

### **Box 1: Adjunctive electroconvulsive therapy in rapid-cycling bipolar disorder: patient examples**

- A 72-year-old man with medication-resistant RCBD received 2 courses of acute ECT in 2017 for his 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 episode 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 responded to repeated administrations 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 much better response to intensive psychotherapy combined with medications.

Supplement 2 includes their detailed case histories.

## **Box 2: Adjunctive chronotherapy in rapid-cycling bipolar disorder: patient examples**

Triple chronotherapy, dark therapy, and blue-light-blocking glasses were used successfully among 2 inpatients.

- 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 medications. Hypomania at admission responded very well to dark therapy within 3-4 days and her antipsychotics could be stopped. She was started on triple chronotherapy when her depressive symptoms began to reappear 2 weeks later. With two courses of this treatment, she remitted completely and remained symptom-free for a month. Blue-light-blocking glasses also helped. Unfortunately, chronotherapy was not continued at home. Her rapid-cycling resumed and a year later she dropped out of treatment.
- A 62-year-old woman with medication-resistant RCBD responded partially to morning bright light treatment combined with medications. 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 2 more patients with treatment-resistant RCBD.

- 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 medications, even though he had responded poorly to medications and ECT earlier.
- 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.

Supplement 2 includes their detailed case histories.

### **Box 3: Adjunctive psychotherapy in rapid-cycling bipolar disorder: patient example**

- A 42-year-old woman with ultra-rapid and ultradian cycling did not improve with medications and ECT. During the third 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.

Supplement 2 includes her detailed case history

#### **Box 4: Conclusions**

- RCBD is a common course variant of BD characterized by greater severity, a predominance of depression, higher levels of disability, and poorer overall outcomes. It is relatively resistant to treatment by conventional pharmacotherapy.
- The ineffectiveness of conventional pharmacological treatment for RCBD suggests that adjunctive non-pharmacological interventions could be useful but these have not been examined adequately.
- According to this review, most of the evidence favoured concomitant electroconvulsive therapy as an acute and maintenance treatment for medication-resistant RCBD. Though 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 highly 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. Though 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 non-pharmacological treatment in RCBD was poor and suffered from several methodological shortcomings. Nevertheless, clinicians can use the existing evidence to select and individualize non-pharmacological treatment options for better management of RCBD.

## Supplement 1-SEARCH STRATEGY

### Search strategy for adjunctive non-pharmacologic treatment of rapid-cycling bipolar disorder

Database searched -PUBMED

#### Search 1

#### Search terms for reviews and studies on adjunctive non-pharmacologic treatment of RCBD

- A. Search - A: #11 AND (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9) ("rapid cycling bipolar disorder"[Title/ Abstract] OR "rapid cycling bipolar disorder"[Title/ Abstract] OR "rapid cycling affective disorder"[Title/ Abstract] OR "rapid cycling affective disorder"[Title/ Abstract]) AND ("Chronotherapy"[MeSH Terms] OR "Phototherapy"[MeSH Terms] OR "dark therap\*"[Title/ Abstract] OR "light therap\*"[Title/ Abstract] OR "Sleep Deprivation"[Title/ Abstract] OR "wake therap\*"[Title/ Abstract] OR ("Electroconvulsive Therapy"[MeSH Terms] OR "electroconvulsive therap\*"[All Fields] OR "electric shock therap\*"[Title/ Abstract] OR "electroshock therap\*"[Title/ Abstract] OR "shock therap\*"[Title/ Abstract] OR "Psychiatric Somatic Therapies"[MeSH Terms]) OR ("Transcranial Magnetic Stimulation"[MeSH Terms] OR "rTMS"[Title/ Abstract] OR "theta burst stimulation\*"[Title/ Abstract] OR "Theta burst stimulation"[Title/ Abstract] OR "repetitive transcranial magnetic stimulation\*"[Title/ Abstract]) OR ("Transcranial Direct Current Stimulation"[MeSH Terms] OR "transcranial direct current stimulation\*"[Title/ Abstract] OR "tdcs\*"[Title/ Abstract] OR "transcranial alternating current stimulation\*"[Title/ Abstract] OR "tacs\*"[Title/ Abstract]) OR ("Vagus Nerve Stimulation"[MeSH Terms] OR "vagal nerve stimulation\*"[Title/ Abstract] OR "vagus nerve stimulation\*"[Title/ Abstract]) OR ("Cognitive Behavioral Therapy"[MeSH Terms] OR "cognitive behavioral therap\*"[Title/ Abstract] OR "cognitive behavioural therap\*"[Title/ Abstract] OR "cognitive behavior therap\*"[Title/ Abstract] OR "cognitive therap\*"[Title/ Abstract] OR "cognitive psychotherap\*"[Title/ Abstract] OR "cbt"[Title/ Abstract]) OR ("psychoeducation\*"[Title/ Abstract] OR "psycho education\*"[Title/ Abstract]) OR ("Family Therapy"[MeSH Terms] OR "family therap\*"[Title/ Abstract] OR "family intervention\*"[Title/ Abstract]) OR ("interpersonal and social rhythm therap\*"[Title/ Abstract] OR "ipsrt\*"[Title/ Abstract] OR "social rhythm therap\*"[Title/ Abstract] OR "interpersonal social rhythm therap\*"[Title/ Abstract]))
- B. Search B - #10 AND (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9) ("Bipolar Disorder"[MeSH Terms] OR "ultradian\*"[Title/ Abstract] OR "rapid cycling bipolar disorder\*"[Title/ Abstract] OR "rapid cycling bipolar disorder\*"[Title/ Abstract] OR "rapid cycling affective disorder\*"[Title/ Abstract] OR "rapid cycling affective disorder\*"[Title/ Abstract]) AND ("Chronotherapy"[MeSH Terms] OR "Phototherapy"[MeSH Terms] OR "dark therap\*"[Title/ Abstract] OR "light therap\*"[Title/ Abstract] OR "Sleep Deprivation"[Title/ Abstract] OR "wake

