Which Elderly Patients With Remitted Depression Remain Well With Continued Interpersonal Psychotherapy After Discontinuation of Antidepressant Medication?

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Objective: *This study was conducted to identify which elderly patients with remitted recurrent major depression remain well with maintenance interpersonal psychotherapy after discontinuation of active antidepressant medication (nortriptyline).* *Method:* *The authors examined outcomes of maintenance therapy over 1 year for 47 elderly patients who were randomly assigned to monthly maintenance interpersonal psychotherapy with placebo (N=19) or to placebo and a supportive medication clinic without interpersonal psychotherapy (N=28). A Kaplan-Meier survival analysis was performed on the basis of treatment assignment and subjective sleep quality assessed by the Pittsburgh Sleep Quality Index, on which good subjective sleep quality is indicated by a score of 5 or lower.* *Results:* *Nine (90%) of 10 patients reporting good subjective sleep quality (by 1 month into continuation treatment) remained well for at least 1 year when treated with monthly maintenance interpersonal psychotherapy, versus five (31%) of 16 patients with good sleep quality assigned to a medication clinic, three (33%) of nine patients with impaired sleep quality treated with maintenance interpersonal psychotherapy, and two (17%) of 12 patients with impaired sleep quality assigned to a medication clinic.* *Conclusions:* *Recovery of good subjective sleep quality by early continuation treatment is useful in identifying which remitted elderly depressed patients will remain well with monthly maintenance interpersonal psychotherapy, following discontinuation of antidepressant medication, and which patients may be more vulnerable to recurrence of major depressive episodes in the absence of antidepressant medication.*

(Am J Psychiatry 1997; 154:958–962)

Major depressive illness in later life often follows a relapsing and chronic course, even among patients whose first lifetime episode occurs only after the age of 60 (1, 2). While episodes of major depression in the elderly can be treated as successfully as those in midlife patients, the rate of relapse during continuation therapy appears to be higher for elderly than for younger patients (3). Successful longer-term (i.e., 1-year) maintenance of short-term therapeutic gains also appears to be achievable for the elderly, by means of nortriptyline (at doses sufficient to achieve steady-state blood levels of 80–120 ng/ml), monthly maintenance interpersonal psychotherapy, or a combination (4). We have reported (4) a preliminary observation that 75%–80% of elderly patients randomly assigned to nortriptyline (with or without concurrent monthly maintenance interpersonal psychotherapy) remain free of major depressive episodes 1 year into maintenance treatment, as do 50% of patients receiving monthly maintenance interpersonal psychotherapy, compared to 20% of patients receiving placebo in a medication clinic treatment paradigm. Despite the success of maintenance pharmacotherapy, some elderly patients will not or cannot take maintenance antidepressant medication. Therefore, it is important to know how to identify patients who are likely to remain well with maintenance interpersonal psychotherapy alone after discontinuation of medication therapy.

In previous reports (5–7) our group has noted that a high delta sleep ratio (the ratio of delta wave counts per minute in the first versus second non-REM sleep period)

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Supported by NIMH grants MH-30915, MH-52247, MH-43832, MH-37869, and MH-00295.

The authors thank the research staff of the Late-Life Depression Clinic at Western Psychiatric Institute and Clinic, for the care of the patients included in this study.

and maintenance interpersonal psychotherapy with high treatment specificity were each associated with significantly longer wellness intervals in the absence of maintenance pharmacotherapy among midlife patients with recurrent unipolar depression. More recently we reported that "high [interpersonal psychotherapy] specificity is of significant prophylactic benefit even with (midlife) patients with a high biological vulnerability for recurrence" (8, p. 461). Our initial analyses of EEG sleep correlates of maintenance therapy outcomes in elderly patients with a history of recurrent unipolar depression indicated that higher levels of phasic REM activity, early in continuation therapy with a combination of nortriptyline and weekly interpersonal psychotherapy, were associated with longer wellness intervals and a lower rate of recurrence during the first year of maintenance therapy (9). In this context, the goal of the present study was to test whether measures of sleep, including both self-report and laboratory-based, could identify which elderly patients with remitted depression remained depression free for 1 year with maintenance interpersonal psychotherapy but without antidepressant medication. Specifically, we hypothesized that patients who recovered good subjective sleep quality upon remission of the index episode would remain well the longest with maintenance interpersonal psychotherapy. Our second hypothesis was that patients with more-abnormal EEG sleep profiles (e.g., shorter REM sleep latency or lower delta sleep ratio) would have shorter wellness intervals during maintenance psychotherapy. The rationale for both hypotheses is strengthened by epidemiologic studies that have shown that persistent sleep disturbance is a significant risk factor for subsequent episodes of depression (10–12).

