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REVIEW

Role of adjunctive nonpharmacological strategies for treatment of rapid-cycling bipolar disorder

Subho Chakrabarti, Amal J Jolly, Pranshu Singh, Nidhi Yadhav

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Subho Chakrabarti, Nidhi Yadhav, Department of Psychiatry, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, Chandigarh UT, India

Amal J Jolly, Department of Psychiatry, Black Country Healthcare NHS Foundation Trust, Dudley DY2 8PS, West Midlands, United Kingdom

Pranshu Singh, Department of Psychiatry, All India Institute of Medical Sciences, Jodhpur 342005, Rajasthan, India

Corresponding author: Subho Chakrabarti, MD, Professor, Department of Psychiatry, Postgraduate Institute of Medical Education and Research, Sector 12, Chandigarh, Chandigarh 160012, Chandigarh UT, India. subhochd@yahoo.com

Abstract

Rapid-cycling bipolar disorder (RCBD) is a phase of bipolar disorder defined by the presence of ≥ 4 mood episodes in a year. It is a common phenomenon characterized by greater severity, a predominance of depression, higher levels of disability, and poorer overall outcomes. It is resistant to treatment by conventional pharmacotherapy. The existing literature underlines the scarcity of evidence and the gaps in knowledge about the optimal treatment strategies for RCBD. However, most reviews have considered only pharmacological treatment options for RCBD. Given the treatment-refractory nature of RCBD, nonpharmacological interventions could augment medications but have not been adequately examined. This review carried out an updated and comprehensive search for evidence regarding the role of nonpharmacological therapies as adjuncts to medications in RCBD. We identified 83 reviews and meta-analyses concerning the treatment of RCBD. Additionally, we found 42 reports on adjunctive nonpharmacological treatments in RCBD. Most of the evidence favoured concomitant electroconvulsive therapy as an acute and maintenance treatment. There was preliminary evidence to suggest that chronotherapeutic treatments can provide better outcomes when combined with medications. The research on adjunctive psychotherapy was particularly scarce but suggested that psychoeducation, cognitive behavioural therapy, family interventions, and supportive psychotherapy may be helpful. The overall quality of evidence was poor and suffered from several methodological shortcomings. There is a need for more methodologically sound research in this area, although clinicians can use the existing evidence to select and individualize nonpharmacological treatment options for better management of RCBD. Patient summaries are included to highlight some of the issues

concerning the implementation of adjunctive nonpharmacological treatments.

Key Words: Rapid-cycling bipolar disorder; Bipolar disorder; Adjunctive therapy; Nonpharmacological treatment

Core tip: Rapid-cycling bipolar disorder (RCBD) is a common and highly disabling phase of bipolar disorder. The ineffectiveness of conventional pharmacological treatment for RCBD suggests that adjunctive nonpharmacological interventions could be useful. However, their role has not received much attention. This review carried out a comprehensive search to identify the existing evidence on the subject. We found that electroconvulsive therapy, chronotherapy, and psychotherapy could effectively augment medication treatment of RCBD. However, the evidence is limited and methodologically inadequate. Therefore, clinicians have to rely on general guidelines for the optimal use of the available nonpharmacological options while managing RCBD.

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INTRODUCTION

Clinical features of rapid-cycling bipolar disorder

Rapid-cycling bipolar disorder (RCBD) is a phase in the longitudinal course of BD characterized by increased episode frequency. The Diagnostic and Statistical Manual of Mental Disorders (DSM) delineates rapid cycling as a specifier of the longitudinal course of BD rather than a distinct form of the disorder[1]. DSM-5 defines rapid cycling as a minimum of four episodes in the previous 12 mo that meet the diagnostic and duration criteria for hypomanic, manic, or major depressive episodes. Each episode is demarcated by either partial or full remission for at least 2 mo, or a switch to a new episode of the opposite polarity. A proportion of patients have shorter cycles of days to weeks (ultra-RCBD) and some have episodes lasting less than a day (ultradian-RCBD)[2-6]. However, DSM-5 does not include these categories.

The phenomenon of rapid cycling occurs among a significant proportion of patients with BD. The 12-mo prevalence of RCBD in patients from specialized mood disorder clinics is about 20% (range: 4%–27%)[4,6-9]. The prevalence is higher (range: 27%–56%) when ultrarapid and ultradian rapid cycling are included[6,7,10,11]. The rates are also higher in community settings (30%–40%) because these studies have included a wide spectrum of RCBD[9,12-14]. Reviews have estimated the annual prevalence rate of RCBD to be about 18% (range: 5%–33%) and lifetime rates of about 31% (range: 26%–43%)[9,15-18]. The rates obtained by different meta-analytic studies also vary from 15% to 24% (range: 12%–56%)[5,19-21].

Apart from its frequent occurrence, RCBD is characterized by clinical features that make it a severe and disabling phenomenon. Depressive episodes or symptoms appear to be the characteristic clinical presentation of RCBD[5,10,15,17,22]. Patients with BD who have depressive onsets are more likely to develop rapid cycling and patients with RCBD are more likely to present with depressive onsets. Episodes of depression are more frequent and severe in patients with RCBD. Depressive episodes are harder to treat compared with manic ones. As a result of this greater depressive burden, most reviews have also found a higher rate of suicidality in RCBD[5,16,21,23,24]. The frequent recurrence of treatment-resistant depression contributes to the treatment-refractory profile of RCBD. The distress and disability associated with unremitting depression are the main hurdles in effectively managing RCBD[10,13,14,22,25]. Although RCBD is a transient phenomenon that lasts about 2 years in most patients[2,6,16,22,24], many studies have found rapid cycling to persist in > 50% of patients[6,25-28]. A longer duration of rapid cycling, more frequent episodes, a depression-mania-free interval pattern, continuous cycling, agitated depression, temperamental disturbances, and poor response to treatment are associated with the persistence of RCBD[6,8,17,29,30]. Lastly, the consistent finding in the literature is that RCBD is associated with poorer outcomes in terms of severity, recurrence risk, chronicity, comorbidity, and treatment resistance [17-20,31]. Given all these adverse clinical features, it is not surprising that RCBD is associated with greater global functional impairment, poor socio-occupational outcomes, higher levels of disability, poorer quality of life, and greater family burden[2,6,9,16,24]. Thus, RCBD adds a great deal to the overall burden of BD[18].