therap\*[Title/ Abstract] OR ("Electroconvulsive Therapy"[MeSH Terms] OR "electroconvulsive therap\*[All Fields] OR "electric shock therap\*[Title/ Abstract] OR "electroshock therap\*[Title/ Abstract] OR "shock therap\*[Title/ Abstract] OR "Psychiatric Somatic Therapies"[MeSH Terms]) OR ("Transcranial Magnetic Stimulation"[MeSH Terms] OR "rTMS"[Title/ Abstract] OR "theta burst stimulation\*[Title/ Abstract] OR "Theta burst stimulation"[Title/ Abstract] OR "repetitive transcranial magnetic stimulation\*[Title/ Abstract]) OR ("Transcranial Magnetic Stimulation"[MeSH Terms] OR "rTMS"[Title/ Abstract] OR "theta burst stimulation\*[Title/ Abstract] OR "Theta burst stimulation"[Title/ Abstract] OR "repetitive transcranial magnetic stimulation\*[Title/ Abstract]) OR ("Transcranial Direct Current Stimulation"[MeSH Terms] OR "transcranial direct current stimulation\*[Title/ Abstract] OR "tdcs\*[Title/ Abstract] OR "transcranial alternating current stimulation\*[Title/ Abstract] OR "tacs\*[Title/ Abstract]) OR ("Vagus Nerve Stimulation"[MeSH Terms] OR "vagal nerve stimulation\*[Title/ Abstract] OR "vagus nerve stimulation\*[Title/ Abstract]) OR ("Cognitive Behavioral Therapy"[MeSH Terms] OR "cognitive behavioral therap\*[Title/ Abstract] OR "cognitive behavioural therap\*[Title/ Abstract] OR "cognitive behavior therap\*[Title/ Abstract] OR "cognitive therap\*[Title/ Abstract] OR "cognitive psychotherap\*[Title/ Abstract] OR "cbt"[Title/ Abstract]) OR ("psychoeducation\*[Title/ Abstract] OR "psycho education\*[Title/ Abstract]) OR ("Family Therapy"[MeSH Terms] OR "family therap\*[Title/ Abstract] OR "family intervention\*[Title/ Abstract]) OR ("interpersonal and social rhythm therap\*[Title/ Abstract] OR "ipsrt\*[Title/ Abstract] OR "social rhythm therap\*[Title/ Abstract] OR "interpersonal social rhythm therap\*[Title/ Abstract]))

