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Change in Quality of Life after Brief Behavioral Therapy for Insomnia in Concurrent Depression: Analysis of the Effects of a Randomized Controlled Trial

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SCIENTIFIC INVESTIGATIONS

Study Objectives: The efficacy of cognitive behavioral therapy for insomnia (CBT-I) has been suggested for insomnia concomitant with depression, but its impact on quality of life (QoL) has not been adequately evaluated. The study aimed to determine which aspects of QoL could be affected by CBT-I and how any changes in QoL were mediated by changes in insomnia and depression.

Methods: We conducted a 4-week randomized controlled trial with 4-week follow-up in outpatient clinics in Japan. Thirty-seven patients with DSM-IV diagnosis of major depressive disorder concomitant with chronic insomnia were randomly assigned to the treatment-as-usual (TAU) alone arm or the TAU with brief behavioral therapy for insomnia (TAU plus psychotherapy) arm using modified CBT-I consisting of 4 weekly individual sessions. We evaluated QoL using norm-based scoring of the Short Form-36 at baseline and at 8 weeks. We also examined associations between QoL subscales and remission in insomnia or depression while controlling for baseline scores of the entire sample.

Results: We tested group effects while controlling for baseline scores. TAU plus psychotherapy resulted in significantly better scores on physical functioning ($p = 0.006$), social functioning ($p = 0.002$), and mental health ($p = 0.041$) subscales than TAU alone at 8 weeks. Patients with either remitted insomnia or depression showed higher QoL scores than non-remitted patients; scores approximated those within the normal range.

Conclusions: For patients with insomnia in depression, adding CBT-I to TAU can produce substantive benefits in some aspects of QoL.

Trial Registration: ClinicalTrials.gov Identifier: NCT00610259, http://www.clinicaltrials.gov/

Keywords: Depressive disorder, sleep initiation and maintenance disorders, behavior therapy, quality of life

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Insomnia occurs comorbidly with many, if not most, Axis I disorders. Estimated concordance rates for depression are as high as 80% to 90% in untreated patients.[1,2] Even after achieving remission from depression, half of these patients still suffer from residual insomnia.[3] Moreover, persistent insomnia might be a risk factor for depression relapse.[4]

Insomnia is not only associated with difficulty initiating and maintaining sleep, but also a variety of daytime sequelae including fatigue, sleepiness, poor concentration and memory, mood disturbance, and impaired interpersonal functioning and work performance, all of which lead to deterioration in quality of life (QoL). QoL refers to both subjective life satisfaction and objective indicators such as health status and external life situations.[5] Assessment of QoL is important for any psychiatric or medical disorder because impaired QoL is typically cited as the impetus for seeking treatment.[6] QoL is severely impaired in patients with depression, as well as in those with comorbid insomnia.[7] According to a study on QoL outcomes, insomnia in depression is associated with increasing problems with daily living and role functioning.[8]

BRIEF SUMMARY

Current Knowledge/Study Rationale: The efficacy of cognitive behavioral therapy for insomnia (CBT-I) has been suggested for insomnia concomitant with depression. However, its impact on quality of life (QoL) has not been adequately evaluated.

Study Impact: For patients with insomnia in depression, adding CBT-I to TAU can produce substantive benefits in some aspects of QoL. Patients with either remitted insomnia or depression showed higher QoL scores than non-remitted patients.

Pharmacological and psychological therapies have been used in the treatment of insomnia. Although benzodiazepines have not been formally studied for their impact on QoL,[7] benzodiazepine receptor agonists (BZRAs) appear to be efficacious

for patients with primary insomnia given the QoL outcomes of previous randomized controlled trials (RCTs).[9,10] In addition, several RCTs have investigated the QoL outcomes of psychotherapy for primary insomnia. Various psychotherapy interventions have been tested including problem-solving therapy,[11] but cognitive behavioral therapy for insomnia (CBT-I) has been a frequently selected intervention strategy, with reported post-intervention improvements in not only sleep quality but also QoL outcomes.[12]

In regard to insomnia concurrent with depression specifically, QoL outcomes from RCTs employing BZRAs in combination with antidepressants have been reported.[13,14] As for psychotherapy, several previous trials including ours have confirmed the efficacy of CBT-I in insomnia in depression.[15,16] However, to the best of our knowledge, no previous trials on psychotherapy for insomnia in depression have reported QoL outcomes, and which aspects of QoL can be changed by psychotherapy are as yet unknown. Moreover, even if QoL outcomes were found to be improved after psychotherapy, questions would still remain as to whether improvement in insomnia or improvement in depression led to better QoL.

