Brief integrated sleep-focused treatment for persistent sleep disturbance in residual depression: an assessor-blind, parallel group, randomised controlled study

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KEY MESSAGES

1. A brief integrated sleep-focused treatment is feasible in clinical practice with reasonable compliance.
2. It is effective in the management of treatment-resistant depression with comorbid sleep symptoms, evidenced by a much higher remission rate and a better clinical outcome.
3. Adjunctive sleep-focused therapy for patients with treatment-resistant depression and comorbid sleep symptoms should be incorporated into clinical practice and delivered by front-line mental health staff.

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Introduction

Major depressive disorder (MDD) is one of the most prevalent major medical conditions with a lifetime and 12-month prevalence of 2%-16% and 8%, respectively, in the United States and local Chinese populations. It is a debilitating and recurrent illness associated with tremendous personal distress, considerable impairment of psychosocial functioning, as well as increased morbidity and mortality. The treatment goal is sustained resolution of symptomatology with remission of MDD. About 15% to 90% of patients continue to experience residual symptoms, particularly sleep disturbances, despite optimised antidepressant treatment. There is an imperative need to explore specific sleep-focused treatments in addition to usual antidepressant prescription in the routine clinical management of depression.

Growing evidence suggests a close interplay between sleep disruption and psychopathology, in which sleep disturbance is associated with susceptibility to the subsequent development of depression, increased risk of non-remission, and exaggeration of other clinical symptoms, and prognostic implication in predicting suicidality. Although empirical support for cognitive behavioural therapy for insomnia has been well documented, especially for primary insomniacs, there is a paucity of clinical studies to evaluate an integrated sleep-symptom-specific treatment strategy in relation to clinical management of MDD.

This study aimed to develop and evaluate a brief sleep-focused cognitive behavioural therapy for depressed patients with residual sleep disturbances (including frequent insomnia and nightmares).

Methods

This study was conducted from October 2012 to April 2015. Patients were recruited from the psychiatric outpatient clinic of Prince of Wales Hospital. Ethical approval was obtained from the Joint Chinese University of Hong Kong – New Territories East Cluster clinical research ethics committee (reference no: 2011.475-T) and the trial was registered with the Chinese Clinical Trial Registry (reference: ChiCTR-TRC-13002976).

This randomised, assessor-blind, parallel-group study was aimed at patients with residual sleep disturbances despite adequate pharmacotherapy (the usual psychotropic medications prescribed from the outpatient clinic including antidepressants and hypnotics); prescriptions for general medical conditions were allowed during the study period.[1] At baseline, eligible subjects were randomly assigned to the group of sleep-focused treatment plus usual treatment or usual treatment alone. An independent clinical assessor who was blinded to the group allocation assessed the patients at baseline and follow-up.

Outcome measures included: (1) clinician-rated severity of clinical symptoms measured by the Hamilton Rating Scale for Depression (HRSD17), Clinical Global Impression Scale- Global Improvement and Severity of Illness (CGI-S &

CGI-I), self-rated Hospital Anxiety and Depression Scale (HADS), Beck Depression Inventory (BDI), and Beck Scale for Suicide Ideation (BSSI); (2) self-rated sleep symptoms measured by the Pittsburgh Sleep Quality Index (PSQI), Insomnia Severity Index (ISI), Nightmare Frequency Questionnaire (NFQ), Nightmare Distress Questionnaire (NDQ), and daily sleep and dream diary; and (3) self-rated quality of life measures measured by the Short-form 36 Health Survey (SF-36).

All analyses were based on the intent-to-treat model. Chi-square analysis and analysis of variance (ANOVA) were used to compare baseline characteristics. Treatment effect on all main outcome variables was analysed using repeated measure ANOVA. All tests were based on a 0.05 level of significance. Remission for depression was defined as a HRSD17 score of <8 and remission for insomnia was defined as an ISI score of <8. A reduction of total scores for HRSD17 and ISI, and a PSQI score >50% when compared with baseline was defined as response. The differences in the rates of remission and response between the intervention group and control group were tested by Chi-square or Fisher's exact test. All statistical analyses were performed using Statistical Package System Software.

Results

The control and intervention groups were comparable in terms of baseline characteristics and clinical symptoms, except for the NFQ score (15.4±9.8 vs 21.5±8.9, P=0.039) [Table 1]. From baseline to 12-month post-intervention, the intervention group had a greater reduction of HRSD17 score than the control group (from 21.5±5.4 to 13.6±7.0 vs from 20.5±4.4 to 17.8±6.7, time*intervention P=0.001, Table 2). The differences in the changes of HRSD17 score remained significant even after the sleep-related items of the HRSD17 scale were excluded from analysis. From baseline to 1-week follow-up, the reduction of the ISI total score was greater in the intervention group than the control group (from 19.0±4.6 to 15.2±6.6 vs from 17.8±5.0 to 16.5±5.1, time*intervention P<0.05). The intervention group also had lower CGI scores (ie more marked overall improvement) than the control group as rated by both the assessor and patients.