## Search 2

Search terms for studies on adjunctive non-pharmacologic treatment of RCBD

Database searched -PUBMED

1. Chronotherapy  
"Chronotherapy" [Mesh] OR "Phototherapy"[Mesh] OR "Dark Therap\*" [Tiab] OR "Light Therap\*" [Tiab] OR "Sleep Deprivation" [Tiab] OR "Wake Therap\*" [Tiab]
2. Electroconvulsive Therapy  
"Electroconvulsive Therapy"[Mesh] OR "Electroconvulsive Therap\*" OR "Electric Shock Therap\*" [Tiab] OR "Electroshock Therap\*" [Tiab] OR "Shock Therap\*" [Tiab] OR "Psychiatric Somatic Therapies"[Mesh]
3. Repetitive Transcranial Magnetic Stimulation  
"Transcranial Magnetic Stimulation"[Mesh] OR "rTMS"[Tiab] OR "Theta-burst stimulation\*[Tiab] OR "Theta burst stimulation"[Tiab] OR "Repetitive Transcranial Magnetic Stimulation\*[Tiab]

4. Transcranial Direct Current Stimulation  
 "Transcranial Direct Current Stimulation"[Mesh] OR "Transcranial Direct Current Stimulation\*" [Tiab] OR "tDCS\*" [Tiab] OR "Transcranial Alternating Current Stimulation\*" [Tiab] OR "tACS\*" [Tiab]
5. Vagus Nerve Stimulation  
 "Vagus Nerve Stimulation"[Mesh] OR "Vagal Nerve Stimulation\*" [Tiab] OR "Vagus Nerve Stimulation\*" [Tiab]
6. Cognitive Behavioural Therapy  
 "Cognitive Behavioral Therapy"[Mesh] OR "Cognitive Behavioral Therap\*" [Tiab] OR "Cognitive Behavioural Therap\*" [Tiab] OR "Cognitive Behaviour Therap\*" [Tiab] OR "Cognitive Behavior Therap\*" [Tiab] OR "Cognitive Therap\*" [Tiab] OR "Cognitive Psychotherap\*" [Tiab] OR "CBT\*" [Tiab]
7. Psychoeducation  
 "Psychoeducation\*" [Tiab] OR "Psycho-education\*" [Tiab]
8. Family Therapy  
 "Family Therapy"[Mesh] OR "Family Therap\*" [Tiab] OR "Family Intervention\*" [Tiab]
9. Interpersonal and Social Rhythm Therapy  
 "Interpersonal and Social Rhythm Therap\*" [Tiab] OR "IPSRT\*" [Tiab] OR "Social Rhythm Therap\*" [Tiab] OR "Interpersonal Social Rhythm Therap\*" [Tiab]
10. Bipolar Disorder  
 "Bipolar Disorder"[Mesh] OR "Ultradian\*" [Tiab] OR "Rapid-cycling Bipolar Disorder\*" [Tiab] OR "Rapid Cycling Bipolar Disorder\*" [Tiab] OR "Rapid Cycling Affective Disorder\*" [Tiab] OR "Rapid-Cycling Affective Disorder\*" [Tiab]
11. Rapid Cycling Bipolar Disorder  
 "Rapid-cycling Bipolar Disorder\*" [Tiab] OR "Rapid Cycling Bipolar Disorder\*" [Tiab] OR "Rapid Cycling Affective Disorder\*" [Tiab] OR "Rapid-Cycling Affective Disorder\*" [Tiab]

**List of reviews on adjunctive non-pharmacologic treatment of rapid-cycling bipolar disorder**

Narrative reviews

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### Systematic reviews

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## Supplement 2-PATIENT SUMMARIES

