

# Interpersonal and Social Rhythm Therapy for Patients With Major Depressive Disorder

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**Objective:** This study aimed to conduct a safety analysis among patients with major depressive disorder receiving interpersonal and social rhythm therapy (IPSRT) with and without cognitive remediation.

**Methods:** This preliminary safety analysis of the outcomes of patients with major depressive disorder was part of a larger randomized controlled trial (RCT) in which patients with bipolar disorder and major depressive disorder received IPSRT; half were randomly assigned to receive additional cognitive remediation. The study focused on patients with major depressive disorder because IPSRT had not been trialed with this group; their outcomes were compared with those of patients with bipolar disorder. Data from the first 30 RCT participants were used to examine whether the intervention had adverse effects, whether mood symptoms and functioning improved over 12 months, and whether there was a signal of benefit. Mood symptoms were measured at baseline and 12 months with the

Longitudinal Interval Follow-Up Evaluation and the Quick Inventory of Depressive Symptoms–Self-Reported; functioning was measured with the Social Adjustment Scale.

**Results:** A total of 63% (N=19) of participants were diagnosed with bipolar disorder and 27% (N=11) with major depressive disorder. No adverse effects were found for those with major depressive disorder, and improvements were seen in mean depressive and functioning scores at 12 months compared with baseline, with moderate to large effect sizes.

**Conclusions:** IPSRT may be a clinically effective intervention for patients with major depressive disorder. Outcomes related to cognitive functioning and the effects of cognitive remediation will be reported at the end of the trial.

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Both bipolar disorder and major depressive disorder are recurrent and disabling mental health conditions. The lifetime prevalence of depression has been identified as 20.6%, with most cases being moderate or severe, lasting more than 6 months, and associated with comorbidity and impairment (1). Depression is the leading cause of disability worldwide (2). In addition to mood symptoms, people with depression experience impairments in physical, social, and occupational functioning (3). Despite the range of pharmacotherapy options, treatment of depression resulting in full symptomatic and functional recovery remains challenging (4). It has been suggested that treatment needs to focus on the outcomes of asymptomatic remission and functional recovery, including improvement in social, interpersonal, work, and family domains (5). Some evidence has shown that these functional impairments are underpinned by residual cognitive impairments and impairments in attention, verbal learning and memory, psychomotor speed, and executive function associated with a depressive episode (6). Cognitive remediation is one intervention designed to target these neurocognitive

impairments through online computerized exercises completed at home and explored in therapy sessions.

Evidence has shown that psychological treatments combined with medication are more effective than medication alone in the treatment of depression (7). Interpersonal psychotherapy (IPT) has been reported to be effective in treating patients with unipolar depression (8) and interpersonal and social rhythm therapy (IPSRT) in treating patients with

## HIGHLIGHTS

- This preliminary safety analysis found no adverse effects and found a signal of benefit in the use of interpersonal and social rhythm therapy (IPSRT) among patients with major depressive disorder.
- Evidence was found for the effectiveness of adjunctive IPSRT for patients with bipolar disorder.
- IPSRT may also be an effective adjunctive intervention for patients with major depressive disorder.

bipolar depression (9). A systematic review of the efficacy of IPT among patients with depressive disorders (10) found that it

was superior to placebo and similar to medication. Clinical guidelines have identified that level-1 evidence supports IPT as a first-line treatment for acute depression (11, 12).

Considerable evidence suggests that circadian and sleep disturbances are important in the pathophysiology of depressive episodes. The circadian hypothesis of depression suggests that the disruption of social rhythms and the resulting disruption of nonphotic zeitgebers that normally entrain physiological circadian rhythms trigger depressive episodes in vulnerable individuals (13). IPSRT is underpinned by findings from chronobiology research, with the social rhythm component—social relationships, social demands or tasks (social zeitgebers)—providing the external scaffolding to entrain circadian rhythms (13). Dysregulation of social rhythms has been proposed to desynchronize circadian rhythms across a range of systems. This hypothesis has been supported by work showing that social rhythms are disrupted and less regular among patients with a mood disorder as well as among individuals undergoing stressful life events (14, 15). Although this process has received considerable attention in research on bipolar disorder, there has been less consideration of the process of regulating social rhythms to synchronize circadian rhythms in research on major depressive disorder. Many aspects of this disorder also involve aspects of circadian disruption (e.g., changes in the sleep-wake cycle, diurnal variation in severity of mood symptoms, variations in cyclic hormones and neurotransmitter levels) (16). Some treatments that directly target the circadian system, for example bright light therapy (17) and sleep deprivation (18), have been found to have an antidepressant effect.

