By including this full range of treatments, it provides a snapshot of the current status of affective chronotherapeutics and, by extension, the contemporary relevance of chronobiology in the management of this illness.

The results of this review identify both significant differences and areas of commonality between the six chronotherapies addressed

<sup>1</sup>Soehner et al (2013) flagged concerns about two specific CBT-I strategies (stimulus control and sleep restriction) as potentially triggering relapse in BP via attendant short-term sleep deprivation. These concerns were investigated in a case series of  $N = 15$  patients with BP and insomnia,<sup>195</sup> which tentatively concluded sleep restriction and stimulus control are safe and efficacious for treating insomnia in patients with BP. The authors note, moreover, that these potentially challenging strategies were infrequently required as part of the case formulation-driven approach, with regularising of bed times and rise times often sufficient. Note: the 15 patients described in Kaplan and Harvey<sup>195</sup> were a subset of those in the pilot RCT of CBTI-BP (Harvey, personal communication June, 2018).

<sup>2</sup>More recently, Harvey and Buysse have emphasised CBTI-BP's transdiagnostic assumptions by renaming the intervention Transdiagnostic Intervention for Sleep and Circadian Dysfunction.<sup>196</sup> There have been no published trials of the intervention under this name (Harvey, personal communication June, 2018).

<sup>3</sup>A larger trial by an independent group<sup>197</sup> is nearing completion.

**TABLE 5** Data Table for Systematic Review of Interpersonal and Social Rhythm Therapy Studies

Study	Design <sup>a</sup>	Groups (N) <sup>b</sup>	Interventions	Duration of Intervention	Outcome Measures
Bouwkamp et al <sup>193</sup>	Case series	N = 27 (includes 5 drop outs)	IPSRT-G = 16 sessions	16 wks	CGI-BP, SRM, Months depressed, months manic, cumulative depression and cumulative mania score (all measured using life chart) Hospital admissions
Frank et al <sup>153</sup>	RCT	N = 175 inpatients and outpatients with BP I	Acute/maintenance treatment with IPSRT and ICM, combined in four different ways: IPSRT/IPSRT (n = 39) vs. IPSRT/ICM (n = 48) vs. ICM/ICM (n = 43) vs. ICM/IPSRT (n = 45)	4 wks acute treatment (n = 175) and 2yrs maintenance treatment (n = 125)	HDRS, BRMS, SRM
Inder et al <sup>157</sup>	RCT	N = 100 adolescents and young adults aged 15-36 BD-I, BD-II, and BD NOS	IPSRT (n = 49) vs. Specialist Supportive Care (SSC, n = 51)	26 to 78 wks	LIFE Depression (primary); LIFE Mania and SAS (secondary)
Miklowitz et al <sup>194</sup>	Comp. study w/o concurrent controls	N = 100	Integrated family and Individual therapy (IFIT) - up to 50 sessions of IPSRT and FFT (n = 30) vs. Historical comparison group crisis management (CM, n = 70)	1 yr	SADS-C, relapse judged based on the classification system of Neuchterlien et al (Schizophrenia Bulletin 1992)
Miklowitz et al <sup>156</sup>	RCT	N = 293 BP depression	IPSRT (n = 62), vs. CBT (n = 75), vs. Family-focused Therapy (FFT, n = 26), vs. Collaborative Care (CC, n = 130)	IPSRT, CBT, FFT: 30 sessions; CC: 3 sessions; Assessed at 1 yr	Clinical Status (Clinical Monitoring Form), MADRS, YMRS
Swartz et al <sup>160</sup>	Comp. study w/o concurrent controls	N = 17 BP II depression	IPSRT	12 wks	HDRS, MADRS, YMRS
Swartz et al, 2012	RCT	N = 25 BP II depression	IPSRT (n = 14) vs quetiapine (n = 11)	12 wks	HDRS, YMRS
Swartz et al <sup>158</sup>	Comp. study w/o concurrent controls	N = 92 BP II depression	IPSRT + quetiapine (n = 47) vs. IPSRT + PBO (n = 45)	20 wks	HDRS, MADRS, YMRS

Note: See Table A2 for legend of all abbreviations used in this table.