Against this background, this study aimed to examine which aspects of QoL changed among patients with insomnia in depression treated with psychotherapy. To do so, we analyzed data obtained in an RCT on brief behavioral therapy for insomnia in depression, using a modified standardized form of CBT-I consisting of 4 weekly individual sessions.[16] We also explored the degree to which changes in depression and sleep outcomes contributed to changes on the QoL subscales.

METHODS

Participants

We recruited patients from February 18, 2008, to April 9, 2009, at 3 psychiatric outpatient departments in Japan. The entry criteria were as follows: (1) refractory depression, defined as currently partially remitted, mild, or moderate major depressive disorder (diagnosed with DSM-IV), even after being on maximum doses of 2 types of antidepressants ≥ 4 weeks each for the index episode; (2) chronic comorbid insomnia; (3) a score between 8 and 23 on the 17-item GRID-HAMD[17]; and (4) a score ≥ 8 on the Insomnia Severity Index (ISI).[18-20] Patients were allowed to continue any psychotropic medications other than methylphenidate or modafinil (due to their probable stimulating effects), including antidepressants and hypnotics and prescriptions for medical conditions.

Study Design and Interventions

Participants were individually randomized to 2 arms: treatment-as-usual (TAU) alone (control) and TAU plus brief behavioral therapy for insomnia (TAU plus psychotherapy). The psychotherapy, based on CBT-I, consisted of 4 weekly individual sessions of approximately 50 min each.[21] Although the number of sessions in this study were fewer than the 6 to 8 offered in traditional CBT-I, previous trials have indicated the efficacy of brief versions of CBT-I in patients with primary insomnia, older adults with chronic insomnia, and patients with alcoholism and insomnia.[22-26] The treatment regimen was highly structured and included modules on sleep hygiene education, an introduction to the behavioral model of insomnia, sleep restriction, stimulus control, sleep titration, and relapse prevention.[16] Five psychiatrists and a psychiatric nurse provided the psychotherapy, and they received a written manual describing the regimen. Before the study began, they participated in a 2-day intensive training course on the psychotherapy, and thereafter received ongoing monthly supervision. Patients assigned to TAU plus psychotherapy arm were asked to self-administer these skills after intervention sessions ended at 4 weeks until the final assessment conducted at 8 weeks.

In the TAU-alone sessions, patients met individually with a psychiatrist once every 2 weeks to discuss their depressive symptoms and insomnia and to obtain medication. Each session typically lasted 10 minutes. We prohibited changes in type and dosage of medication during the first 4 weeks of the study unless depression rapidly worsened. Physicians were allowed to discuss sleep hygiene (as defined in the study handout) with the patients but not sleep restriction or stimulus control for insomnia.

Assessment Measures

We assessed patients at baseline and at 4 and 8 weeks, but collected QoL data only at baseline and at 8 weeks. Patients who discontinued the intervention were still asked to complete the assessments.

We evaluated QoL using Short Form 36 (SF-36), which consists of 8 subscales (physical functioning, role limitations due to physical health problems [role physical], bodily pain, general health perception, vitality, social functioning, role limitations due to emotional health problems [role emotional], and mental health).[27,28] We did not calculate 2 global scales (mental health and physical health subscales), based on research that QoL assessment should comprise at least the following 4 domains: physical functional status, disease and treatment-related physical symptoms, psychological functioning, and social functioning.[29] For all the SF-36 subscales, we used norm-based scoring for the general Japanese population (mean, 50; SD, 10). The scale has no units, and scores can theoretically range from 0 to 100. Higher scores indicate better health. We assessed insomnia using the ISI. For depression, the GRID-HAMD was evaluated through face-to-face semi-structured interviews by raters at each assessment. For these 2 variables, higher scores indicated worse status. Patients were considered insomnia remitters when their ISI score was < 8, and depression remitters when their 17-item HAMD score was < 8.[30,31]