Pharmacotherapy of RCBD

Since pharmacotherapy is the principal means of treating BD, the primary focus of research has been on the efficacy of medications in RCBD. Several reviews of the subject exist in the current literature. These include narrative reviews[4,24,27,30,32], systematic reviews[6,16,17,29,31], and meta-analyses[5,18,20,21,33] (Supplementary Material includes a complete list of all the reviews consulted).

The main finding of this research is that RCBD is resistant to treatment by conventional pharmacotherapy for BD[6,20,27,29,30]. RCBD comprises the largest group among patients with treatment-resistant BD[34]. Patients with RCBD have poorer treatment response and outcome compared to patients without rapid cycling[26,27,29,30,35]. Although initial studies suggested that RCBD responds poorly to lithium, it is now clear that rapid cycling is resistant to all mood-stabilizing treatments[6,20,36-38]. Treating depressive episodes in RCBD poses greater problems than treating mania/hypomania. The acute efficacy of medications is usually better than their long-term effects[8,11,18,29,32]. Recommendations regarding effective treatment options vary, but most of the evidence appears to favour second-generation antipsychotics, lithium, valproate, lamotrigine, thyroxine, and even antidepressants[17,18,24,31,39]. There is a considerable consensus that response to monotherapy is often inadequate. Therefore, combinations of mood stabilizers and antipsychotics are the more practical, if not the evidence-based options for treatment[17,40-43]. However, the prevailing concern about medication treatments for RCBD is the lack of research data and guidance on suitable evidence-based options, particularly for long-term treatment[17,18,24,29,31]. Not only is there a lack of randomized controlled trials (RCTs) on the subject, but there are also several methodological lacunae such as small sample sizes, uncertainties about the definition of RCBD, and inadequate study designs[6,11,18,20,44].

Nonpharmacological therapy for RCBD

The shortcomings of pharmacological treatment indicate an unmet need for more effective management options for RCBD. Adjunctive nonpharmacological interventions could fill the existing gap in managing RCBD[18,36,45-47]. Treatments such as electroconvulsive therapy (ECT), chronotherapy, and psychotherapy can potentially augment the inadequate response obtained with medications. However, the role of adjunctive nonpharmacological treatments has not received much attention. A systematic review conducted in 2007 considered the different biological and psychotherapeutic options that could augment the pharmacological treatment of RCBD[45]. It found some evidence for the efficacy of ECT and sleep deprivation for acute and maintenance management of RCBD, especially in treatment-resistant patients. Light therapy was not efficacious and there was no data on recurrent transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS), and psychotherapeutic treatments. The authors acknowledged that the evidence was based only on case reports and open trials and not RCTs. However, they concluded that adjunctive nonpharmacological treatments could be used to manage RCBD based on clinical experience and their usefulness in BD. They recommended the early institution of adjunctive treatments such as ECT in patients who were severely ill and needed immediate relief. Subsequent reviews of the treatment of RCBD have also noted the potential for concomitant use of nonpharmacological treatments and the lack of controlled trials in this area[17,18,32,46,47].

There are several reasons for examining the role of combined pharmacological and nonpharmacological therapy in RCBD. At present, there is no consensus or guidance on the optimal management of RCBD because pharmacological and nonpharmacological treatments have proved less effective[17,18,25,45]. Apart from the inadequate response to standard pharmacotherapy, many other factors make rapid cycling difficult to treat. These include its high prevalence, greater severity, depressive colouring, comorbidities, poorer outcomes, higher levels of disability, side-effect burden, and inadequate medication adherence[15,17,18,24,36]. Adjunctive nonpharmacological treatments can address some of these issues such as persistent depressive symptoms and risks of harm[45], comorbidities[2,10,40], psychosocial stressors, functional impairment[25,32,48-50], and treatment nonadherence[25,30,45,51,52].

Aims of this review

This review aimed to summarize the existing evidence on the role of nonpharmacological therapies as adjuncts to medications in RCBD. It attempted to expand on the previous review[45] by conducting a more comprehensive and updated search of this area.

LITERATURE REVIEW

Although this was not a systematic review, it relied on comprehensive electronic (PubMed) and manual searches to identify the existing literature on nonpharmacological treatments in RCBD from 1980 to April 2023. The accompanying figure depicts this search. Supplementary Material includes the details of the search terms used. The Reference Citation Analysis tool was used for searching articles and ranking them according to their impact (Figure 1).

This search identified 53 narrative reviews, 21 systematic reviews, and nine meta-analyses on the treatment of RCBD. These reviews were used to collate information regarding various nonpharmacological therapies in RCBD. A second round of electronic and manual searches identified 17 studies or reports of ECT, 16 of chronotherapy, six of psychotherapy, two of VNS, and one of rTMS. Patients consented to the presentation of their treatment histories. All patient details have been anonymized.

RESULTS

Adjunctive ECT in RCBD

ECT has proven efficacy in BD in treating acute episodes of both mania and depression. It is particularly useful in medication-resistant episodes that are severe, psychotic, or with a high risk of self-harm. The evidence also suggests that maintenance ECT in combination with medication is efficacious for patients with highly recurrent illnesses if they have