Nonetheless, the differences between the change in ISI for the two groups did not reach significance at subsequent follow-ups from 1 month to 12 months. From baseline to 12-month follow-up, the intervention group had better improvement in the PSQI score than the control group (from 14.5±3.6 to 12.0±4.2 vs from 13.7±3.9 to 12.3±4.8, time*intervention P=0.028).

Compared with the control group, the intervention group had higher remission rate (24.2% vs. 6.1%, P<0.05) and response rate (33.3% vs. 12.1%, P<0.05) of depression at 1 week and 12 months (24.2% vs. 6.1%, P<0.05 and 33.3% vs. 12.1%, P<0.05, respectively) [Table 3].

Discussion

Sleep-focused treatment was effective in the management of depressive symptoms in patients with persistent sleep disturbances and depression. The treatment effect was sustained for over 12 months with improved depressive symptoms. Nearly

TABLE 1. Baseline characteristics of subjects*

Baseline characteristic	Control (n=33)	Intervention (n=33)	P value
Age (years)	51.1±9.4	50.2±8.6	0.71
No. (%) of females	20 (60.6)	21 (63.6)	0.80
Body mass index (kg/m^2)	24.5±2.7	24.3±4.7	0.91
Hamilton Rating Scale for Depression	20.5±4.4	21.5±5.4	0.42
Insomnia Severity Index	17.8±5.0	19.0±4.6	0.29
Pittsburgh Sleep Quality Index	13.7±3.9	14.5±3.6	0.38
Morningness Eveningness Questionnaire	48.6±11.8	49.0±8.9	0.89
Epworth Sleepiness Scale	9.0±5.0	9.9±4.8	0.48
Nightmare Distress Questionnaire	44.4±5.8	44.2±6.1	0.84
Nightmare Frequency Questionnaire	15.4±9.8	21.5±8.9	0.039
Beck Scale for Suicide Ideation	71.7±24.8	75.8±21.9	0.49
Short-form 36 Health Survey	51.6±13.1	50.2±11.2	0.65
Hospital Anxiety and Depression Scale	22.5±7.3	21.5±7.0	0.54
Beck Depression Inventory	15.9±6.2	15.6±6.6	0.83

* Data are presented as mean±SD or No. (%) of subjects

TABLE 2. Changes in outcome measures for intervention and control groups

Outcome measure	Control group					Intervention group					P value for time* intervention
	Baseline	1 week	1 month	6 months	12 months	Baseline	1 week	1 month	6 months	12 months	
Hamilton Rating Scale for Depression	20.5±4.4	18.7±6.7	18.4±6.9	17.5±7.1	17.8±6.7	21.5±5.4	14.1±7.2	14.7±6.8	14.8±8.0	13.6±7.0	0.001
Hamilton Rating Scale for Depression (no sleep)	16.0±4.1	14.9±5.9	14.8±6.0	13.9±6.3	14.3±6.0	16.9±4.9	11.5±6.0	11.7±5.7	11.9±6.6	11.0±5.8	0.003
Insomnia Severity Index	17.8±5.0	16.5±5.1	14.7±5.3	14.4±5.3	13.9±5.7	19.0±4.6	15.2±6.6	15.4±7.0	15.7±7.0	15.0±6.6	0.20
Pittsburgh Sleep Quality Index	13.7±3.9	13.1±4.5	12.7±4.2	12.1±4.3	12.3±4.8	14.5±3.6	11.3±4.6	12.1±4.8	12.1±4.6	12.0±4.2	0.028
Epworth Sleepiness Scale	9.0±5.0	9.3±4.9	9.7±4.5	9.2±5.0	9.1±5.6	9.9±4.8	9.5±5.8	8.6±4.7	8.8±4.7	8.9±4.4	0.41
Nightmare Distress Questionnaire	44.4±5.8	46.1±6.5	46.0±6.2	45.6±7.4	44.3±6.3	44.2±6.1	45.9±5.5	46.8±6.2	45.7±8.8	46.5±8.7	0.58
Nightmare Frequency Questionnaire	10.3±10.8	12.6±11.9	8.9±9.8	10.3±10.3	9.3±11.9	14.3±12.7	12.5±13.1	10.9±12.4	9.6±11.0	9.7±11.7	0.37
Short-form 36 Health Survey	51.6±13.1	50.2±15.2	53.4±14.7	55.2±13.5	53.6±12.8	50.2±11.2	54.7±11.1	52.9±11.9	52.1±10.9	54.6±10.9	0.061
Hospital Anxiety and Depression Scale	22.5±7.3	22.5±8.6	21.0±8.1	20.4±7.2	20.2±8.5	21.5±7.0	20.1±5.8	18.9±5.3	19.1±6.9	18.2 ±5.7	0.88
Beck Depression Inventory	15.9±6.2	14.0±7.8	13.9±7.0	13.6±7.1	13.8±5.8	15.6±6.6	14.4±6.2	13.6±6.6	14.9±6.4	13.2±6.1	0.71
Clinical Global Impression Scale											
Physician-rated	-	3.7± 0.9	3.8±1.0	3.3±1.0	3.5±1.2	-	3.1±0.9	3.0±0.8	2.9±1.0	3.0±1.1	0.035
Self-rated	-	3.3±1.0	3.6±1.4	3.2±1.5	3.4±1.3	-	2.5±0.9	2.8±1.1	2.9±1.4	3.0±1.4	0.036

