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ORIGINAL RESEARCH

Effect of adjuvant sleep hygiene psychoeducation and lorazepam on depression and sleep quality in patients with major depressive disorders: results from a randomized three-arm intervention

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Background: Sleep disturbances are a common co-occurring disturbance in patients with major depressive disorders (MDDs) and accordingly deserve particular attention. Using a randomized design, we investigated the effects of three different adjuvant interventions on sleep and depression among patients with MDD: a sleep hygiene program (SHP), lorazepam (LOR), and their combination (SHP–LOR).

Methods: A total of 120 outpatients with diagnosed MDD (mean age: 48.25 years; 56.7% females) and treated with a standard SSRI (citalopram at 20–40 mg at therapeutic level) were randomly assigned to one of the following three conditions: SHP (n=40), LOR (1 mg/d; n=40), SHP–LOR (1 mg/d; n=40). At the beginning and at the end of the study 8 weeks later, patients completed two questionnaires, the Pittsburgh Sleep Quality Index to assess sleep and the Beck Depression Inventory to assess symptoms of depression.

Results: Sleep disturbances decreased over time and in all groups. No group differences or interactions were observed. Symptoms of depression decreased over time and in all three groups. Reduction in symptoms of depression was greatest in the SHP–LOR group and lowest in the LOR group.

Conclusion: The pattern of results suggests that all three adjuvant treatments improved symptoms of sleep disturbances and depression, with greater benefits for the SHP–LOR for symptoms of depression, but not for sleep. Nevertheless, risks and benefits of benzodiazepine prescriptions should be taken into account.

Keywords: sleep hygiene, psychoeducation, pharmacotherapy, lorazepam, sleep disturbances, depression

Introduction

Restoring sleep is associated with a broad variety of physical,[1] emotional,[2,3] cognitive,[4,5] and social benefits.[6] Poor and nonrestoring sleep, in contrast, leads to impairments on physiological, emotional, cognitive, and social levels. In other words, poor sleep is associated with impaired daily functioning. This observation holds particularly true for people with mental disorders; sleep disturbances are nearly universal features of psychiatric disorders, especially mood disorders. Indeed, research investigating associations between sleep and affective illness has largely focused on depression and major depressive disorder (MDD).[7–10]

In this regard, epidemiological data indicate that people with psychiatric disorders account for 30%–40% of those in the community reporting symptoms of insomnia.[11]

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Of those individuals with insomnia, 40%–60% display features of depression. Likewise, disturbances in sleep and wakefulness, such as insomnia, excessive sleepiness, and fatigue, are experienced by most individuals suffering from depression, and sleep disorder is among the most prevalent symptoms of depression, with rates of ~80%.[12,13] As regards the direction of influence (whether sleep disturbances lead to depressive symptoms, or depressive symptoms lead to sleep disturbances), there is growing evidence that sleep disturbances are at the beginning of increasing symptoms of depression. In their meta-analysis, Lovato and Gradisar[14] showed that sleep disturbances preceded symptoms of depression among adolescents. In adults, a history of persistent insomnia has been associated with a significantly increased risk of developing a new episode of depression and bipolar disorder.[15] Likewise, poor objective sleep has predicted the recurrence of a further depressive episode,[10,16,17] and it is estimated that poor sleep precedes an episode of depression in 40% of cases.[9] Further, there is strong evidence that preexisting insomnia contributes greatly to the course and severity of depressive disorders and even predicts relapse or poor outcome.[18] In addition and most dramatically, poor sleep increases the risk of suicidal ideation[19–21] and also the likelihood of a poorer response to combined pharmacological and psychological treatments of depression.[17]

There have typically been three options for the treatment of sleep disturbances in general and in patients with MDD: psychopharmacotherapy,[22–25] psychotherapy/psychoeducation,[26–28] and the combination of psychopharmacotherapy and psychotherapy.[29–33] Riemann and Perlis[30] have argued the need for further research on the option of combining psychopharmacotherapy and psychotherapy. We took this observation into account and compared all three possibilities as adjuvant treatments of MDD with a standard SSRI in a randomized three-arm study. Specifically, patients with MDDs and sleep disturbances were randomly assigned to one of the following conditions: adjuvant sleep hygiene program (SHP), adjuvant psychopharmacotherapy (lorazepam [LOR], 1 mg/d), and adjuvant sleep hygiene program combined with adjuvant psychopharmacotherapy (lorazepam [SHP-LOR], 1 mg/d). In this way, we expected to find some answers as regards to the treatment options for sleep disturbances in patients with MDD.