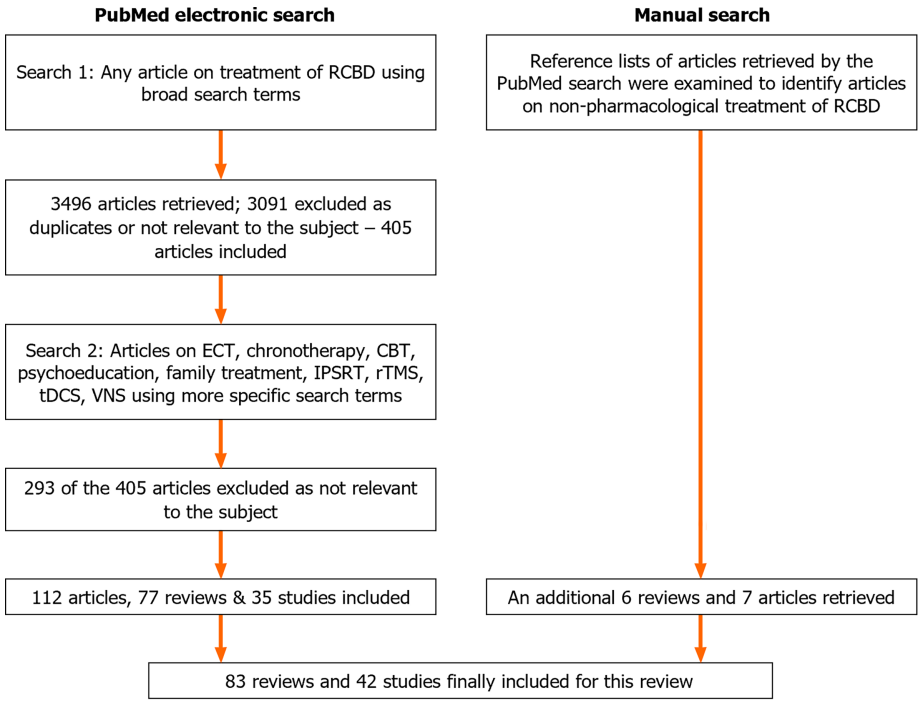

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Figure 1 Search strategy for identifying articles on nonpharmacological treatment of rapid cycling bipolar disorder. Search terms are listed in (Supplementary Material). CBT: Cognitive behavioural therapy; IPSRT: Interpersonal and social rhythm therapy; RCBD: Rapid-cycling bipolar disorder; rTMS: Recurrent transcranial magnetic stimulation; tDCS: Transcranial direct current stimulation; VNS: Vagus nerve stimulation; ECT: Electroconvulsive therapy.

responded well to acute ECT[3,45,53-55]. Consequently, ECT has been used for similar indications in patients with RCBD. However, the evidence is limited and based on either case reports or naturalistic studies with small numbers of patients. These studies are included in Table 1[56-72].

Despite these limitations, acute ECT seems to be effective in patients with medication-resistant RCBD with complete or partial remission rates ranging from 70% to 100% in some studies[69,72]. Others have reported lower response rates[64,66,67,70]. Nevertheless, sustained periods of remission and better response to mood stabilizers are reported after acute ECT[64,65,67,70,72]. Acute ECT also reduces the number of episodes and the time spent ill. Though there are fewer studies, the combination of maintenance ECT and mood stabilizers appears to be effective with response rates ranging from 67% to 100%[68,70,71]. Adjunctive maintenance ECT prevents relapses, reduces the need for hospitalization and the length of hospital stay, decreases the time spent in episodes, and increases the duration of interepisodic intervals[68,70,71,73,74]. Patients with RCBD and ultra-RCBD may respond better to ECT than other patients with BD[41,45]. ECT is particularly helpful in patients with RCBD who have failed multiple medication trials, those who are intolerant to medication side effects, and those who are at high risk of self-harm[3,45,49]. ECT is effective in medication-resistant patients with mania[3,30,47,75,76], depression[32,41,68,72,75], or mixed states[49,72] as a part of RCBD. However, the best response is often obtained in patients with bipolar depression[32,41,67,68,72]. Other predictors of good response are depressive episodes with psychotic symptoms or catatonic features[41,68,72]. Minnai *et al*[71] carried out a multivariate analysis to identify the predictors of good response to maintenance ECT in RCBD. Young age, male sex, type II BD, and hyperthymic temperament emerged as factors associated with a higher chance of depression-free intervals with ECT. The better response in those with type II BD and hyperthymic temperament could be because a large proportion of these patients were included in their sample. However, hyperthymic temperament is often associated with antidepressant-induced rapid cycling[6], while ECT may be less likely to cause rapid cycling than antidepressants[4]. The use of ECT has shown to be safe with minimal side effects even when it is combined with mood stabilizers and used for long periods[62,63,68,71,72]. ECT is also less likely than antidepressants to cause manic/hypomanic switches or induce rapid cycling[4,48,49,64,76].

Thus, despite the scarcity of evidence, acute ECT is recommended for treating medication-refractory manic and depressive episodes in RCBD[30,32,45,49,76]. Maintenance ECT can be considered in those patients who improve with acute ECT or relapse on pharmacotherapy[45,73-77]. ECT is more effective if started early in the course of treatment because the outcome is likely to be worse if it is delayed[45,69].

Two of our patients (numbers 1 and 2) received acute ECT with varying degrees of success (Supplementary Material).

Adjunctive ECT in RCBD patient examples

A 72-year-old man with medication-resistant RCBD received two courses of acute ECT in 2017 for episodes of severe depression. The response to the first course was good with complete remission from depression. However, he did not respond as well with the second course a few months later. The depressive episodes did not remit and his rapid cycling continued. He had physical complications during ECT and was unwilling to try ECT further. Later, his rapid cycling

Table 1 Studies of adjunctive electroconvulsive therapy in rapid-cycling bipolar disorder