METHOD

The subjects were participants in an ongoing trial evaluating the maintenance or long-term efficacy (over 3 years) of nortriptyline and interpersonal psychotherapy, singly and in combination, with respect to preventing recurrence of major depressive episodes. The subjects provided written informed consent to participate in this study, in accordance with procedures approved by our Biomedical Institutional Review Board. We have described the protocol design and preliminary 1-year maintenance outcomes elsewhere (4). Briefly, the study group consisted of patients aged 60 or older with at least two lifetime episodes of unipolar major depression and an interepisode wellness interval of no longer than 3 years before the index episode. After open combined treatment with nortriptyline and interpersonal psychotherapy, patients in remission were assigned randomly to double-blind maintenance therapy with 1) nortriptyline plus medication clinic (i.e., general supportive care without psychotherapy); 2) placebo plus medication clinic; 3) monthly maintenance interpersonal psychotherapy plus nortriptyline; and 4) monthly maintenance interpersonal psychotherapy plus placebo. During the maintenance phase of the study, the patients attended the research clinic once monthly for a total of 3 years or until recurrence of a major depressive episode, whichever came first.

The current study group consisted of 47 patients randomly assigned to a nonnortriptyline maintenance treatment, that is, maintenance interpersonal psychotherapy with placebo or medication clinic with placebo. The rationale for selecting the two nonnortriptyline cells for analysis derives from the goal of the study, namely, to identify which patients remain well for 1 year of maintenance interpersonal psychotherapy without active medication, with controls for the nonspecific effects of the general supportive care available to patients in the placebo/medication clinic condition.