The following four hypotheses were formulated. First, following previous findings,[34–37] we expected an improvement in symptoms of depression over time as an effect of the standard treatment with an antidepressant, irrespective of the adjuvant treatment. Second, in light of previous findings,[26–28] we expected a more beneficial effect of the adjuvant SHP on sleep, compared with the other two treatment options (SHP–LOR and LOR). Third, again following previous findings,[29–33] we expected a more beneficial effect of the adjuvant combined treatment (SHP–LOR) on depression, compared with the other two treatment methods (SHP and LOR). Fourth, on the basis of previous findings,[10,38–41] we anticipated that symptoms of depression and sleep disturbances would be associated both at the beginning and at the end of the study.

Methods

Procedure

Eligible outpatients were approached and recruited between September 2013 and April 2014 at the outpatient's center of the Farshchian Psychiatry Hospital of Hamedan (Iran). Of the 245 patients approached, 129 (52.65%) met the inclusion and exclusion criteria ("Sample" section) and agreed to participate; 120 completed the study (statistical data analysis was made per protocol, and the CONSORT flow diagram [Figure 1] shows sampling and participants' assignments). Participants were fully informed about the aims of the 8-week study and the voluntary basis of their participation. Further, patients were assured of the anonymous nature of the data gathering. Next, they signed a written informed consent. Thereafter, psychopharmacological treatment of MDD was initiated. Two to three weeks before the study commenced, patients began treatment with citalopram, a standard SSRI, at therapeutic levels (20–40 mg/d), which was kept constant throughout the entire study. Psychiatrists and clinical psychologists not otherwise involved in the study performed a clinical assessment, including a diagnostic interview ("Sample" section). Patients completed questionnaires related to sleep disturbances and to depression ("Tools" section) both at the beginning and at the end of the study. The Ethical Committee of the Hamadan University of Medical Sciences approved the study, which was executed according to the ethical standards laid down in the Declaration of Helsinki. Further, the study was registered in Iranian Registry of Clinical Trials (IRCT number: 2012100411004N1).

Sample

Outpatients with diagnosed MDD were enrolled in the study. The inclusion criteria were 1) diagnosis of MDDs without psychotic features, according to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; 2) reported sleep disturbances; 3) aged between 18 years and 65 years; and 4) willing and able to follow the study protocol