Ref.	Sample	Results
Case reports		
Berman and Wolpert[56], 1987	18-yr-old woman with medication-resistant RCBD	ECT during mania led to complete remission, which was maintained for 14 mo without medications
Mizukawa *et al* [57], 1991	81-yr-old woman with medication-resistant ultra-RCBD	ECT did not prevent the recurrence of episodes over a period of 35 yr of observation
Benjamin and Zohar[58], 1992	45-yr-old man with treatment-resistant RCBD	Depressive episodes responded transiently to total sleep deprivation and psychotherapy but complete remission was only achieved with acute ECT
Kho[59], 2002	79-yr-old woman with medication-resistant RCBD	ECT and lithium was used successfully during acute and maintenance treatment
Zavorotnyy *et al* [60], 2009	63-yr-old woman with medication-resistant bipolar disorder	The patient developed ultra-rapid cycling during acute ECT, which responded to the continuation of ECT and addition of lithium
Amino *et al*[61], 2011	63-yr-old woman with medication-resistant RCBD	Continuation-ECT for 12 mo prevented rehospitalization
Huber and Burke [62], 2015	67-year-old woman with medication-resistant ultra-RCBD	ECT was used to successfully treat depression and manic episodes that developed on discontinuation of lithium
Kranaster *et al*[63], 2017	21-yr-old woman with medication-resistant ultra-RCBD	ECT was used to successfully treat a treatment-resistant depressive episode
Observational studies		
Kukopulos *et al* [64], 1980	87 patients with RCBD	11 patients treated only with ECT for 7–35 yr remained in remission for long periods
Kukopulos *et al* [65], 1983	87 patients with RCBD	ECT was more effective than antidepressants in treating severe depression and when combined with lithium led to longer remissions
Wehr *et al*[66], 1988	24 patients with medication-resistant RCBD	None of the patients remitted with ECT
Mosolov and Moshchevitin[67], 1990	8 patients with mood stabilizer-resistant RCBD	Acute ECT lead to remission for 6 mo in 3 patients. The number of episodes and the time spent in mood episodes was reduced. Mood stabilizers were more effective following acute ECT treatment
Vanelle *et al*[68], 1994	Four patients with medication-resistant RCBD	Maintenance ECT for 18 mo led to full or partial remission in all 4 patients. Time spent in the hospital was reduced. Response was better in depressive episodes with psychotic symptoms
Wolpert *et al*[69], 2013	Six patients with continuous cycling	ECT started early in the course of cycling was effective in reducing recurrences
Koukopoulos *et al* [70], 2003	43 patients of RCBD who received ECT	11 patients remitted with ECT and mood stabilizer combinations and maintained in this state for 2–36 yr. Temporary improvement was noted in the others. Two out of 3 patients on maintenance ECT had good response
Minnai *et al*[71], 2011	14 patients with medication-resistant RCBD treated with maintenance ECT. Comparisons of 2-yr periods before and after ECT	All patients improved. Eight did not relapse over 2 yr and 6 had only one episode annually. Time spent ill was reduced and interepisodic periods were longer. Young males with type II BD and hyperthymic temperament had better outcome
Mosolov *et al*[72], 2021	1-year prospective study of 30 patients with RCBD and ultra RCBD with poor response to mood stabilizer treatment. Comparisons of 1-yr periods before and after acute ECT	40% achieved and maintained remission with ECT and lithium treatment; 30% showed partial response with the combination and 30% did not respond. Duration of mood episodes was significantly reduced with ECT. Mixed depression with/without catatonia had better response to acute ECT

ECT: Electroconvulsive therapy; RCBD: Rapid-cycling bipolar disorder; type II BD: Bipolar disorder type II; Ultra-RCBD: Ultra-rapid-cycling with shorter cycles of days to weeks; Ultradian-RCBD: Ultradian rapid-cycling with episodes lasting less than a day.

responded to repeated administration of partial sleep deprivation during depressive episodes and dark therapy during hypomanic episodes. A 42-year-old woman with medication-resistant, ultra-rapid, and ultradian cycling was administered ECT in 2005 during an episode of psychotic depression with high suicidal risk. She improved but her cycling did not stop. She was administered ECT again in 2015 for a mixed episode with psychosis and suicidal risk. Response to ECT was inadequate on this occasion and she had physical complications during ECT. Since then, her rapid-cycling pattern has shown a better response to intensive psychotherapy combined with medication. The detailed treatment histories of these patients (Supplementary Material) illustrate some of the disadvantages of ECT in RCBD including the variable response, greater acute than maintenance effects, and the higher risk of adverse effects in some patients[32,45,55,75]. Although ECT is used more commonly in RCBD than in the non-rapid-cycling group, it is still underutilized in RCBD because of these concerns[78,79].

Other neurostimulatory treatments in RCBD

There are few reports of rTMS and VNS treatment in RCBD. A case report described a 60-year-old woman with medication-resistant RCBD who improved after acute administration of rTMS and remained in remission for 6 mo with maintenance rTMS[80]. Another report of a 60-year-old woman with RCBD found that 12 mo of treatment with VNS reduced the severity of her depressive symptoms and the duration of her depressive episodes[81]. Finally, nine patients with treatment-resistant RCBD were treated with VNS for 1 year in a pilot study[82]. They had significant improvements in overall illness severity, the severity of depressive symptoms, and functioning. The VNS treatment was well-tolerated.

Adjunctive chronotherapy in RCBD

Chronotherapy refers to treatment based on controlled exposure to environmental stimuli such as light to alter circadian rhythms or manipulation of the sleep–wake cycle to benefit patients with psychiatric disorders[83-87]. Chronotherapy includes bright light therapy (BLT), wake therapy (total or partial sleep deprivation in the second half of the night), phase-advance of the sleep–wake cycle, triple chronotherapy (combinations of wake therapy, BLT, and sleep phase-advance) dark therapy, blue-light-blocking sunglasses, interpersonal and social rhythm therapy (IPSRT), cognitive behavioural therapy (CBT) for insomnia, and exogenously administered melatonin[84,86,88,89]. These treatments are effective among patients with BD.

Among the various options, BLT appears to be the one best supported by the evidence[86,89]. Several meta-analyses have shown medium to large effects of BLT during acute treatment of bipolar depression[89-93]. It is effective in seasonal and nonseasonal depression[94-98]. Adding BLT to antidepressants or sleep deprivation treatment yields a better response[90,99]. BLT is well tolerated and the risk of manic switches is not increased with it[93,100-103]. However, the efficacy of BLT is based on few RCTs and some meta-analyses have found no conclusive evidence for its efficacy[100,102,103].