Data Management and Analysis

Before the study began, we calculated the number of patients who should be included in the study based on a power analysis conducted on the ISI scores.[16] The dependent outcomes of this study were the 8 SF-36 subscales. For all these subscales, we used analysis of covariance to test group effects between TAU plus psychotherapy and TAU alone while controlling for baseline scores. Moreover, we tested mean differences in QoL subscales between non-remitters (no remission in either insomnia or depression) and remitters (remission in insomnia and/or depression) while controlling for baseline scores of the entire sample. For subscales where significant superiorities

Table 1—Clinical characteristics of participants at baseline

Characteristic	Psychotherapy + TAU (n = 20)	TAU alone (n = 17)	All Patients (N = 37)
Age, mean (SD), year	52.9 (11.6)	47.8 (10.1)	50.5 (11.1)
Sex, No. (%)			
Female	15 (75.0)	8 (47.1)	23 (62.2)
Male	5 (25.0)	9 (52.9)	14 (37.8)
Occupation, No. (%)			
Employed, full time	3 (15.0)	6 (35.3)	9 (24.3)
Employed, part time	3 (15.0)	3 (17.6)	6 (16.2)
Homemaker	11 (55.0)	5 (29.4)	16 (43.2)
Unemployed	3 (15.0)	3 (17.6)	6 (16.2)
Duration of treatment for index episode, mean (SD), month	18.1 (11.1)	27.8 (46.5)	22.5 (32.4)
Insomnia Severity Index, mean (SD)	15.3 (4.7)	17.4 (3.3)	16.3 (4.2)
Hamilton Depression Rating Scale, mean (SD)	15.0 (3.6)	16.8 (4.2)	15.8 (3.9)
SF-36: Norm-based Scoring			
Physical functioning, mean (SD)	41.2 (13.2)	40.6 (15.4)	41.0 (14.1)
Role-physical, mean (SD)	37.1 (16.3)	32.2 (16.4)	34.9 (16.3)
Bodily pain, mean (SD)	46.0 (10.0)	43.1 (13.9)	44.7 (11.9)
General health perception, mean (SD)	40.2 (5.8)	33.6 (9.5)	37.2 (8.3)
Vitality, mean (SD)	39.0 (9.4)	31.2 (7.6)	35.4 (9.4)
Social functioning, mean (SD)	40.3 (15.9)	32.3 (19.2)	36.7 (17.7)
Role-emotional, mean (SD)	37.6 (15.6)	31.1 (14.7)	34.6 (15.4)
Mental health, mean (SD)	38.9 (11.5)	29.9 (9.5)	34.7 (11.4)

TAU, treatment as usual.

were observed in remitters, we used a multiple linear regression model to determine if changes in the ISI and HAMD scores (baseline to 8 weeks) mediated changes in the QoL subscales by entering both scores into the model. We set a p-value < 0.05 to test the null hypothesis without correcting for multiple tests to avoid β (type II) rather than α (type I) errors because this was the first study to investigate QoL outcomes in psychotherapy for insomnia concomitant with depression. To avoid multiple tests, we did not conduct statistical tests to detect baseline differences between the two arms. Also, our decision to adjust for baseline data in RCTs should not depend upon statistical significance of baseline differences.[32] We computed inferential statistics using SPSS for Windows 21.0.

The ethics committees of all the recruiting centers approved the protocol in this study. Study staff introduced the purpose, procedures, and potential risks or discomforts of the study to those who satisfied eligibility criteria by using the standard informed consent form which emphasized that all potential participants who declined to participate or otherwise did not participate were eligible for usual treatment, and were not disadvantaged in any other way by not participating in the study. Following this explanation, all participants in the study provided written informed consent.

RESULTS

Thirty-seven patients satisfied the eligibility criteria, among whom 20 were randomly assigned to TAU plus psychotherapy arm and 17 to TAU alone arm. **Table 1** summarizes the participants' clinical characteristics at baseline. During the study, antidepressant dosage was changed for 2 participants in each of the 2 groups. Hypnotic dosage was changed for 2 participants in TAU plus psychotherapy group, and none in the TAU alone group. We observed no statistically significant between-group differences in defined daily doses[33] of either drug for either class of medication. One subject in TAU plus psychotherapy arm and one in TAU alone arm were admitted to the hospital due to exacerbation of depression. Nevertheless, no data were missing because all participants completed all the study assessments at 8 weeks.