<sup>a</sup>Corresponds to the NHMRC study designs

<sup>b</sup>All groups contain male and female, BDI and II outpatients, unless otherwise specified. N refers to the total number of BD subjects.

<sup>c</sup>Score A is the first time point of statistically significant separation from comparator; Score B is the time to reach  $\geq 50\%$  reduction in primary outcome measure

**TABLE 6** Data Table for Systematic Review of Cognitive Behavioral Therapy for Insomnia, Adapted for Bipolar Disorders, Studies

Study	Design <sup>a</sup>	Groups (N) <sup>b</sup>	Interventions	Duration of Intervention	Outcome Measures
Harvey et al <sup>133</sup>	RCT	N = 58 euthymic BP I with insomnia disorder	CBTI-BP, 8 wkl sessions of 50-60 minutes (n = 30) vs. Psychoeducation (n = 28)	8 wks	Mood relapse, number of days spent in bipolar episodes; Sleep, diagnosis, severity, and functional impairment Assessment at 8 and 24 wks

Note: See Table A2 for legend of all abbreviations used in this table.

<sup>a</sup>Corresponds to the NHMRC study designs

<sup>b</sup>All groups contain male and female, BDI and II outpatients, unless otherwise specified. N refers to the total number of BD subjects.

<sup>c</sup>Score A is the first time point of statistically significant separation from comparator; Score B is the time to reach  $\geq 50\%$  reduction in primary outcome measure

Main Results	Effect Size, NNT, or Odds Ratio	Tolerability/ NNH	Serious Adverse Event	Mood Switch Potential	Speed of Response <sup>c</sup>		Modified Jadad Scale	Level of Evidence
					Score A	Score B		
CGI-BP and SRM scores significantly reduced post-treatment; Number of months depressed significantly reduced post-treatment; cumulative mania and depression scores not significantly reduced post-treatment; Number of hospital admissions was significantly reduced	NA	NA	NA	Mod	NA	NA	1	IV
No significant difference between IPSRT and ICM in time to remission or in remission rate (IPSRT, 70%; ICM, 72%). Participants assigned to IPSRT in the acute phase survived significantly longer without a new mood episode	Acute ICM vs Acute IPSRT, hazard ratio = 0.34	None	None	NA	NA	NA	7	II
Both groups showed significant improvement on primary and secondary measures. No differences between treatments	NA	NA	NA	NA	NA	NA	1	II
Significantly lower SADS-C in the IFIT group driven by a greater reduction in SADS-C depression scores; IFIT associated with longer survival intervals than CM	Relapse Hazard ratio = 0.07 favoring IFIT	NA	NA	NA	NA	NA	1	III-3
IPSRT Recovery Rate: 64.5% (HR, 1.48   ≤ 2 moderate symptoms for ≥ 8 of the previous wks) IPSRT, CBT, FFT and were associated with more rapid recovery and greater likelihood of being well during any study month compared to collaborative care. No differences among IPSRT, CBT, FFT.	IPSRT vs. CC (OR 1.61; SE = 0.20; 95% CI, 1.09-2.37)	NA	NA	NA	NA	NA	2	II
At wk 12, 41% responded to IPSRT, 41% dropped out, and 18% did not respond. At wk 20, 53% achieved response ( 50% reduction in the HRSD-17) and 29% full remission.	NA	NA	NA	Low	NA	>28 d	1	III-3
Both groups showed considerable declines in depression and mania rating scales over time but no group-by-time interaction	NA	NA	NA	NA	>28 d	>28 d	3	II
Overall response rate = 67.4% (≥50% reduction in HRSD-25) with no significant between-group difference	NA	None	None	Low	NA	>28 d	1	III-3

Main Results	Effect Size, NNT, or Odds Ratio	Tolerability/ NNH	Serious Adverse Event	Mood Switch Potential	Speed of Response <sup>c</sup>		Modified Jadad Scale	Level of Evidence
					Score A	Score B		
No difference in relapse rates or time in episodes at 8 wks. During follow-up, significantly lower mania/ hypomania relapse rates in CBTI-BP vs. PE (4.6% vs. 31.6%, P = .036;).	Relapse Prevention for: Mania/hypomania NNT = 3.7; Depression NNT = 8.3; Any relapse NNT = 3.5	None	None	Low	>28 d	>28 d	4	II