### Patient 1

A 72 -year-old, retired electrician was referred to the psychiatric outpatient clinic in 2014 by the hepatology services with possible oxcarbamazepine-induced elevation in liver transaminases. He had an 18-year history of type II bipolar disorder which was initially treated with lithium and later with oxcarbamazepine along with several antidepressants and antipsychotics. He had a rapid-cycling pattern of illness and continued to cycle between severe episodes of depression and hypomania at a rate of 4 or more episodes per year. The rapid-cycling had responded poorly to adequate trials of medications with adequate adherence. He was switched to lithium in 2014, but it had to be stopped after the first few months because of poor tolerance. He continued to have a rapid-cycling pattern. Additionally, he was diagnosed with Parkinson's disease in 2016 and was started on levodopa. He received 2 courses of acute ECT in 2017 for severe depression. Response to the first course was good, but he did not have adequate improvement with the second course. ECT did not stop his rapid-cycling. He had physical complications during ECT and was unwilling to try ECT further. He was tried on a succession of mood stabilizers including valproate and lamotrigine in combination with second-generation antipsychotics. Antidepressants were avoided because of hypomanic switches. Eventually he was switched to oxcarbamazepine and quetiapine again with careful monitoring of liver functions, but continued to cycle frequently. In 2018 he was persuaded to try partial sleep deprivation (wake therapy), exposure to natural light, and phase advance of sleep (triple chronotherapy) during his depressive episodes and extended rest in the dark for his hypomanic episodes (dark therapy). After initial hesitation, he undertook the sleep deprivation sessions and his mood improved following these sessions. He also tried dark therapy during hypomania and found it to be useful. He maintained a regular routine of getting up early, exercising in the daylight, and resting in the dark for his hypomanic episodes. His response to mood stabilizers improved following these interventions. Over the last 4 years, his rapid-cycling pattern has more or less



ceased. His parkinsonian symptoms are under control and he has no functional impairment.

## **Patient 2**

A 42-year-old woman with type I bipolar disorder and RCBD (rapid-cycling bipolar disorder) was first seen in the psychiatric outpatient clinic in 2003. Her rapid-cycling pattern was ultra-rapid and later ultradian cycling. She had very frequent episodes of episodes of mania/hypomania, severe depression, and mixed states. During her depressive and mixed episodes, she had frequent thoughts of suicide. She had to give up her job as an air-hostess because of the illness. He had extensive physical and psychiatric comorbidities including migraine, hypothyroidism, chronic pancreatitis, and hypertension. She also a strong family loading for bipolar disorder, schizophrenia, migraine, and hypothyroidism. She was tried on valproate, lithium, lamotrigine, antipsychotics like aripiprazole, risperidone, quetiapine, olanzapine, clozapine, and antidepressants such as bupropion and sertraline without much response. She also had intolerable side effects such as hair loss with valproate, polyuria with lithium, rashes with lamotrigine and galactorrhoea with aripiprazole and risperidone. She was admitted in 2005 for a severe depressive episode with psychotic symptoms and high suicidal risk. She received 7 ECTs. She was somewhat better following this but her cycling did not stop. This pattern continued till 2015 when she had 5 outpatient ECTs for a mixed episode with psychotic symptoms. Response to ECT was inadequate on this occasion and she had physical complications during ECT. Eventually, she was hospitalized twice in 2015. In the second admission she was treated with adjunctive psychotherapy. This included problem solving strategies to deal with day-to-day stresses and mood swings as well as supportive-expressive therapy to deal with more enduring problems such as interpersonal conflicts such as interpersonal conflicts, and regrets about not working or marrying. She was continued on clozapine and divalproex sodium. With regular psychotherapy sessions she had the most stable period of her illness. Her cycling ceased, her symptoms minimized, and she became hopeful of getting a job. However, she dropped out of the sessions and was following up irregularly since then although she has continued to take her medications. She

continued to remain free from any severe mood episodes with medications. She has been attending regularly again for the past few months. Unfortunately, she had a relapse following reduction in the doses of her medications in an attempt to minimize side effects. Doses have been hiked again, but she required intensive support to deal with her current episode. Nevertheless, she has responded to the crises intervention sessions and has now started sessions of supportive psychotherapy.

### **Patient 3**

A 69-year-old missionary who was first seen in the psychiatric outpatient clinic in 2010. She had type II bipolar disorder with RCBD since 2001. The workload at the mission, interpersonal conflicts with other staff, and staying far from home appeared to have contributed to the onset of her illness. She had an ultra-rapid pattern of illness with very short periods of remission in between. She had been treated by private psychiatrists with combinations of mood stabilizers and antidepressants without any change in her rapid-cycling pattern and with very brief periods of remission in between. From 2010 in our clinic, she was tried on combinations of mood stabilisers such as lithium and lamotrigine. She had prolonged spells of depression, which would eventually respond only to antidepressants. However, she would develop hypomanic episodes although these usually responded to second-generation antipsychotics. The functional impairment was not very severe, but because of the demands of her job and poor relations with other staff she was considered a problem at her mission. She had developed subclinical hypothyroidism with lithium and had other physical ailments that were adequately controlled with treatment. Her frequent switches into hypomania were minimized to an extent by avoiding antidepressants. She continued in this pattern for the next 5 years, after which her depressive episodes became worse. She was hospitalized in 2017. She was in a hypomanic phase at admission, but this responded very well to dark therapy within 3-4 days and her antipsychotics could be stopped. She remained in complete remission for about 2 weeks. When she started to develop depression again, she was tried on a night's partial sleep deprivation, followed by exposure to natural light the next morning, and sleep-phase advance for