Although we did not intend to perform any statistical tests to compare pre- and post-scores, data for all subjects were available at baseline and at 8 weeks. Mean scores of all SF-36 subscales increased in the psychotherapy plus TAU group at the 8-week follow-up, whereas mean scores in 3 subscales decreased in the TAU alone group: physical functioning, role physical, and social functioning. At 8 weeks, psychotherapy plus TAU resulted in significantly higher subscale scores for physical functioning ($p = 0.006$), social functioning ($p = 0.002$), and mental health ($p = 0.041$) than TAU alone (**Figure 1**). The other subscales tended to favor the psychotherapy plus TAU arm, but differences were not statistically significant.

Among all 37 participants, 13 remitted at 8 weeks (2 [10%] in the psychotherapy plus TAU group and 0 in the TAU alone group for insomnia only, 2 [10%] and 1 [6%] for depression only, and 8 [40%] and 0 for both insomnia and depression, respectively). Aggregated remitters in insomnia and/or depression showed significantly higher QoL subscale scores for physical functioning ($p = 0.033$), role physical ($p = 0.003$), general health perception ($p = 0.008$), vitality ($p = 0.001$),

social functioning ($p < 0.0005$), role emotional ($p = 0.027$), and mental health ($p = 0.005$) than those in non-remitters, except the bodily pain subscale ($p = 0.067$) (**Figure 2**). Mean scores of all QoL subscales in remitters were around 50 (equivalent to mean scores of a normal sample in Japan). In analyses exploring mediation of insomnia and depression symptoms to QoL, changes in ISI scores contributed to changes on the vitality subscale ($p = 0.027$), and changes in HAMD scores contributed to changes on subscales for role emotional ($p = 0.031$) and mental health ($p = 0.021$) (**Table 2**). No other changes in insomnia or depression outcomes contributed to the significant changes on these subscales.

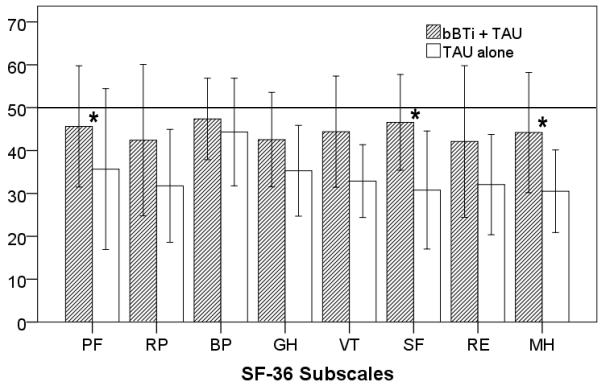
DISCUSSION

To our knowledge, this study is the first to report QoL outcomes based on an RCT with CBT-I in treatment refractory patients with depression. We found that, although not all SF-36 components were affected, insomnia treatment improved functioning in both physical and social situations and mental health status. Associations between remission and QoL subscales in the entire sample (N = 37) indicated significantly better QoL scores in remitters than those in non-remitters, and were within the normal range on almost all subscales. The bodily pain subscale revealed no significant difference because the mean score even at baseline was most likely not far from the normal range in both arms. For some of QoL, improvement was associated with improvement in insomnia or in depression. These aspects included vitality associated with insomnia, and role emotional and mental health with depression.