Chronotherapeutic treatments	Acute phase		Maintenance/ prophylaxis	
	Mania	Depression	Mania	Depression
Bright Light Therapy	X	✓	°	°
Sleep Deprivation/ Wake therapy	X	✓	°	°
Dark Therapy	✓	X	°	°
Melatonin <sup>a</sup> or melatonergic agonists	°	°	°	°
IPSRT	°	✓	✓	✓
CBTI-BP	°	°	✓ <sup>b</sup>	°

**TABLE 7** Evidence-informed Practice Recommendations

Note: ✓ = Recommended: The treatment is supported by literature review-based evidence, which demonstrates efficacy, minimal safety risks, and a positive tolerability profile.

° = No Recommendation: Insufficient or conflicting data which does not permit recommendation at this time. This designation indicates neither endorsement nor rejection.

X = Not Recommended: There is expert consensus that the treatment is contraindicated based on this literature review along with other, external (clinical, pre-clinical, animal, or epidemiologic) research.

Refer to text for further description and basis for above designations

IPSRT: interpersonal and social rhythm therapy.

CBTI-BP: cognitive behavioral therapy for insomnia modified for Bipolar Disorder

<sup>a</sup>Instant or slow release

<sup>b</sup>Only applies to euthymic subjects with BD who have insomnia.

here. First and foremost, this field has a small evidence base and the number of eligible outcome studies available for each treatment were limited, ranging from a low of 1 for CBTI-BP to as many as 21 for treatments employing SD. Related, the studies themselves typically have small N's. Outside of a handful of larger reports on MA and IPSRT, the vast majority of the eligible studies had between ten to fifty subjects. Second, apart from the research on SD where over half the publications were from over 20 years ago, the chronotherapy outcome literature is generally recent, with increasing publications over the past decade. Third, there was significant variability in the study design, level of evidence, study quality, outcome measures, and administration protocols for most of the reviewed chronotherapies. The study design ranged from case series with a low level of evidence, to comparative studies without controls, to rigorous, placebo-controlled, randomized controlled trials (RCTs). As a trend, the literature on SD relied the most on case series and open-label studies, whereas the reports on LT, MA, and some on IPSRT more often employed placebo-controlled, RCTs. Multiple outcome measures were used but more recent studies gravitated toward standardized instruments such as the HDRS, YMRS, and MADRS. Last, as might be expected from a younger field, the treatment protocols themselves differed markedly between studies. For example, SD studies used one or multiple nights of wakefulness; LT studies used different timing, intensity and duration of light exposure; the dose, timing, and formulation of MA was not uniform across studies. Standardization of treatments was greater in the studies on DT and IPSRT.

The practice recommendations of this report derive from the consensus opinions of the authors based on a synthesis of the efficacy and tolerability data generated here. These recommendations differ from practice guidelines which are disorder-based evaluations

and rankings of all available clinical options. The following text descriptively summarizes the clinical status of the chronotherapies reviewed here. These descriptions are then translated into one of three categories—Recommended, No Recommendation, or Not Recommended—presented in Table A2. The first two categories were decided based on the presence or absence of efficacy and tolerability data reviewed here. The last category was used when there was sufficient evidence to determine that a *lack* of efficacy existed or when a treatment was judged to pose significant risk. These risk determinations were based both on the findings of this literature review along with other relevant preclinical, animal, and epidemiologic research drawn from external sources. For example, the presence of a low rate of manic switching with SD found in this review was combined with other clinical evidence of sleep loss precipitating mania and animal models of sleep deprivation-induced mania, to designate SD as contraindicated in the acute treatment of mania.