TABLE 3. Rates of remission and response of depression and insomnia at each time point*

Outcome measure	Remission (%)				Response (%)			
	1 week	1 month	6 months	12 months	1 week	1 month	6 months	12 months
Hamilton Rating Scale for Depression								
Control group	6.1	3.0	3.0	6.1	12.1	6.1	12.1	12.1
Intervention group	24.2	15.2	21.2	24.2	33.3	21.2	30.3	33.3
P value	0.039	0.19	0.054	0.039	0.040	0.15	0.13	0.040
Insomnia Severity Index								
Control group	0	6.1	9.1	12.1	0	12.1	21.2	15.2
Intervention group	12.1	18.2	15.2	18.2	15.2	12.1	18.2	18.2
P value	0.114	0.258	0.708	0.733	0.053	1	0.757	0.741

* Remission is defined as a Hamilton Rating Scale for Depression score of <8 and an Insomnia Severity Index score of <8; response is defined as a reduction of >50% in both scores compared with baseline

one-quarter of treatment-resistant patients with depression had achieved remission at 12-month follow-up compared with only 6% of the control group. Sleep-focused treatment was also effective in management of sleep disturbances, with the most prominent effects seen in the first week after intervention. In addition, the treatment was shown to improve quality of life in depressed patients.

Sleep-focused treatment was effective in reducing insomnia symptoms. Nonetheless, the differences in the changes of the ISI total score between the two groups were not sustained 1-month post-treatment. This could be explained by a significant improvement of insomnia in the control group rather than a rebound of insomnia symptoms in the intervention group. The exact reason was unclear, but there was a possibility that the patients in the control group had received add-on treatment

with hypnotics from the attending clinicians in the outpatient clinic when their insomnia symptoms persisted. Indeed, the reduced ISI total score in the control group emerged 1-month post-treatment (from 17.8±5.0 to 14.7±5.3). Our findings were consistent with those of the study by Blom et al[2] wherein patients who received cognitive behavioural therapy for insomnia did not differ in their insomnia severity to those in the control group at 36 months, because the control group had used more sleep medications and received additional insomnia treatments during the follow-up period. Further analysis of medication use in both groups throughout the 12-month follow-up period is warranted.

There are several reasons for the improved outcome for depression following adjunctive sleep-focused treatment. The reduced overall HRSD17 score might have been mediated by the reduced scores for sleep-related items in the HRSD17 scale. Nonetheless, the difference in the changes of the HRSD17 between the two groups persisted, even after excluding three sleep-related items. In this regard, the reduced HRSD17 score in the intervention group was independent of the improvement in sleep symptoms. In addition, when both depression and insomnia are present, depression may be more often caused or maintained by insomnia, suggesting that treating insomnia might improve depression.[3] By using the experience sampling method, sleep quality during the previous night was shown to be associated with the affect during the next day, especially positive affect.[4] Therefore, the improvement in sleep quality by sleep-focused treatment may have had an added benefit of improving daytime depressive symptoms. Finally, it has been shown that sleep deprivation is an effective treatment for depression.[5] A sleep restriction technique in sleep-focused treatment may improve depressive symptoms through partial sleep deprivation.

Conclusions

This brief integrated sleep-focused treatment was effective in the management of treatment-resistant depression with comorbid sleep symptoms, evidenced by a much higher remission rate and a better clinical outcome. Our findings strongly suggest the need for adjunctive sleep-focused therapy for patients with treatment-resistant depression and comorbid sleep symptoms.

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