Although treatment of the acute phase of major depressive disorder is important, research has identified that impairments in functioning remain persistent even after 3 years of recovery from depressive symptoms (19) and are correlated with unemployment, disability, and decreased work performance (20). Most psychotherapy and pharmacotherapy trials for treatment of depression have focused on a reduction in depressive symptoms rather than an improvement in functioning (21). Unfortunately, reduction in symptom severity among depressed patients does not always denote normal quality of life or functioning (22).

Because of the association between mood and circadian rhythm disruption, a good theoretical rationale supports providing IPSRT to patients with major depressive disorder because this psychotherapy focuses on helping patients reduce circadian and interpersonal stressors that may lead to relapse. It has the potential to promote both symptomatic and functional recovery from major depressive disorder. This study focuses on patients with major depressive

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disorder and compares their outcomes with those of patients with bipolar disorder. Because of the sample size for this preliminary study,

however, the statistical analysis has limitations. To our knowledge, no studies have examined the effectiveness of IPSRT among patients with a major depressive disorder diagnosis.

The aim of this study was to evaluate the safety of using IPSRT with patients diagnosed as having major depressive disorder to ensure that the absence of adverse effects and the presence of a signal of benefit.

## METHODS

The design was a preliminary safety analysis of the symptomatic and functional effectiveness of IPSRT among patients with a diagnosis of major depressive disorder compared with those with a bipolar disorder diagnosis within a randomized controlled trial (RCT) of IPSRT with and without cognitive remediation (CR). We hypothesized that IPSRT would have no adverse effects and would bring about a reduction in both mood and functional symptoms from baseline among patients with major depressive disorder.

### Randomized Controlled Trial

The aim of the RCT was to compare the effect of a 12-month adjunctive enhancing recovery intervention involving IPSRT and cognitive remediation (IPSRT-CR) with that of IPSRT alone on cognitive functioning among patients with a recurrent mood disorder who reported current cognitive difficulties. Patients were recruited on discharge from specialist mental health services after treatment for a depressive episode (bipolar disorder I or II or major depressive disorder). The primary hypothesis for the RCT was that IPSRT-CR, compared with IPSRT alone, would result in significantly improved cognitive functioning over the 12-month treatment period. The blind has not been broken, and data for both groups will be reported at the conclusion of the trial. Ethical approval was obtained from the New Zealand Health and Disability Ethics Committee (16/NTA64). Participants signed informed consent to take part in the study, and the principles of the Declaration of Helsinki were followed.

### Sample

The data from the first 30 patients recruited into the RCT were analyzed. Patients with bipolar disorder I, bipolar disorder II, or major depressive disorder who had cognitive difficulties reported by their referring clinician were recruited on discharge from mental health services. Diagnosis was confirmed by using the Structured Clinical Interview for DSM-IV Axis I Disorders (23). Exclusion criteria were minimal but included schizophrenia or schizoaffective disorder, severe alcohol or

drug dependence, having completed a course of IPSRT or CR in the past 18 months, or having history of severe brain injury (loss of consciousness longer than 1 hour).

The enhancing recovery intervention is based on 12 months of IPSRT, and half of the patients also received cognitive rehabilitation.

### Interpersonal and Social Rhythm Therapy

IPSRT has almost exclusively been used among patients with bipolar disorder and combines IPT with social rhythm therapy. It has been described in detail by Frank et al. (9). IPSRT is underpinned by the hypothesis that although biological factors play the strongest role in the pathophysiology of bipolar disorder, the timing of individual episodes is strongly related to environmental, psychological, and psychosocial factors. IPSRT has the usual IPT problem areas (interpersonal disputes, interpersonal sensitivity, role transitions, and grief) and includes an additional problem area: grief for loss of healthy self. The intervention was delivered over 12 months rather than the usual 3 months for IPT, which allowed for a more intensive examination of interpersonal patterns and social rhythms and how they affect mood symptoms and interpersonal functioning. The intervention involved weekly sessions for 10–12 weeks followed by sessions every 2 weeks (biweekly) and then monthly.