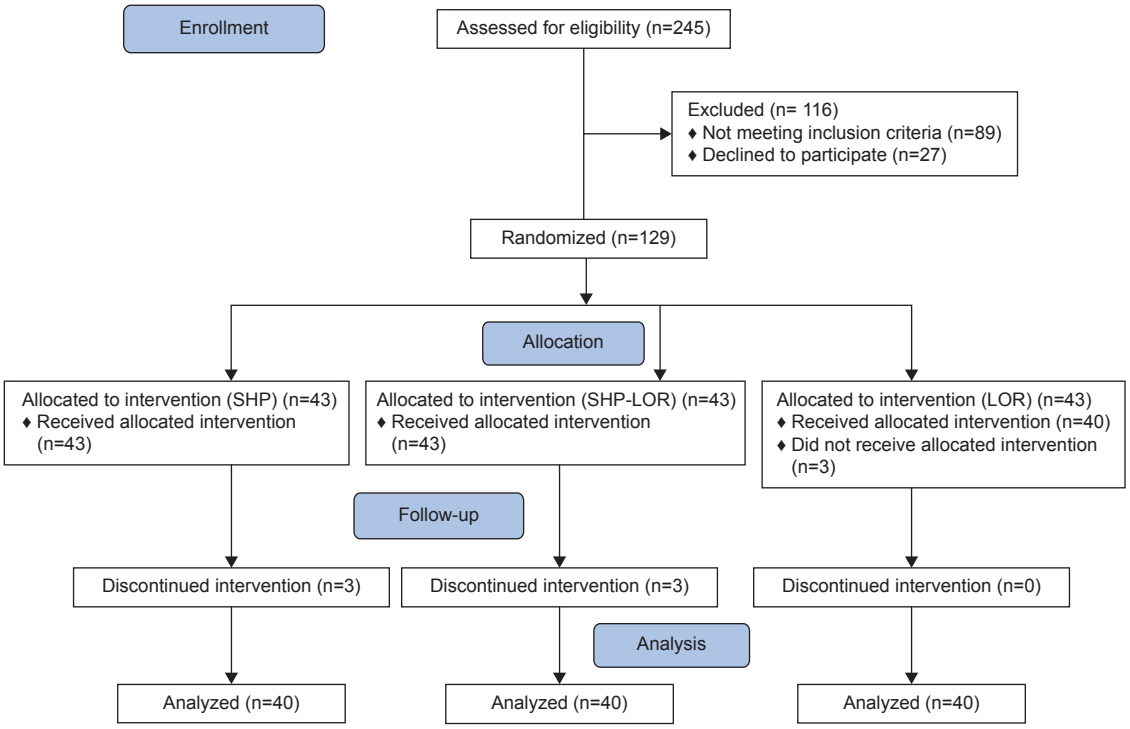

Figure 1 CONSORT 2010 flow diagram.
Abbreviations: SHP, sleep hygiene program; SHP-LOR, sleep hygiene program + lorazepam (1mg/d); LOR, lorazepam (1mg/d).

and to complete the questionnaires. Exclusion criteria were 1) not meeting the inclusion criteria; 2) presence of a progressive illness (eg, cancer and dementia) directly related to the onset and course of insomnia; 3) use of medications with sleep-altering effects (eg, steroids); 4) lifetime diagnosis of any psychotic or bipolar disorder; 5) alcohol or drug abuse within the past year; 6) sleep apnea or restless legs ("Sleep-related assessment" section); and 7) night-shift work or irregular sleep pattern. All patients were treated with a standard SSRI, that is, with citalopram at a therapeutic level (20–40 mg/d).

Psychiatric assessment

Experts not further involved in the study performed the psychiatric assessment with the Mini International Neuropsychiatric Interview[42] to allow selection of patients according to the inclusion and exclusion criteria.

Sleep-related assessment

First, experts asked about current sleep quality based on the Insomnia Severity Index.[43] Further, to exclude sleep disturbances due to sleep apnea and restless legs, the following questions were asked: sleep apnea: "Are you regularly snoring loudly during the night?" and "Does your partner [or somebody else] tell you that you stop breathing during the night?"; restless legs syndrome: "Do you feel discomfort in your legs in the evening such as an itch you can't scratch, a 'buzzing sensation', an unpleasant 'tickle that won't stop', a 'crawling'?" and "Do feelings of discomfort disappear when you start moving your legs?". Answering "yes" to one of the abovementioned questions led to exclusion from the study.

Randomization and intervention groups

A psychologist not further involved in the study prepared a total of 129 raffle tickets, 43 in each of three different colors, put them in a ballot box and stirred. At the start of the study, patients drew a raffle ticket and were assigned the group with the defined color.

The following groups and interventions were defined: 1) SHP (n=43), 2) tablet 1 mg of LOR nightly (n=43), and 3) SHP–LOR nightly (n=43).

Interventions

Sleep hygiene program

In addition to the standard treatment with citalopram, patients received four sessions (30–45 minutes; group or individual sessions) of a SHP, based on Silberman's Insomnia workbook.[44] Psychologists not further involved in the study delivered these sessions. The first session took place at the beginning of the study, and the last session 2 weeks before the end of the study. Specifically, participants learned