As for primary insomnia, a previous trial[12] investigated changes in various QoL aspects by examining the efficacy of CBT-I in patients with primary insomnia and long-term hypnotic drug use, and found that those treated with CBT-I had better outcomes than those without this additional treatment in SF-36 dimensions of vitality at 3 months and physical functioning and mental health at 6 months. For pharmacotherapy, patients treated with BZRAs had significantly better QoL scores than those with placebo at 6 months in SF-36 domains of role physical, bodily pain, general health perception, vitality, and social functioning.[10] Similarly, the same drug led to better QoL scores than a placebo during a 2-week study on the domains of the 16-item Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q),[34] including physical health, mood, household activities, leisure time activities, and medication.[9] As mentioned above, no psychotherapy trials reported QoL outcomes for insomnia concomitant with depression. The efficacy of pharmacotherapy on QoL outcomes remains controversial, given that one trial has been for BZRAs and antidepressants[13] and the other against them.[14] Our results and those of previous studies lead us to conclude that adding psychotherapy to usual clinical care could produce statistically significant and clinically substantive added benefits in some aspects of QoL in patients with insomnia in depression, as shown in previous trials on primary insomnia. Above all, the present study is the first randomized trial investigating the efficacy of CBT-I in Japan. We believe our results will contribute to further dissemination of the therapy in Japan.

As for associations between QoL improvements in insomnia and depression, the recovery process was initially hypothesized to occur in the following order: (1) psychotherapy alleviated insomnia, (2) better sleep reduced severity of depression, and (3) better mood improved physical and mental functioning in daily life. Behind these assumptions, we speculated that improvement in QoL was better explained by changes in

Figure 1—SF-36 Norm-Based Subscales and Allocation Status at 8 weeks



*p < 0.05. A bar and an error bar indicate a mean and a standard deviation, respectively. bBTi, brief behavioral therapy for insomnia; BP, bodily pain; GH, general health perception; MH, mental health; PF, physical functioning; RE, role emotional: RP, role physical; SF, social functioning; TAU, treatment as usual; VT, vitality

Table 2—SF-36 subscales and regression coefficients for insomnia and depression variables

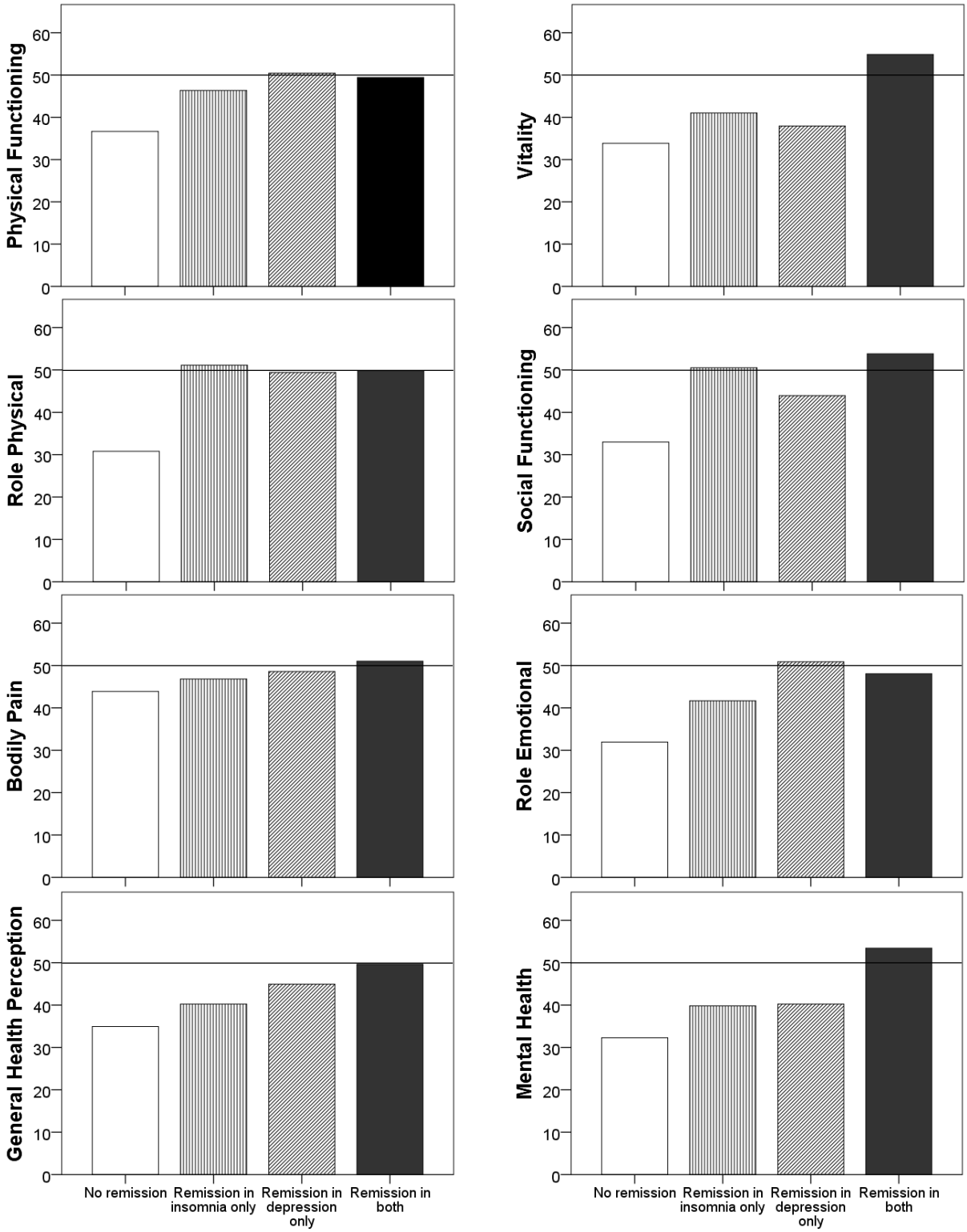
		ISI		HAMD	
SF-36 subscales	**Adjusted R^2**	**B (SE)**	**beta**	**B (SE)**	**beta**
Physical functioning	22.2%	-0.37 (0.35)	-0.21	-0.44 (0.24)	-0.36
Role physical	0.5%	0.30 (0.56)	0.12	-0.53 (0.38)	-0.30
Bodily pain	NA				
General health perception	14.4%	-0.23 (0.29)	-0.17	-0.30 (0.19)	-0.31
Vitality	37.4%	-0.62 (0.27)	-0.40*	-0.32 (0.18)	-0.30
Social functioning	5.8%	-1.15 (0.63)	-0.39	0.20 (0.42)	0.10
Role emotional	8.9%	0.43 (0.47)	0.19	-0.71 (0.32)	-0.47*
Mental health	16.3%	0.08 (0.36)	0.05	-0.60 (0.25)	-0.49*