### Treatment Integrity

IPSRT was delivered according to a manualized protocol. Five therapists trained in IPSRT delivered the therapy. Group supervision was led by two experienced therapists who had received training in IPSRT from Holly Swartz of the University of Pittsburgh. All therapists participated in biweekly group supervision focused on treatment integrity that entailed presenting case formulations of patients with progress reviews and addressing individual patient issues, such as the impact of comorbidity while maintaining fidelity to IPSRT. Subject to patient consent, all psychotherapy sessions were audiotaped. One audiotaped session per month per therapist was selected by the research coordinator and reviewed for adherence to the treatment modality by a senior therapist. A therapy rating scale from the study by Frank et al. (9), consisting of a 22-item Likert scale focusing on the somatic, interpersonal, and social rhythm content of the therapy, was used to guide the process of evaluating fidelity. All cases were regularly reviewed at a biweekly multidisciplinary team meeting.

### Cognitive Remediation

CR involved patients engaging in cognitively stimulating activities that have been reported to produce changes in brain structure (24) and function (25). Patients in the IPSRT-CR group received access to the computerized program and weekly support from therapists in order to complete activities focused on improving executive function, problem solving, memory, and concentration for three 30-minute sessions per week for 12 weeks (<https://www.scientificbraintrainingpro.com>). The intervention started in week 5.

### Measures

The data were collected between October 2016 and February 2018. The following measures were completed at baseline and 12 months. The Social Adjustment Scale (SAS) was used as a measure of social functioning (26). The SAS is a 45-item questionnaire that rates social functioning over the previous 2 weeks across 11 domains: work outside home, housework, social and leisure activities, extended family, marriage, parental relationships, family unit, performance, feelings and satisfaction, friction, and interpersonal behavior. Each item is scored on a 5-point Likert scale, with higher scores reflecting greater impairment.

The Longitudinal Interval Follow-Up Evaluation (LIFE) (27) was used to obtain mean depression scores. The LIFE rates the severity of depression on a week-by-week basis retrospectively over a 6-month period. Individuals are rated on a 0–5 scale on which 0 indicates no symptoms, 3 indicates marked symptoms but that do not meet diagnostic criteria, and 4 and 5 indicate meeting diagnostic criteria.

The Quick Inventory of Depressive Symptoms–Self-Reported (QIDS-SR) (28) is a 16-item self-report measure of depressive symptoms: sleep, mood, appetite, weight, concentration, self-perception, suicidality, and energy. In addition, safety was evaluated according to number of adverse events, withdrawals from intervention, and mood symptom scores at follow-up.

### Analysis

Per protocol, analyses were conducted with IBM SPSS Statistics, version 25. Analyses were conducted separately for the participants according to bipolar disorder and major depressive disorder diagnosis. Frequencies, percentages, means, and standard deviations were used to describe the demographic and clinical characteristics of the sample. Cohen's *d* effect sizes were calculated to determine the impact of the intervention on depression and functioning.

## RESULTS

Of the first 30 participants who received the enhancing recovery intervention, 63% (*N*=19) had bipolar disorder and 37% (*N*=11) had major depressive disorder. The group of patients with major depressive disorder had three dropouts (one moved out of the country, and two withdrew); the group of patients with bipolar disorder had two dropouts (one had major surgery, and one withdrew). The mean number of sessions for those who completed treatment was 25.6 in the group of patients with bipolar disorder and 26.5 in the group of patients with major depressive disorder. Those who dropped out completed a mean of nine sessions. Among those with bipolar disorder, the majority were female (79%), and the group had a mean  $\pm$ SD age of  $42.3 \pm 11.8$  years. In contrast, 54% of the group with major depressive disorder were female, and the group had a younger mean age of  $30.5 \pm 11.01$  years (Table 1).