The evidence for total or partial sleep deprivation is less convincing. Although 50%–60% of patients respond to a single session of wake therapy, the positive effects of wake therapy are usually transient[86,89,104,105]. The evidence base consists mainly of uncontrolled trials. Moreover, there may be a higher risk of manic switches. Nevertheless, several meta-analyses have concluded that wake therapy combined with medications causes significant reductions in symptoms of bipolar depression[106-109]. Combining sleep deprivation with antidepressants or mood stabilizers, BLT, or sleep phase-advance treatment also sustains its effects[107,110-112]. The treatment might be particularly effective for those with bipolar rather than unipolar depression[113-117]. There is no difference in efficacy between total and partial sleep deprivation[106,108,118,119]. Lastly, the rates of manic switches are low, except in patients with RCBD[104,107,112].

Triple chronotherapy is a treatment regimen designed to prevent the early relapse of symptoms with wake therapy [110,112,116]. It consists of one or more nights of wake therapy, followed by morning administration of BLT, and 3–5 d of sleep phase advance[84]. A systematic review[87] and a meta-analysis[120] showed that triple chronotherapy was effective in bipolar depression. Response rates ranged from 33% to 62% and the effects lasted several weeks. It was not associated with adverse effects and the rates of switching were low.

Dark therapy involves keeping patients with mania/hypomania in dark rooms for extended periods of rest and sleep [84]. This treatment can reduce manic symptoms but has not been examined in RCTs[84,86,117]. A more practical option is the use of glasses that block blue light. This treatment reduced manic and depressive symptoms and improved sleep efficiency in two RCTs[121,122].

A few RCTs of IPSRT have shown positive effects on bipolar depression during acute and maintenance treatment and a single RCT showed that CBT for insomnia improves sleep and decreases depressive symptoms[86,89].

RCBD is the prototypical example of the link between mood disorders and abnormalities of the circadian system and the sleep–wake cycle[28,123-126]. Compared to patients without rapid cycling, the circadian rhythm system in patients with RCBD is more vulnerable to the effects of environmental stimuli, for example, light and dark, irregular sleep patterns and sleep loss, and changes in the social environment such as stressful life circumstances[3,54,55,124,125]. Disturbances in circadian rhythms[3,28,124,126] and social rhythms[28,45,55,127], abnormalities of circadian genes[46,85,128,129], evening chronotypes[125,130], and hormonal abnormalities occur at a higher rate in RCBD[46,85]. However, despite this knowledge and the evidence for the efficacy of chronotherapy in BD, chronotherapy of RCBD is still an evolving area[86]. Since most of the RCTs of chronotherapy in BD usually exclude patients with RCBD, the current evidence is limited to case reports and observational studies with small sample sizes. Table 2 includes these studies and reports of chronotherapy of RCBD[58,70,127,131-143].

Despite the limited evidence, treatments such as wake therapy, BLT, dark therapy, and triple chronotherapy have been used successfully in the acute and maintenance treatment of patients with RCBD. Chronotherapy combined with medications is effective even in patients resistant to medications, ECT, or psychotherapy. There is some concern about the adverse effects of these treatments, particularly the risk of manic/hypomanic switches and exacerbation of rapid cycling with wake therapy. Early studies reported higher rates of switching with wake therapy in RCBD[110,113,114,118,119]. However, these studies mostly used total sleep deprivation. Recent studies of partial sleep deprivation have reported lower rates[115]. Moreover, the high rates are based on a small number of patients with RCBD and the rate of treatment-induced switches is probably no different from the rate of spontaneous switches in RCBD[86,115]. Lastly, such switches can be easily treated or prevented by combining sleep deprivation with medications, BLT, and phase-advance treatment [110,112,115].

Adjunctive chronotherapy in RCBD: patient examples

Four of our patients have been treated successfully with adjunctive chronotherapy. Triple chronotherapy, dark therapy, and blue-light-blocking glasses were used successfully in two inpatients: (1) A 69-year-old woman with a long history of ultra-rapid RCBD was hospitalized after 6 years of unsuccessful treatment with different combinations of medication.

Table 2 Studies of adjunctive chronotherapy in rapid-cycling bipolar disorder

Ref.	Sample	Results
Case reports		
Christodoulou *et al* [131], 1978	26-yr-old woman with rapid-cycling episodes of severe recurrent depression resistant to medications	Inpatient and outpatient total sleep deprivation every week for 36 wk led to remission for a period of 10 mo. The patient committed suicide after stopping the maintenance sleep deprivation treatments
Lovett Doust and Christie[132], 1980	48-yr-old woman with medication-resistant RCBD	Five nights of total sleep deprivation combined with medications during depressive episodes for 8 mo led to reduction in intensity and duration of depression. Switches into hypomania were recorded
Churchill and Dilsaver[133], 1990	47-yr-old woman with rapid-cycling episodes of severe recurrent depression	Partial sleep deprivation on alternate nights combined with an antidepressant led to complete remission from depression for 6 wk
Benjamin and Zohar[58], 1992	45-yr-old man with treatment-resistant RCBD resistant to antidepressants	One night of sleep deprivation was successful in aborting depressive episodes, but led to prolonged hypomania on one occasion and did not prevent the rapid-cycling pattern
Gann *et al*[134], 1993	64-yr-old man with ultradian-RCBD	Total sleep deprivation for 3 nights led to reduction of depressive symptoms for 2 wk. Further improvement occurred with carbamazepine
Eagles[135], 1994	50-yr-old man with medication-resistant ultradian-RCBD	Daily morning BLT for 2 mo produced sustained remission without hypomanic switches
Kusumi *et al*[136], 1995	2 patients with medication-resistant RCBD and nonseasonal depressions	Morning BLT led to improvement in sleep and mood. Withdrawal of BLT did not result in relapse. Remission was maintained for several months
Wehr *et al*[137], 1998	51-yr-old man with medication-resistant RCBD treated with 10–14 h of darkness, rest, and sleep over 1.5 yr	Dark therapy helped in stabilizing sleep, reducing hypomanic symptoms, and attenuating rapid cycling for the period of treatment. Lower doses of antipsychotics were required and hospital stay was shorter
Wirz-Justice *et al* [138], 1999	70-yr-old woman with medication-resistant ultra-RCBD	Rapid-cycling ceased on initiation of 10–14 h of darkness, rest, and sleep. Depression improved with mid-day BLT and remission was achieved with morning BLT. Patient remained on valproate and was stable for a year
Leibenluft and Suppes[127], 1999	42-yr-old woman with medication resistant ultra-RCBD	A lifestyle intervention that ensured a regular sleep–wake schedule in combination with medications led to decrease in rapid cycling
Observational studies		
Papadimitriou *et al* [139], 1981	5 patients with treatment-resistant RCBD	Weekly regimens of total sleep deprivation administered over several months reduced relapses and increased the duration of remissions
Wehr *et al*[140], 1982	9 patients with RCBD treated with 1 night of total sleep deprivation during depressive episodes	Depressive symptoms improved in 8 patients with sleep deprivation but 7 developed mania or hypomania
Papadimitriou *et al* [141], 1993	5 medication-free patients with RCBD treated with total sleep deprivation twice a week for 4 wk	All 5 patients responded to sleep deprivation treatment with > 50% improvement in depressive symptoms and remained in remission for a year with weekly sleep deprivation treatments. Rapid-cycling, young age, female sex, family history of mood disorder and illness duration < 10 yr predicted response. Hypomania was observed in 1 patient
Gill *et al*[142], 1993	3 patients with treatment-resistant RCBD treated with total sleep deprivation and mood stabilizers and antidepressants	Duration of response was significantly better when sleep deprivation treatment was administered late rather than early in the depressive episodes
Leibenluft *et al* [143], 1995	9 patients with RCBD treated with 3 mo of BLT and medications versus 3 mo of only medication treatment	Mid-day BLT was more effective in reducing depressive symptoms and days spent depressed than morning or evening BLT. Morning BLT precipitated hypomanic switches
Koukopoulos *et al* [70], 2003	2 women with RCBD	Sleep deprivation resulted in a temporary improvement of depression

