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by Subho Chakrabarti

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The role of adjunctive non-pharmacological strategies in the treatment of rapid-cycling bipolar disorder: A review

ABSTRACT
Rapid-cycling bipolar disorder (RCBD) is a phase of bipolar disorder defined by the presence of 4 or more mood episodes in a year. It is a fairly common phenomenon characterized by greater severity, a predominance of depression, higher levels of disability, and poorer overall outcomes. Moreover, it is relatively 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, non-pharmacological interventions could augment medication treatments but have not been adequately examined. This review carried out an updated and comprehensive search for evidence regarding the role of non-pharmacological therapies as adjuncts to medication treatments in RCBD. It identified 83 reviews and meta-analyses concerning the treatment of RCBD. Additionally, it found 42 reports on adjunctive non-pharmacological 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. Though there is a need for more methodologically sound research in this area, clinicians can use the existing evidence to select and individualize non-pharmacological treatment options for better management of RCBD. Patient summaries are included to highlight some of the issues concerning the implementation of adjunctive non-pharmacological treatments.

Key Words: Rapid-cycling; Bipolar disorder; Adjunctive; Non-pharmacological 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 non-pharmacological 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. It indicated that electroconvulsive therapy, chronotherapy, and psychotherapy could effectively augment the medication treatment of RCBD. However, the evidence is limited and methodologically inadequate. Therefore, clinicians have to rely on certain general guidelines for the optimal use of the available non-pharmacological options while managing RCBD.

INTRODUCTION
Clinical features of rapid-cycling bipolar disorder
Rapid-cycling bipolar disorder (RCBD) is a phase in the longitudinal course of bipolar disorder (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]. The DSM-5 defines rapid-cycling as a minimum of 4 episodes in the previous 12 months 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 months, 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, the DSM-5 does not include these categories.

The phenomenon of rapid-cycling occurs among a significant proportion of patients with BD. The 12-month prevalence of RCBD in patients from specialized mood disorder clinics is about 20% (range 4%-27%) [4, 6-9]. The prevalence is higher (27%-56%) when ultra-rapid 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 on the subject 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%-24% (range 12%-56%) [5, 19-21].

Apart from its frequent occurrence, RCBD is characterized by certain clinical features that make it a severe and disabling phenomenon. Depressive episodes or depressive 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 much harder to treat compared to 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. Moreover, the distress and disability associated with unremitting depression are the main hurdles in effectively managing RCBD [10, 13, 14, 22, 25]. Though 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 more than 50% of the patients [6, 25-28]. A longer duration of rapid-cycling, more frequent episodes, a depression-mania-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 existing 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 medication treatments 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]. (Supplement 1 includes a complete list of all the reviews consulted.)

The main finding of this research is that RCBD is relatively 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]. Moreover, 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, 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 the long-term treatment of RCBD [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].
Non-pharmacological therapy for RCBD

The shortcomings in the pharmacological treatment indicate an unmet need for more effective management options for RCBD. Adjunctive non-pharmacological interventions could fill the existing gap in managing RCBD [18, 36, 45-47]. Neurostimulatory treatments such as electroconvulsive therapy (ECT), chronotherapy, and psychotherapy can potentially augment the inadequate response obtained with medications. However, the role of adjunctive non-pharmacological 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 treatment 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 non-pharmacological treatments could be used to manage RCBD based on clinical experience and their usefulness in BD. Moreover, 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 non-pharmacological 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 non-pharmacological therapy in RCBD. At present, there is no consensus or guidance on the optimal management of RCBD because pharmacological
and non-pharmacological treatments have proved somewhat ineffective [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 non-pharmacological 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 non-adherence [25, 30, 45, 51, 52].

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

METHODS
Though this was not a systematic review, it relied on comprehensive electronic (PUBMED) and manual searches to identify the existing literature on non-pharmacological treatments in RCBD from 1980 to April 2023. The accompanying figure depicts this search. Supplement 1 includes the details of the search terms used. The search and ranking of articles according to their impact also used the Reference Citation Analysis tool.

Figure here
This search identified 53 narrative reviews, 21 systematic reviews, and 9 meta-analyses on the treatment of RCBD. These reviews were used to collate information regarding various non-pharmacological therapies in RCBD. A second round of electronic and manual searches identified 17 studies or reports of ECT, 16 of chronotherapy, 6 of psychotherapy, 2 of VNS, and 1 of rTMS in RCBD. 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, particularly for 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 medications is efficacious for patients with highly recurrent illnesses if they have 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 (reference numbers [56-72]).