5 days (triple chronotherapy). She responded very well and her depressive symptoms remitted for 2 weeks again. She had two more treatments of triple chronotherapy, following which she had complete remission for a month. Before discharge she was given written instructions to follow the triple chronotherapy regimen at her mission with the help of the staff. She was advised dark therapy and blue-light-blocking glasses for her hypomanic episodes. She was continued on lithium and lamotrigine. Unfortunately, she was unable to adhere to the chronotherapeutic treatments at the mission and her rapid-cycling returned. Finally, she dropped out of treatment about a year later.

#### **Patient 4**

A 62-year-old woman with type II bipolar disorder and RCBD was first seen in the psychiatric outpatient clinic in 2016. For the first 2 years, she was treated with carbamazepine and quetiapine but continued to demonstrate an ultra-rapid pattern of cycling. Lithium was added to carbamazepine in 2018 and with this combination the frequency of her episodes decreased substantially. She dropped out of follow-up in 2019 and sought treatment elsewhere. By the time she returned in 2021, her cycling had become much more frequent, though she had mostly moderate depressive and hypomanic episodes. She was treated mainly with lithium, lamotrigine and quetiapine, but these medications had no effect on her ultra-rapid cycling pattern. A combination of wake therapy, bright light treatment, and sleep-phase advance (triple chronotherapy) was suggested and a detailed plan was explained to her and her family members. However, she could not carry out partial sleep deprivation sessions at home. Instead, she procured a light box, which had become readily available by then. Daily morning exposure to bright white light of 10,000 lux intensity for several weeks during her depressive episodes was commenced. The timing of the exposure was determined by administering the Morningness-Eveningness Questionnaire (MEQ) and lasted 1 hour. She had no adverse effects with light treatment. Her depressive symptoms decreased in intensity and duration with light treatment combined with medications. However, she still continued to have mainly depressive episodes almost every month. She was recently admitted to the inpatient unit. Her depressive episodes

were treated with 2 cycles of triple chronotherapy. She achieved faster and more complete remission with this treatment. She developed hypomanic symptoms subsequently because the dose of quetiapine was reduced. These symptoms also responded to 5 days of dark therapy and wearing blue-light-blocking glasses. Currently, she is completely remitted after several years of ultra-rapid cycling.

### **Patient 5**

A 52-year-old homemaker with type II bipolar disorder and ultra-rapid RCBD was first seen in the psychiatric outpatient clinic in 2020. Her problems started in 2009, but for the first 4 years she would only have bouts of early morning awakening once or twice a year, which would get better with medications within 1-2 months. From 2012, she started having hypomanic and depressive episodes lasting about a week each, about 4 times a year mostly during the change of seasons. Subsequently, she started having many more such episodes, each lasting about 2 weeks and occurring in succession. The symptom-free periods lasted only 2-3 weeks. She was treated with combinations of mood stabilizers and other medications without any effect on her rapid-cycling. In our clinic, she was treated with lithium, lamotrigine, and quetiapine. She was also treated for subclinical hypothyroidism. With this treatment, her hypomanic episodes were controlled but she continued to have depressive episodes. Supportive psychotherapy was tried, especially during the time when her young daughter who was training to be a dentist died in a traffic accident. However, this did not stop the frequent recurrences of depression. A combination of wake therapy, bright light treatment, and sleep phase-advance (triple chronotherapy) was suggested at this point. However, she was not able to carry out partial sleep deprivation even when her husband tried to help her out. A light box was used for daily morning exposure to bright white light of 10,000 lux intensity for several weeks during her depressive episodes was tried. The timing of the exposure was determined by administering the MEQ and lasted 1 hour. She tolerated this treatment well. With repeated light treatment, her depressive episodes have become less intense and are much shorter in duration. She has been in remission ever since she has been on bright light therapy.