*p < 0.05. HAMD, Hamilton Depression Rating Scale; ISI, Insomnia Severity Index; NA, not applicable.

depression severity, and that a time lag might exist between improvements in insomnia or depression and improvements in QoL. However, considering the results of the present study and of our previous study on insomnia and depression outcomes,[16] it now seems more likely that insomnia, depression and QoL almost simultaneously improve to a normal range when a patient responds successfully to treatment.

Although the findings of this study are very promising, there were some methodological limitations. First, sample sizes were small enough to raise concerns about the generalizability of

Figure 2—SF-36 Norm-Based Subscales and Remission Status at 8 weeks



A bar indicates a mean.

the results. Moreover, long-term consequences remain unclear because we evaluated patients for no more than 8 weeks. Further replication studies with a larger sample and longer follow-up period are needed to evaluate outcomes with more confidence. Second, we cannot state whether psychotherapy itself or careful patient monitoring was responsible for improvement in QoL outcomes. However, our aim was to examine the added value of psychotherapy to usual clinical care, not the efficacy of psychotherapy itself. Third, we set a significance level of p-values at 0.05, although this definition was applied many times during analysis and might have led to errors in multiple comparisons. Although we did this to avoid β (type II) rather than α (type I) errors, again, a further replication study with a larger sample and an appropriate threshold for statistical significance is needed.

On the other hand, the strengths of our study include our patient follow-ups in which there were no missing data, which produced robust results. Moreover, we reported eight subdomains of QoL even though previous reports often aggregated QoL into one[13] or two scales (mental health and physical health subscales).[35] Studies have indicated that QoL assessments should comprise at least four domains, as we stated in the Methods section.[29] We believe that our decision to employ eight subdomains is in line with this recommendation. All of these strengths should contribute to the greater applicability and feasibility of our findings.

In conclusion, adding psychotherapy to usual clinical care can produce clinically substantive benefits in some aspects of QoL in treating patients with insomnia in depression.

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DISCLOSURE STATEMENT

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