BLT: Bright light therapy; RCBD: Rapid-cycling bipolar disorder; Ultra-RCBD: Ultra-rapid-cycling with shorter cycles of days to weeks; Ultradian-RCBD: Ultradian rapid-cycling with episodes lasting less than a day; Partial sleep deprivation: Sleep deprivation during the second half of the night; Total sleep deprivation: Sleep deprivation for 36 h.

Hypomania at admission responded well to dark therapy within 3–4 d and her antipsychotics could be stopped. She was started on triple chronotherapy when her depressive symptoms began to reappear 2 wk later. With two courses of this treatment, she remitted completely and remained symptom-free for 1 mo. Blue-light-blocking glasses also helped. Unfortunately, chronotherapy was not continued at home. Her rapid cycling resumed and 1 year later she dropped out of treatment; and (2) A 62-year-old woman with medication-resistant RCBD responded partially to morning bright light treatment combined with medication. Her depressive symptoms became less intense and the depressive episodes shorter. However, she was not able to carry out sleep deprivation treatment at home and her ultra-rapid cycling continued. She was hospitalized recently. Her depression responded to two cycles of triple chronotherapy and subsequent hypomanic symptoms responded to dark therapy and wearing blue-light-blocking glasses. She has achieved complete remission with

adjunctive chronotherapy after several years. Triple chronotherapy on an outpatient basis was planned for two more patients with treatment-resistant RCBD. It could not be implemented, but these patients responded to BLT, wake and dark therapy: (1) A 72-year-old man was able to undertake partial sleep deprivation for depression and dark therapy for hypomania at home with the help of his wife. He has achieved almost complete remission for the last 4 years with chronotherapy combined with medication, even though he had responded poorly to medications and ECT earlier; and (2) A 52-year-old woman with ultra-rapid RCBD could not undertake sleep deprivation at home. She has been undergoing morning bright light treatment for depression. Her response has been better since this treatment was added to her mood-stabilizer regimen. She has achieved almost complete remission after a long time. The treatment histories (Supplementary Material) of these patients illustrate the benefits and challenges of administering chronotherapy in RCBD[144]. Although wake therapy, BLT, triple chronotherapy, dark therapy, and blue-light-blocking glasses were successful, conducting these treatments at home was difficult because patients are unwilling to undertake sleep deprivation. Additionally, light boxes are expensive and few patients can afford them.

Adjunctive psychotherapy in RCBD

The existing literature on the treatment of BD indicates that the concomitant use of pharmacotherapy and psychotherapy significantly improves several patient outcomes[145-149]. The most effective forms of psychotherapy are psychoeducational treatments, CBT, and family-focused treatments. These are useful in decreasing symptom severity, reducing the duration of manic and depressive episodes, preventing recurrences, reducing residual depressive symptoms, and decreasing the number and duration of hospitalizations. Additionally, they improve medication adherence, illness management skills, coping abilities, and functional outcomes.

Despite the extensive evidence on the positive effects of adjunctive psychotherapy in BD, there are only a few reports of psychotherapy in RCBD. Table 3 shows these studies[51,58,150-153]. They provide some support for adjunctive psychoeducational treatments, CBT, family intervention, and supportive psychotherapy in RCBD. The outcomes obtained are similar to those shown by RCTs of adjunctive psychotherapy in BD.

The lack of studies on concomitant psychotherapies in RCBD is surprising because these treatments could yield better outcomes in RCBD. Moreover, this is contrary to the advice that psychoeducation, CBT, family interventions, and supportive psychotherapy should be used in RCBD because of the strong evidence base supporting the efficacy of adjunctive psychotherapy in BD[25,32,45,48,51].

Adjunctive psychotherapy in RCBD: patient example

One of our patients with treatment-resistant RCBD received adjunctive supportive therapy. A 42-year-old woman with ultra-rapid and ultradian cycling did not improve with medications and ECT. During the third period of hospitalization in 2015, she was started on regular sessions of structured psychotherapy. The strategies adopted included problem-solving to deal with day-to-day stresses and mood swings and supportive–expressive sessions to deal with more enduring problems such as interpersonal conflicts, and regrets about not working or marrying. She had her best period of mood stabilization for several months while she underwent psychotherapy. Unfortunately, she dropped out of the sessions and was following up irregularly till recently. Nevertheless, she remained free from any severe mood episodes with medications. She has had a recent relapse when medication doses were reduced to minimize side effects but improved with crisis intervention sessions. She has resumed supportive psychotherapy. Her treatment history (Supplementary Material) shows the usefulness of psychotherapy even in those who have not responded adequately to medications or ECT.