Among current chronotherapeutic options, this review identified LT in the acute treatment of bipolar depression as the modality with the strongest evidence base from existing outcome studies. Endorsed by three RCTs, a pseudorandomized trial, five open label studies and a prior meta-analysis, it received substantial empiric support. When combined with a generally benign safety profile and tolerability ratings, LT emerges as a credible acute treatment option for bipolar depression. The status of LT in the maintenance treatment of bipolar depression remains to be investigated. Finally, based on clinical evidence of LT-induced switching found in this review, along with other clinical, animal, and epidemiologic data, it is the consensus opinion of this report that LT is contraindicated in the acute treatment of manic states. Whether modified doses and timing of LT might have a role in the prophylaxis of manic states,

for example, in the prevention of manias that arise from preceding depressions in illness courses that run from depression to mania to euthymic interval, remains to be seen and thus receives “No Recommendation.”

The 21 publications on the acute antidepressant efficacy of SD consisted mainly of case series or uncontrolled open label studies, along with one RCT. The documented acute antidepressant response rates from the better level III and one level II studies were approximately 60%. Response was rapid, most often occurring within seven days. Apart from treatment emergent affective switches, which occurred at a low rate of 0 to 5% in over 60% of treated subjects, the procedure was well tolerated and had no other adverse effects. Practice recommendations for the use of SD require the balancing of mainly level III evidence, low but not insignificant risk of TEAS, and its rapid response potential. As such, this review suggests that SD may be considered after more established options fail, when they are not tolerated, or when rapid antidepressant response is required. Performing a meta-analysis of the existing studies on bipolar subjects, similar to one published on all depressive subtypes in 2015, could strengthen the evidence for SD and its placement on acute treatment algorithms for BD depression. There is insufficient data to evaluate the maintenance potential of SD for bipolar depression. As with LT, the studies found in this review along with other external data argue that SD is contraindicated in the acute treatment of manic states. More study is required to determine if limited SD might play a role in the prevention of manic relapse.

The efficacy on adjunctive DT for mania was based on three publications: one case series, a comparative study with controls and one RCT. The latter two articles each found a rapid and statistically significant reduction in manic symptoms, lower doses of antimanic medication usage, and, in one study, shorter hospital stays in the DT group compared to treatment as usual. Apart from a 15% incidence of emerging depressive symptoms that were easily managed by dose reduction in the DT group, darkness exposure was well-tolerated. The incidence of treatment emergent depressive symptoms suggests that further dose-finding studies and risk factor analysis are required to optimize efficacy and minimize affective reversals. Beyond efficacy and tolerability, this adjunctive modality is convenient and inexpensive. The overall positive risk/benefit profile of DT argues for its routine utilization in inpatient environments where response can be carefully monitored. Further investigation is necessary to evaluate feasibility, efficacy, and safety in outpatient practice and for maintenance treatment. Although the data reviewed in this paper did not directly address this point, using other research, the consensus opinion of this report is that extended DT is contraindicated in the acute treatment of bipolar depression.

The outcome data from the seven studies identified on MA treatment of BD were inconsistent. While supported by two case studies, two larger RCTs found no acute antimanic effects from MA therapy, hence MA cannot be currently recommended for this phase of the illness. The findings on acute antidepressant activity of MA were sparse and insufficient to generate a positive treatment recommendation.

Two other, large placebo-controlled RCTs obtained conflicting evidence of maintenance efficacy among euthymic subjects with BD, with one showing a statistically significant reduction in relapse rates and the other, using variable but low doses of ramelteon, stopping prematurely due to meeting futility criteria. While the study designs were similar, the former used doses of ramelteon that were 10 to 80 x higher than in the latter. Thus, there is a need for follow-up dose-finding studies of maintenance efficacy. Apart from its effect on mood, two of the included case series reported increased sleep duration and sleep quality with MT. Tolerability was high for MAs with somnolence as the most common side effect. Two studies noted the onset of treatment emergent depressive reactions and suicidality associated with MA use, the larger RCT documenting a rate of 1.8%. In summary, MA do not have a current place in the acute treatment of either manic or depressive states, display conflicting evidence of maintenance efficacy, and lower-level case series support of improved sleep in BD. When combined with a small but serious risk of affective switch, there does not appear to be any current role for MA in the treatment of this illness.