At baseline, seven patients in the group with major depressive disorder—including one with bipolar disorder I and one with bipolar disorder II—met criteria for a current major

**TABLE 1. Baseline demographic and clinical characteristics of patients with bipolar disorder and major depressive disorder**

| Characteristic                            | Bipolar disorder (N=19) |      | Major depressive disorder (N=11) |      |
|---|-------------------------|------|----------------------------------|------|
|   | N                       | %    | N                                | %    |
| Gender (female)                           | 15                      | 78.9 | 6                                | 54.5 |
| Age (M±SD)                                | 42.3±11.8               |      | 30.5±11.01                       |      |
| Ethnicity (New Zealand European)          | 17                      | 89.5 | 9                                | 81.8 |
| LIFE depression score (M±SD) <sup>a</sup> | 1.16±1.06               |      | 2.39±.94                         |      |
| SAS score (M±SD) <sup>b</sup>             | 2.29±.45                |      | 2.62±.52                         |      |

<sup>a</sup> LIFE, Longitudinal Interval Follow-Up Evaluation. Possible scores of severity of depression range from 0, no symptoms, to 5, meeting diagnostic criteria.

<sup>b</sup> SAS, Social Adjustment Scale. Possible scores range from 1 to 5, with higher scores indicating higher levels of impairment.

depressive episode, and one patient with bipolar disorder II met criteria for hypomania. Although most of the patients with bipolar disorder no longer met the criteria for a full acute episode when they were recruited into the study after discharge from mental health services, 64% of those who had been treated for major depressive disorder were in episode when recruited. The group of patients with bipolar disorder received a mean of 25.6 sessions, and the group of patients with major depressive disorder received a mean of 26.5 sessions.

No adverse events were reported in either group. Two patients in the group with major depressive disorder withdrew from the intervention. Both groups had moderate to large effect-size improvement in mean depressive scores measured with the LIFE and the QIDS-SR and moderate effect sizes for improved functioning measured with the SAS (Table 2). Given that this preliminary analysis was concerned with response to IPSRT and that the cognitive response to the combined intervention is the objective of the RCT, we do not report those results here.

**DISCUSSION**

To our knowledge, this is the first investigation of IPSRT among patients with major depressive disorder, and the results suggest that it is safe and may be an effective treatment

for these patients. The analysis, although underpowered, indicates that IPSRT had a positive impact on both depressed mood and functioning. Notably, the effect sizes for the depression ratings on both the LIFE and the QIDS-SR for the group with major depressive disorder were particularly high, although caution should be used in interpreting these results because of the small sample size. The use of IPSRT among patients with major depressive disorder has a strong theoretical rationale on the basis of the principles of chronobiology, and this study suggests that this therapy may be effective in practice. The emphasis on both the stabilization of the social rhythms that underpin circadian rhythms and the treatment of interpersonal issues may have contributed to the improvement in both mood and functioning. Most of the patients with major depressive disorder still met the criteria for a full major depressive episode at baseline, which suggests that most of these patients either still met the criteria for full episode when discharged from mental health services or relapsed within 3 months of discharge.

Several psychological interventions have been reported to improve mood symptoms among patients with unipolar depression (29), and other interventions have been reported to improve symptoms among patients with bipolar depression (30), with some research reporting additional improvement in functioning. The effect sizes reported here are considerably higher than those reported for psychotherapy plus pharmacology for mood disorders. A meta-analysis of pharmacotherapy and psychotherapy for bipolar disorder reported a small mean effect size of 0.19 (range -0.21 to 0.60) (31), and effect sizes for major depressive disorder without pharmacotherapy were small in high-quality studies (d=0.22) and moderate to high (d=0.74) in other studies (32). A meta-analysis of the effect of psychotherapy for depression on improvements in social functioning found a small to moderate effect size across the included studies that was not fully explained by improvements in depressive symptoms (33). Improvement in social functioning is important because these improvements do not automatically follow amelioration of depressive symptoms (34). This is of particular interest because psychosocial impairment is a risk factor for recurrence of mood episodes (35). Reasons for the higher effect sizes in our study may be related to natural remission,