DISCUSSION

Treating RCBD remains a challenge for clinicians. Difficulties arise from its high prevalence, severity, poor outcomes, and high disability. The response to pharmacotherapy is often not adequate or complete. Therefore, nonpharmacological treatments are necessary for effectively managing RCBD[18,36,46-48]. However, research on adjunctive nonpharmacological treatments is still scarce[17,18,46,54]. This review shows that there has been limited progress in this area in the last 15 years[45]. A principal reason for the lack of data is the difficulty in conducting methodologically sound treatment trials in RCBD[18,44]. The treatment-resistant nature of RCBD creates further hurdles. Consequently, most RCTs of nonpharmacological treatments for BD usually exclude patients with RCBD.

Nevertheless, there are some promising developments. Not surprisingly, there have been more studies and reports since the 2007 review. Similar to the previous review, the current one also found that most of the evidence favours concomitant ECT as an acute and maintenance treatment in RCBD. Adjunctive acute ECT is effective for severe mood episodes in RCBD that are refractory to medication and have high risk of harm. Adjunctive maintenance ECT may prevent further rapid cycling, especially in those who respond favourably to acute ECT. There is an increasing interest in chronotherapy for BD, but the evidence concerning RCBD is still limited. However, unlike the earlier review, there appears to be preliminary evidence that wake therapy, BLT, dark therapy, and triple chronotherapy can provide better outcomes when combined with medication. Widespread use of these treatments has been hampered by a lack of funding for researchers and lack of awareness and expertise among clinicians[85,154]. Several other factors also hinder the use of chronotherapy, including the cost of equipment such as light boxes, the difficulty of conducting these treatments in outpatient settings or homes, and the problems in ensuring adherence to the treatment protocols[144,155-157]. Lastly, the scarcity of research on adjunctive psychotherapy in RCBD was particularly disappointing. Although psychotherapy appear to be commonly used in clinical settings, the lack of controlled evidence possibly reflects the difficulty in

Table 3 Studies of adjunctive psychotherapy in rapid-cycling bipolar disorder

Ref.	Type of study	Sample	Intervention	Results
Levy and Remick[51], 1986	Observational study	8 women with RCBD	Supportive psychotherapy with patients and family regarding treatment response and adherence	Complete remission in 5 patients and partial remission in 3 patients for 7–40 mo with combined psychotherapy and medications
Spurkland and Vandvik [150], 1989	Case report	13-yr-old girl with RCBD	Family therapy to reduce conflicts and improve adherence	Family therapy combined with medications led to lasting remission
Benjamin and Zohar[58], 1992	Case report	45-yr-old man with treatment-resistant RCBD	Supportive psychotherapy	Psychotherapy provided relief from the rapid-cycling pattern for 3 mo
Satterfield [151], 1999	Case report	33-yr-old man with medication-resistant RCBD	Pharmacotherapy and concomitant CBT	Significant reductions in the severity of manic, depressive, and anxiety symptoms with adjunctive CBT
Reilly-Harrington *et al*[152], 2007	Uncontrolled trial	10 patients with RCBD	CBT included psychoeducation, cognitive restructuring, and teaching illness-management skills	CBT over 5 mo led to significant improvements in depressive symptoms for 2 mo after the treatment in 6 patients who completed the trial
Lenz *et al* [153], 2016	Controlled trial	16 patients with RCBD; 14 wk of adjunctive psychotherapy and 12-mo follow-up	CPT *vs* BT. CPT included psychoeducation and CBT; BT consisted of reading and discussing a book on bipolar disorder	Significant effects of both treatments - reductions in illness severity, reductions in the number of all episodes with CPT and depressive episodes with BT, reductions in the number and duration of hospitalizations, reductions in disability, and improvement in medication adherence and illness concepts. CPT was better than BT

BT: Bibliotherapy; CBT: Cognitive behavioural therapy; CPT: Cognitive psychoeducational therapy; RCBD: Rapid-cycling bipolar disorder.

conducting psychotherapy trials for RCBD. Nevertheless, there is reason to believe that psychotherapy may be effective in RCBD because it can augment the response to medication, reduce acute and residual depression, improve functioning, promote recovery, and decrease family burden[45,48,51,158]. Studies show that childhood maltreatment, stressful life events, and disturbed family environments are more common in RCBD[2,9,25,48,50]. Adjunctive psychotherapy that addresses these factors and reduces psychosocial stress may be helpful in RCBD[45]. Medication nonadherence is a significant problem in BD. It is associated with adverse clinical and psychosocial outcomes among patients and their families. Although some studies show greater nonadherence in RCBD, the majority do not[159]. Nonadherence may be more common in those with more frequent episodes, higher disability, and in those with comorbid substance use disorders[10,40,160,161]. Rapid cycling with these features may contribute to nonadherence and inadequate adherence may worsen cycling[51]. Psychoeducational treatments help improve adherence and attitudes towards medication for BD [145,149]. Similarly, adjunctive psychosocial treatment can positively impact treatment adherence in RCBD by improving treatment attitudes, managing comorbid disorders, and minimizing disability[51,153]. Thus, despite the limited evidence many authors have recommended that adjunctive psychotherapy should form an essential part of the overall management of RCBD[26,32,45,49,158].

CONCLUSION

RCBD is a common phase in the course of BD characterized by greater severity, a predominance of depression, higher levels of disability, and poorer overall outcomes. It is resistant to treatment by conventional pharmacotherapy. The ineffectiveness of conventional pharmacological treatment for RCBD suggests that adjunctive nonpharmacological interventions could be useful but these have not been examined adequately.

According to this review, most of the evidence favoured concomitant ECT as an acute and maintenance treatment for medication-resistant RCBD. Although ECT is effective in refractory mania as a part of RCBD, a better response is obtained in depression with psychotic or catatonic symptoms. ECT is safe and the risk of inducing rapid cycling is low.