about basics of sleep hygiene such as keeping a regular sleep–wake schedule; avoiding abundant, late, and fatty dinners, but eating small, light, and easily digested meals to avoid being hungry during the night; moving a lot during the day and even in the evening;[45] avoiding naps; keeping a sleep and activity log for seven consecutive days; avoiding stimulants in the evening (coffee, tea, coke, high sugar soft drinks, alcohol, drugs, and nicotine); going to bed later and getting up early to increase sleep need; and using the bedroom exclusively for romance and sleep (thus, avoiding screen time and eating in the bed room/bed). Further, during the sessions, participants were instructed in relaxation techniques to improve their ability to relax body and mind in the evening and so fall asleep more easily. During the four sessions, these techniques were practiced. Finally, patients also received a leaflet comprising information regarding sleep hygiene, the importance of sleep, and sleep hygiene practices. It contained representative information regarding adult's sleep and healthy sleep practices in general, as well as recommendations about sleep duration for adults, recommendations about the temporal organization of sleep, information about different behaviors and environmental factors that can influence sleep quality, and about the importance of sleep and consequences of sleepiness. The leaflet also contained an example of a sleep–wake diary and an explanation for its use. It was designed by professional graphic designers on a single unfolded sheet of paper, printed on both sides. The dimensions of the leaflet were 21×21 cm^2.

Pharmacotherapy

In addition to the standard treatment with citalopram, patients in the pharmacotherapy group were treated for 8 weeks with LOR. LOR is a benzodiazepine. Although the manufacturer advises discontinuing regular LOR intake after 3–4 weeks, the US Federal Drug and Food Administration has approved all hypnotics since 2005 without restriction as to duration of use.[23] The focus of the four pharmacotherapy sessions (30–45 minutes) was on medication management; this involved education about medications, adjustment of dosage and dosage schedules, and discussions of adverse effects. All patients in the pharmacotherapy conditions began treatment with LOR at 1 mg/d.

Combined sleep hygiene program and pharmacotherapy

In addition to the standard treatment with citalopram, patients assigned to this study condition had four sessions (45–50 minutes) each on sleep hygiene and on medication management, as described in the "Sleep hygiene program" and "Pharmacotherapy" sections. Thus, participants in this treatment condition received both the SHP and the medication (LOR).

Tools

Assessment of sleep patterns and quality (self-rating)

To assess sleep patterns and quality, the Persian[46] version of Pittsburgh Sleep Quality Index (PSQI)[47] was employed. The PSQI is a self-report questionnaire that assesses sleep quality over a 1-month interval. It consists of 19 individual items generating seven "component" scores: subjective sleep quality, sleep latency (ie, how long it takes to fall asleep), sleep duration, habitual sleep efficiency (ie, the percentage of time in bed that one is asleep), sleep disturbances, use of sleep medication, and daytime dysfunction. Nazifi et al[46] have reported appropriate internal consistency (Cronbach's alpha of 0.85) for its clinically calculated seven components.[48,49] Nazifi et al's findings are consistent with those for the English version of the PSQI.[47–49] Scores are combined according to the scoring criteria included with the form to produce a Global PSQI Score. Scores above 5 indicate clinically relevant levels of disturbed sleep.

Assessment of symptoms of depression (self-rating)

The Persian version of Beck Depression Inventory (BDI[50]) was used to measure depressive symptoms.[51] The BDI samples self-reported symptoms of depression. The questionnaire consists of 21 items and asks about different dimensions such as depressive mood, loss of appetite, sleep disorders, suicidality, and similar issues. Each question has a set of at least four possible responses reflecting a range of intensity; for example, "sadness": 0= "I do not feel sad"; 1= "I feel sad"; 2= "I am sad all the time and I can't snap out of it"; 3= "I am so sad or unhappy that I can't stand it". Higher scores reflect greater severity of depressive symptoms (Cronbach's alpha =0.88).

Statistical analysis

Of the 129 patients initially enrolled, all but nine completed the study. The statistical analysis was performed as per protocol.

A series of chi-squared tests were computed to check for possible sociodemographic (sex, socioeconomic status, civil status, and job position) differences between the three groups. A one-way analysis of variance was calculated to check for possible age differences. To test whether symptoms of depression and sleep quality differed over time or between

groups, two analyses of variance for repeated measures were performed with the factors time (pre vs post), group (SHP, LOR, and LOR–SHP), and time by group interaction, and as dependent variables symptoms of depression and sleep quality. Post-hoc tests were performed with Bonferroni–Holm corrections for *P*-values. Effect sizes were reported as partial eta squared (η^2_p), and the nominal level of significance was set at $\alpha \leq 0.05$. All statistics was performed with SPSS® 23.0 (IBM Corporation, Armonk, NY, USA) for Apple Mac®.