**TABLE 2. Depressive symptoms and social functioning scores among patients with bipolar disorder and major depressive disorder at baseline and end of treatment**

| Characteristic                     | Major depressive disorder (N=9) |     |                  |     |                         | Bipolar disorder (N=17) |     |                  |     |                         |
|------------------------------------|---------------------------------|-----|------------------|-----|-------------------------|-------------------------|-----|------------------|-----|-------------------------|
|                                    | Baseline                        |     | End of treatment |     | Effect size (Cohen's d) | Baseline                |     | End of treatment |     | Effect size (Cohen's d) |
|                                    | M                               | SD  | M                | SD  |                         | M                       | SD  | M                | SD  |                         |
| LIFE depression score <sup>a</sup> | 2.2                             | 1.0 | 1.1              | 1.2 | .9                      | 1.2                     | 1.1 | .4               | .6  | .6                      |
| QIDS-SR score <sup>b</sup>         | 13.1                            | 6.7 | 6.8              | 5.3 | 1.4                     | 7.5                     | 6.2 | 4.4              | 4.6 | .6                      |
| SAS score <sup>c</sup>             | 2.6                             | .6  | 2.2              | .5  | .7                      | 2.3                     | 0.5 | 2.1              | .5  | .4                      |

<sup>a</sup> LIFE, Longitudinal Interval Follow-Up Evaluation. Possible scores of severity of depression range from 0, no symptoms, to 5, meeting diagnostic criteria.

<sup>b</sup> QIDS-SR, Quick Inventory of Depressive Symptoms. Possible scores range from 0 to 27, with higher scores indicating greater severity of depression. Data missing for one patient with major depressive disorder.

<sup>c</sup> SAS, Social Adjustment Scale. Possible scores range from 1 to 5, with higher scores indicating higher levels of impairment. Data missing for one patient with major depressive disorder.

inadequate power, that this study was not an RCT, and that there was no placebo.

Frank et al. (36) reported that IPSRT improved occupational functioning in patients with bipolar depression at follow-up and at 2 years by ameliorating interpersonal and role-functioning issues. The emphasis on stabilization of social rhythms may have contributed to functional improvement because biological rhythm disturbance has been identified as a predictor of functional impairment (37). IPT has been identified as being effective in preventing new depressive episodes and in preventing relapse; this effectiveness becomes more marked as the number of sessions increases to more than 10 (8). The intervention delivered in this study was intensive, and although it was delivered over 12 months, the spacing of sessions meant patients received an average of 25 sessions. This longer duration, which enabled detailed exploration of interpersonal and social rhythm patterns, may have been a factor in these encouraging outcomes. Therapists involved in the delivery of the intervention had regular supervision and reported that patients with major depressive disorder were as responsive as those with bipolar disorder to in-session therapy techniques and in recording the out-of-session social rhythm metric.

This preliminary safety analysis was conducted under RCT conditions. Patients and therapists could not be blinded to treatment conditions. The study was small and examined the data of the first 30 participants; thus, the study had limitations associated with statistical quantification of the effects of IPSRT. Future research should focus on designing RCTs of IPSRT for treatment of patients with major depressive disorder. The patients recruited into this study had received mental health service treatment, had been identified as having cognitive difficulties, and had chosen to take part in a psychotherapy study, so they may not be representative of broader clinical populations.

We investigated the impact of CR in this study. About half of the patients in this sample were also receiving CR, but because the RCT is still underway it was not possible to control for CR in this study. It is possible that some part of the benefits of IPSRT among those with major depressive disorder may have been due to the effects of adjunctive CR in a subset of participants. This small study was not designed or powered to examine mechanisms of change, which will be examined once the full trial is complete. The lack of a nontherapy control meant that we could not account for nonspecific effects of therapy and of being in a clinical trial.

## CONCLUSIONS

This analysis, although limited by sample size, found no adverse effect of the use of IPSRT among patients with major depressive disorder and found a signal of benefit. The results indicate that IPSRT may be an effective adjunctive intervention and that it may improve not only mood symptoms but also functioning. The effect sizes were particularly encouraging.

## AUTHOR AND ARTICLE INFORMATION

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