Among chronotherapeutic techniques, sleep deprivation or wake therapy has been the option most frequently investigated. Sleep deprivation is effective in relieving depressive symptoms but there is a high rate of relapse and the risk of inducing manic switches. Triple chronotherapy, which combines partial sleep deprivation, bright light treatment, and phase advance of the sleep cycle produces enduring effects and lowers the risk of manic switches. Although there are no studies of triple chronotherapy, examples of patients included in this review suggest that it can be successful in medication-resistant patients. Similarly, there are no studies of dark therapy or blue-light-blocking glasses, but these techniques have been successfully used to treat hypomania in individual patients. Case reports and studies also suggest that bright light treatment can be effective for patients with depression as a part of RCBD.

A few studies provide some support for adjunctive psychoeducational treatments, CBT, family intervention, and supportive therapy in medication-resistant RCBD. The overall quality of evidence for the usefulness of adjunctive nonpharmacological treatment in RCBD was poor and suffered from several methodological shortcomings.

It is apparent from this review that there are large gaps in the existing literature on the usefulness of adjunctive nonpharmacological treatments in RCBD. Therefore, examining the role of these treatments remains a priority for research. However, the current evidence regarding effective pharmacological and nonpharmacological treatment is inconclusive. Thus, clinicians may find treating RCBD a formidable task in the absence of specific guidelines. One option could be to select nonpharmacological treatments effective in BD[27,30,45,49]. Alternatively, treatment decisions can rely on the current evidence on nonpharmacological treatments in RCBD[18]. Clinicians can use this evidence to undertake the sequential or concurrent use of several pharmacological and nonpharmacological interventions[26,45]. Although this remains an exploratory exercise, such combinations are likely to succeed if individualized to meet the needs of patients with RCBD and their families. Table 4 includes principles derived from the existing recommendations that could guide clinicians in managing RCBD. As always, the key to successful treatment of RCBD requires patience, perseverance, and a strong collaborative relationship with patients and their families.

Table 4 Suggestions for the use of adjunctive nonpharmacological treatments in rapid-cycling bipolar disorder

	Suggestions
Goals of acute treatment[18,45]	The priority for acute treatment is to ensure that patients respond to treatment and no longer meet criteria for an acute mood episode
	A rapid response is necessary to provide relief for patients and their families and reduce the risks of self-harm, aggression, and physical complications
	The concurrent and early use of treatments such as ECT or wake therapy for depression, and dark therapy for mania may be considered if there is inadequate response to pharmacotherapy
	Treatments that are likely to be useful during long-term treatment should guide the use of treatments in the acute phases
Goals for long-term treatment[29,30,45,51,55]	Rather than focusing on acute treatment, the primary objective should be to prevent further episodes of rapid cycling
	The model for a chronic medical disorder with acute exacerbations should guide the long-term treatment plan for RCBD
	Adjunctive maintenance ECT, wake therapy, bright light treatment, dark therapy, and triple chronotherapy can be considered at this stage
	Education, support, and the involvement of the family is useful for all patients. Psychoeducational treatments, CBT, family treatment can be implemented if required
Improved functioning rather than complete remission should be the goal of long-term treatment[18,20,25,30]	Full remission and complete absence of recurrences is an unrealistic goal
	Clinicians should focus on an enduring response that consists of reduced frequency, intensity, and duration of mood episodes
	Clinicians should attempt to restore optimal functioning in the occupational, family, and social spheres
Basic tasks[2,4,54,55,162]	Careful diagnosis and comprehensive assessment of the patient including psychosocial factors
	Avoidance of precipitants such as stress, irregular sleep routines, and antidepressant medications when it worsens the course of RCBD
	Treatment of physical and psychiatric comorbidities especially hypothyroidism and substance use
Longitudinal approach and use of life charts [2,26,45,55,163]	Acute episodes should be viewed in the context of the long-term course of bipolar disorder/RCBD
	Life charts may be used to delineate the course of illness, possible precipitants, and treatment response. They might help patients and families understand the course of RCBD and the longitudinal approach to treatment
Use of treatments effective in bipolar disorder[27,30,45,49]	Options for adjunctive nonpharmacological treatment should be chosen based on the evidence for their efficacy in BD
Sequential trials of treatment for long durations[25-27,30,51]	Treatment of RCBD requires several trials of each treatment regimen lasting for about 3–4 mo before the acute-phase efficacy of the treatment regimen can be determined
	Frequent changes in treatment should be avoided since they might worsen rapid cycling
Combining pharmacological and nonpharmacological treatments[25,30,32,45,163]	One option is to add nonpharmacological treatments only in refractory patients in whom several medications have been tried and have failed
	An alternative option recommends the early use of adjunctive nonpharmacological patients even in those patients who are not medication resistant
Monitoring treatment response[17,18,25,35,	More intensive monitoring during acute phases which can be relaxed once the patient becomes more stable

51]	Mood charts can be used to assess response to treatment At least 12 mo of treatment is required to determine the efficacy of long-term treatment
Working with patients and families[4,32,45,51,127]	Education: explaining RCBD, its causes, and the treatment approach including lifestyle changes is necessary for ensuring the collaboration of patients and families. Psychoeducational treatments that reduce stress, improve attitudes to treatment, enhance treatment engagement, and reduce caregiver burden can be tried. CBT is another option Support: ongoing support for patients and families is essential. This can be provided by developing a strong collaborative relationship. Nonadherence can also be addressed by fostering a strong treatment alliance Patience: the protracted nature of the illness requires the clinician to accept that it will take a long time for the results to become apparent. Patience and perseverance on the part of patients and families has to be stressed repeatedly so that they learn to focus on long-term goals Sleep hygiene: regular sleep routines can be advised in all patients. Chronotherapeutic techniques can be tried when required and feasible

CBT: Cognitive behavioural therapy; ECT: Electroconvulsive therapy; RCBD: Rapid-cycling bipolar disorder.

FOOTNOTES

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Country/Territory of origin: India

ORCID number: Subho Chakrabarti 0000-0001-6023-2194; Amal J Jolly 0009-0005-9172-5692; Pranshu Singh 0000-0003-0283-0430; Nidhi Yadhav 0009-0002-0924-4717.

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