Evidence of the prophylactic efficacy of adjunctive IPSRT in preventing depressive and manic recurrence and hastening depressive recovery was demonstrated in three RCTs. Two comparative studies without controls and one RCT established additional, acute antidepressant activity for IPSRT monotherapy for BDII depression. There is insufficient evidence to evaluate the acute antimanic efficacy of IPSRT. When added to a clean safety profile, this review supports the wide dissemination and adoption of this behavioral chronotherapeutic strategy found in most current treatment guidelines. In contrast, CBTI-BP is backed by a single RCT showing prophylactic efficacy in reducing manic/hypomanic relapse among euthymic bipolar subjects with comorbid insomnia. While promising, further replication is necessary before it can be recommended and incorporated into clinical practice guidelines.

What are the reasons for the small, varied, and often low level of evidence of literature in this field? The absence of pharmaceutical industry funding is contributory. Clinical research on chronotherapy proceeds without the annual, multi-billion dollar support for research, development, and promotion of the pharmaceutical industry.<sup>166,167</sup> The difficulty of devising valid placebo controls is a second challenge to chronotherapeutic research: what is an appropriate placebo control for bright light, wakefulness, and darkness? Failure to overcome this difficulty has confined many studies on LT, SD, and DT to a lower level of evidence. Variable patient acceptance is another factor that may limit research and clinical dissemination in this area. Chronotherapeutic treatments often require significant time and behavioral commitment to improve mood. Finally, chronobiology and chronotherapy are not part of the standard training received by psychiatric residents or psychology graduate students.

What can be done to improve chronotherapeutic research and advance chronotherapeutic practice going forward? Circadian output variables—such as the rest-activity cycle, sleep-wake cycle, activity phase and amplitude measures, dim light melatonin onset, core body, or skin temperature timing—should be

included as a standard part of future investigations. The timing, dose, and duration of the study treatments should be examined and compared to optimize efficacy and clarify whether different administration timing effects either outcome or adverse events. The latter point would help to clarify underlying chronobiologic mechanisms. Related, chronotype status should be regularly incorporated into and investigated as an independent variable in subsequent research. Beyond the sole example of SD reviewed here, which included bundled interventions, further study of integrated chronotherapeutic arrangements may reveal potential synergies of effect.<sup>168</sup> The work of Benedetti and others provides evidence that treatments using multiple interventions may be more effective than single strategies.<sup>38,169</sup> Finally, the predominant focus on separate strategies in this paper may have obscured larger chronobiologic principles that transcend individual interventions. For example, while light and dark therapy have each received distinct endorsements of efficacy, there is evidence that entrainment and circadian health are contingent on the entire 24-hour cycle of light and darkness, with optimal contrast between them.<sup>170,171</sup> The related concepts of light hygiene and chronodisruption also underlie and connect many of the individual modalities examined in this review.<sup>172,173</sup> Standard psychoeducational practice and general treatment guidelines of BD would be enhanced by the routine inclusion of these overarching circadian principles.

## ACKNOWLEDGMENTS

Michael Young provided statistical assistance throughout this project.

## ORCID

John F. Gottlieb  <https://orcid.org/0000-0002-2838-8567>


Francesco Benedetti  <https://orcid.org/0000-0003-4949-856X>

Pierre A. Geoffroy  <https://orcid.org/0000-0001-9121-209X>

Greg Murray  <https://orcid.org/0000-0001-7208-5603>

Marie Crowe  <https://orcid.org/0000-0002-7220-8658>

Bruno Etain  <https://orcid.org/0000-0002-5377-1488>

Bartholomeus C. M. Haarman  <https://orcid.org/0000-0002-9006-8863>

Maree Inder  <https://orcid.org/0000-0002-6326-6100>

Richard Porter  <https://orcid.org/0000-0002-8695-3966>

Jan Scott  <https://orcid.org/0000-0002-7203-8601>

Shenghao Chen  <https://orcid.org/0000-0002-5835-1634>

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#### SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

**How to cite this article:** Gottlieb JF, Benedetti F, Geoffroy PA, et al. The chronotherapeutic treatment of bipolar disorders: A systematic review and practice recommendations from the ISBD task force on chronotherapy and chronobiology. *Bipolar Disord*. 2019;21:741-773. <https://doi.org/10.1111/bdi.12847>