Results

Psychosocial dimensions of the sample

Table 1 reports the descriptive and inferential statistics of the sample, separately by the interventions (SHP, LOR, and SHP–LOR).

The three groups did not differ in age, sex distribution, socioeconomic status, civil status, or job position. Accordingly, these dimensions were not introduced as possible confounders.

Sleep disturbances

Table 2 gives all statistical indices (descriptive and inferential statistics); therefore, statistical indices are not repeated in the text.

As shown in Table 2 and Figure 2, sleep disturbances decreased significantly over time. Neither group differences nor the time by group interaction was significant.

Depression scores

As shown in Table 2 and Figure 3, symptoms of depression decreased significantly over time. Compared with SHP and LOR–SHP groups, the LOR group had higher depression scores. The significant time by group interaction showed that symptoms of depression decreased significantly more over time in the SHP and SHP–LOR groups than in the LOR group.

Correlations between symptoms of depression and sleep disturbances at the beginning and at the end of the study

Table 3 gives an overview of the correlations between symptoms of depression and sleep disturbances at the beginning and at the end of the study. While symptoms of depression at the beginning and at the end of the study did significantly correlate, no significant or meaningful correlations were found for sleep disturbances.

Discussion

The key findings of this first randomized study of three different adjuvant treatment methods to improve sleep and depression among a sample of outpatients with MDD were as follows. All three methods (SHP, LOR, and SHP–LOR) improved sleep, with no advantages for any one method. They improved symptoms of depression, with advantages for the SHP and SHP–LOR conditions; more specifically, the combination (SHP–LOR) reduced symptoms of depression most effectively, a finding, which expands upon the current literature in an important way. Four hypotheses were formulated, and each of these is considered in turn.

Our first hypothesis was that symptoms of depression would reduce over time, and this was fully confirmed. Therefore, the present results confirm the wealth of studies[34–37] showing a favorable effect of antidepressants on both symptoms of depression and sleep.

Our second hypothesis was that the adjuvant combined treatment (SHP–LOR) would have a more beneficial effect on sleep than the other two treatment methods (SHP and LOR), but this was not confirmed; all three interventions had comparable effects. Therefore, the pattern of results is at odds with previous research.[26–28] The pattern of results suggests that treatment with adjuvant LOR and with adjuvant psychoeducation had similarly beneficial effects on sleep. However, given the possible risk of benzodiazepine dependence,[52,53]

Table 1 Descriptive and inferential statistics of sociodemographic variables, separately for the three study conditions (SHP, LOR, and SHP–LOR)

Sociodemographic variables	Groups			Statistics
	SHP	LOR	SHP–LOR	
n	40	40	40	
Sex (f/m)	23/17	21/19	34/16	χ^2(N=120, *df*=2) =0.48, *P*>0.1
Age (years)	46.88 (8.60)	49.23 (7.92)	48.65 (8.73)	*F*(2, 117) =1.43, *P*>0.1
Socioeconomic status (low/middle/high)	26/14/0	33/7/0	27/13/0	χ^2(N=120, *df*=2) =3.53, *P*>0.1
Civil status (single/married/single-separated)	2/36/2	4/35/1	5/31/4	χ^2(N=120, *df*=4) =3.68, *P*>0.1
Job position (employed/housework/unemployed)	27/5/8	24/3/13	23/7/10	χ^2(N=120, *df*=4) =3.18, *P*>0.1

Abbreviations: SHP, sleep hygiene program; LOR, lorazepam; f/m, female/male; SHP–LOR, sleep hygiene program combined with lorazepam.