Table 1 here

Despite these limitations, acute ECT seems to be effective in patients with medication-resistant RCBD with complete or partial remission rates ranging
from 70%-100% in some studies [69, 72]. Others have reported much 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]. Acute ECT also reduces the time 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%-100% [68, 70, 71]. Adjunctive maintenance ECT prevents relapses, reduces the need for hospitalization and the length of hospital stays, decreases the time spent in episodes, and increases the duration of inter-episodic 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 appears to be 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 appears to be 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 such 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 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 (Box 1/Supplement 2). Their treatment illustrates 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 under-utilized in RCBD because of these concerns [78, 79].

Box 1 here

Other neurostimulatory treatments in RCBD

There are very 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 months with maintenance rTMS [80]. Another report of a 60-year-old woman with RCBD
found that 12 months of treatment with VNS reduced the severity of her depressive symptoms and the duration of her depressive episodes [81]. Finally, 9 patients with treatment-resistant RCBD were treated with VNS for a 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 treatments 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]. Chronotherapeutic treatments include 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-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 the acute treatment of bipolar depression [89-93]. It is effective in seasonal and non-seasonal 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 very 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 days 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%-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 2 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, for example, 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 chronotherapeutic treatments 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 (reference numbers [58, 70, 131-143]). Table 2 here

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 medication treatment 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 treatment. Recent studies of partial sleep deprivation report much 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].

Four of our patients have been treated successfully with adjunctive chronotherapy. Their treatment histories (Box 2/Supplement 2) illustrate the benefits and challenges of administering chronotherapy in RCBD [144]. Although wake therapy, BLT, triple chronotherapy, and dark therapy 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.

Box 2 here

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 (reference numbers [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.

Table 3 here

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].

One of our patients with treatment-resistant RCBD (number 2) received adjunctive supportive therapy. Her treatment history (Box 3/ Supplement 2) shows the usefulness of psychotherapy even in those who have not responded adequately to medications or ECT.

Box 3 here
DISCUSSION

Treating RCBD remains a challenge for the clinician. Difficulties arise from its high prevalence, greater severity, poorer outcomes, and higher disability. Moreover, the response to pharmacotherapy is often not adequate or complete. Therefore, non-pharmacological treatments are necessary for effectively managing RCBD [18, 36, 46-48]. However, research on adjunctive non-pharmacological 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 since the earlier one [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 non-pharmacological treatments for BD usually exclude patients with RCBD.

Nevertheless, there are some promising developments. Not surprisingly, there are 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 medications and have high risks of harm. Adjunctive maintenance ECT may prevent further rapid-cycling, especially in those who respond favourably to acute treatment. There is an increasing interest in chronotherapeutic treatments 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 medications. Then again, the widespread use of these treatments has been hampered by the lack of funding for researchers.
and a 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]. The scarcity of research on adjunctive psychotherapy in RCBD was particularly disappointing. Although psychotherapeutic treatments appear to be commonly employed in clinical settings, the lack of controlled evidence possibly reflects the difficulty in 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 medications, 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 non-adherence is a significant problem in BD. It is associated with adverse clinical and psychosocial outcomes among patients and their families. Though some studies show a greater extent of non-adherence in RCBD, the majority do not [159]. Non-adherence may be commoner in those with more frequent episodes, higher disability, and in those with comorbid substance use disorders [10, 40, 160, 161]. Rapid-cycling could contribute to non-adherence and inadequate adherence may worsen cycling [51]. Psychoeducational treatments help improve adherence and attitudes towards medication taking in 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].

CONCLUSIONS
The conclusions of this review are enumerated below.

Box 4 here

It is apparent from this review that there are large gaps in the existing literature on the usefulness of adjunctive non-pharmacological treatments in RCBD. Therefore, examining the role of these treatments remains a priority for research. However, the current evidence regarding effective pharmacological and non-pharmacological treatment is inconclusive. Thus, clinicians may find treating RCBD a formidable task in the absence of specific guidelines. One option could be to select non-pharmacological treatments effective in BD [27, 30, 45, 49]. Alternatively, treatment decisions can rely on the current evidence on non-pharmacological treatments in RCBD [18]. Clinicians can use this evidence to undertake the sequential or concurrent use of several pharmacological and non-pharmacological 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.

Table 4 here

As always, the key to successful treatment of RCBD requires patience, perseverance, and a strong collaborative relationship with patients and their
families.