Table 2 Descriptive and inferential statistical overview of self-rated symptoms of depression and sleep quality, separately for the three study conditions (SHP, LOR, and SHP–LOR)

	Groups						Statistics			
	SHP		LOR		SHP–LOR		Time, F, η^2_p	Group, F, η^2_p	Time–group interaction, F, η^2_p	Post hoc analyses
	Pre, M (SD)	Post, M (SD)	Pre, M (SD)	Post, M (SD)	Pre, M (SD)	Post, M (SD)				
n	40	40	40	40	40	40				
BDI	29.07 (2.19)	18.15 (3.06)	31.25 (1.81)	23.78 (3.29)	30.28 (3.64)	17.68 (4.76)	677.02,*** 0.85	31.13,*** 0.35	14.43,*** 0.20	Post: LOR > SHP; LOR > SHP–LOR
PSQI	9.55 (4.89)	5.73 (5.15)	8.65 (3.81)	6.37 (4.20)	9.88 (4.26)	4.75 (5.42)	37.96,*** 0.25	0.10, 0.00	1.84, 0.03	–

Notes: Degrees of freedom factors: time: (1, 117); group and time by group interaction: (2, 117). ***$P \leq 0.001$.
Abbreviations: SHP, sleep hygiene program; LOR, lorazepam; M, mean; SD, standard deviation; BDI, Beck Depression Inventory; PSQI, Pittsburgh Sleep Quality Index; SHP–LOR, sleep hygiene program combined with lorazepam.

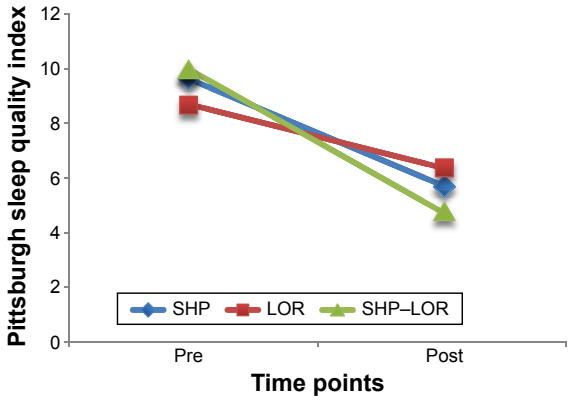

Figure 2 Sleep disturbances significantly decreased over time irrespective of intervention.
Note: Points are mean values.
Abbreviations: SHP, sleep hygiene program; LOR, lorazepam; SHP–LOR, sleep hygiene program combined with lorazepam.

clinicians should balance the risks and benefits of LOR or benzodiazepine prescription against psychoeducational interventions; these latter in the short term need more engagement to acquire the necessary skills but in the long run have no side effects and improve patients' self-efficacy.

To explain why psychoeducational interventions may work, theoretical models suggest that knowledge alone is rarely sufficient to achieve behavioral change. Rather, according to social cognitive models such as the theory of planned behavior, behavior is influenced by intentions and perceived control of behavior and the importance accorded to the intervention by significant others. To put it another way, the determining factors are whether the recipients of sleep education perceive the behavior to be desirable, positive, or worthwhile and the degree to which others, such as relatives, friends, or colleagues, approve of healthy sleep behavior.[54–56]

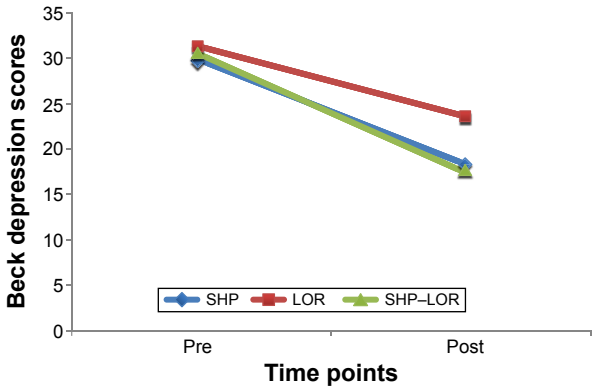

Figure 3 Symptoms of depression decreased significantly over time in all three interventions.
Notes: Compared with the LOR condition, the SHP and the SHP–LOR had superior effects on symptoms of depression. Points are means.
Abbreviations: SHP, sleep hygiene program; LOR, lorazepam; SHP–LOR, sleep hygiene program combined with lorazepam.

Table 3 Overview of the correlations (Pearson's *r*) between symptoms of depression and sleep disturbances at the beginning and at the end of the study

	BDI and PSQI	Groups			
		1, *r*	2, *r*	3, *r*	4, *r*
1	BDI pre	–	0.25*	–0.04	0.17
2	BDI post		–	–0.06	0.07
3	PSQI pre			–	–0.03
4	PSQI post				–

Note: *$P<0.05$.
Abbreviations: BDI, Beck Depression Inventory; PSQI, Pittsburgh Sleep Quality Index.

Our third hypothesis was that the adjuvant combined treatment (SHP–LOR) would have a more beneficial effect on depression than the other two treatment methods (SHP and LOR), and this was confirmed; this combination of treatments led to a greater reduction in symptoms of depression, though the SHP alone also produced greater improvement than the intervention with LOR which had the smallest impact. These findings, therefore, accord with previous research.[31,32,57,58] In light of these findings, and if we again consider the potential risk of benzodiazepine dependence,[52,53] clinicians should balance the risks and benefits of LOR or benzodiazepine prescription. This caution is particularly relevant given that psychotherapeutic and psychoeducational programs usually have a long-lasting effect for a broad variety of mental illnesses,[59] depression,[60–63] and sleep problems.[64–68]

Our fourth hypothesis was that symptoms of depression and sleep disturbances would be associated both at the beginning and at the end of the study, but the results did not support this. Rather, the results pattern suggests that symptoms of depression and sleep disturbances were not connected. This finding demands particular attention given that symptoms of depression and sleep disturbances are usually highly intertwined.[10,38–40] Specifically, Fava[41] reported that insomnia and daytime sleepiness were often associated with depression. Strikingly, Lovato and Gradisar[14] showed in their meta-analysis that, among adolescents, sleep disturbances preceded symptoms of depression and not vice versa. The evidence available from the present study cannot shed any light on the underlying psychological and physiological mechanisms. However, we offer the following speculative interpretations. First, it is conceivable that the tool (PSQI[47]) was too coarse grained to detect subtle changes in sleep. Responses restricted to a four-point Likert scale might be too insensitive to register changes. On the other hand, the PSQI is an internationally well-regarded and validated instrument in sleep research. Second, floor effects are possible given that one item asks for intake of sleep medication, and patients were bound to score high because they were under antidepressant treatment and in case of the LOR group, under additional benzodiazepine. Third, there was really no higher improvement.

The novelty of the findings should be balanced against the following limitations. First, participants were not blind as to treatment, and therefore, it is conceivable that expectancies and motivational processes might have biased the results. Second, it is also conceivable that further latent but unassessed psychophysiological factors might have biased two or more variables in the same or opposite direction. Third, evidence at the neuronal and endocrinological levels such as cortisol, growth hormone, alpha-amylase, or BDNF could have shed more light on the neurophysiological processes underlying the positive changes in symptoms of depression and sleep disturbances. Fourth, objective sleep measurements (actigraphy and sleep-EEG) would have been helpful in estimating objective changes in sleep. However, for larger samples such as the present one, questionnaires are still the gold standard.[69] Fifth, we relied on self-ratings. Future studies might also collect experts' ratings as regards patients' symptoms of depression. Specifically, experts could have rated patients' symptoms of depression with the Montgomery–Asberg Depression Rating Scale, which consists of ten items and has been recently validated.[70] Sixth, we assessed neither the intensity nor the quality of the patient–therapist time. Though patients in the LOR condition had four pharmacotherapy sessions, it is conceivable that patients in the sleep hygiene psychoeducation had further benefits from the psychotherapeutic setting. Seventh, we performed a per protocol analysis, whereas an intention-to-treat approach would have been more correct; however, comparing the pattern of results of the two statistical approaches, no descriptive or significant differences were observed. Last, it would have been very useful and important to follow up these patients, as there is some, but as yet insufficient, evidence that psychotherapeutic interventions have a long-lasting effect than psychopharmacotherapy.[29]

Conclusion

The findings of this study indicate that an adjuvant SHP and its combination with LOR can produce greater improvements in symptoms of depression. As regards to sleep disturbances, no intervention (SHP, LOR, and SHP–LOR) showed superior effects. Therefore, in light of the increased risk of benzodiazepine dependence, clinicians should carefully balance the risks and benefits in prescribing LOR as an add-on to treat both depressive disorders and sleep disturbances.

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Disclosure

The authors report no conflicts of interest in this work.

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