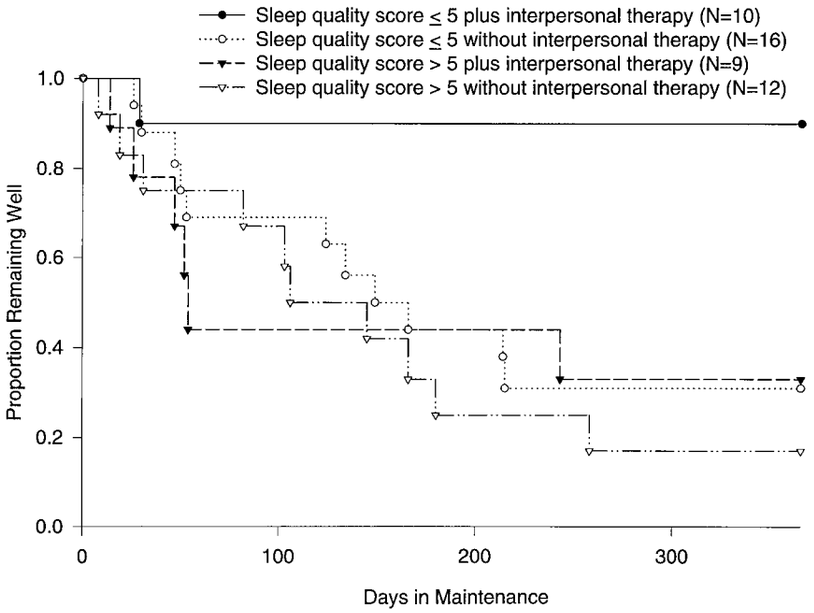
Initial Cox proportional hazards models stratified on treatment assignment (maintenance interpersonal psychotherapy, medication clinic) were used to determine significant covariates of time to recurrence. Measures at pretreatment baseline (time 1) and during early continuation treatment (time 2) were examined as possible covariates. On the basis of our prior studies with midlife patients (7) and late-life patients (9), we examined six EEG sleep measures (sleep efficiency, REM latency, total REM activity count, REM density, REM activity during the first REM period, and delta sleep ratio), each assessed at time 1 and time 2, and one subjective or self-report measure of sleep quality, the Pittsburgh Sleep Quality Index (13), also administered at time 1 and time 2. After finding that self-reported sleep quality (Pittsburgh Sleep Quality Index score) at time 2 was the only significant covariate of time to recurrence, we divided the groups by sleep quality at time 2, early in continuation treatment when the patients had met the study criteria for remission (a Hamilton Depression Rating Scale score of 10 or less for 3 consecutive weeks). Sleep quality was classified according to the method of Buysse et al. (13): good sleep quality was defined as a score of 5 or less on the Pittsburgh Sleep Quality Index, and impaired sleep quality was defined as a score higher than 5. The use of a Pittsburgh Sleep Quality Index score higher than 5 to identify subjects with impaired sleep quality has been validated against both sleep disorder diagnoses and polysomnographic measures (13). This partitioning resulted in a total of four groups: 1) those with good sleep quality assigned to maintenance interpersonal psychotherapy plus placebo (N=10), 2) those with good sleep quality assigned to a medication clinic plus placebo (N=16), 3) those with poor sleep quality assigned to maintenance interpersonal psychotherapy plus placebo (N=9), and 4) those with poor sleep quality assigned to a medication clinic plus placebo (N=12). (The groups were of unequal sizes because EEG sleep and sleep quality evaluations were available for approximately 80% of the patients in the larger study.) Kaplan-Meier survival curves on the first maintenance year for these four groups and selected covariates were examined and tested by using the approximate chi-square statistic for the log-rank test.

RESULTS

As shown in figure 1, the patients with good subjective sleep quality by early continuation therapy who received monthly maintenance interpersonal psychotherapy had significantly higher survival rates (and hence longer depression-free intervals) than did patients in any of the other three groups. Specifically, 90% of the patients with good sleep quality remained depression free for 1 year with monthly maintenance interpersonal psychotherapy (nine of 10 patients; 95% confidence interval=71–100), versus 31% of the patients with good sleep quality assigned to a medication clinic (five of 16; 95% confidence interval=9–54), 33% of the patients with poor sleep quality receiving monthly maintenance interpersonal psychotherapy (three of nine; 95% confidence interval=3–64), and 17% of the patients with poor sleep quality assigned to a medication clinic (two of 12; 95% confidence interval=0–38).

Median time to recurrence was estimated by means of Kaplan-Meier survival analysis as 157 days for the patients with good sleep quality assigned to a medication clinic (95% confidence interval=53–indeterminate, because of censoring), 54 days for those with poor sleep quality given monthly maintenance interpersonal psychotherapy (95% confidence interval=47–indeterminate), and 126 days for those with poor sleep quality assigned to a medication clinic (95% confidence interval=82–180). (The median time to recurrence was in-

FIGURE 1. Length of Remission in Relation to Subjective Sleep Quality[a] and Maintenance Treatment Assignment for Elderly Patients With Recurrent Depression[b]



[a]Sleep quality was assessed with the Pittsburgh Sleep Quality Index early in maintenance treatment. A score of ≤5 was classified as good sleep quality; a score of >5 was classified as poor sleep quality.
[b]Significant difference among groups (log-rank χ^2=9.89, df=3, p<0.02).

determinate for the patients with good sleep quality who were treated with monthly maintenance interpersonal psychotherapy because fewer than 50% of these patients had a recurrence during the 1-year period of observation.)

We further examined pretreatment (time 1) and early continuation (time 2) demographic, clinical, and sleep characteristics across the four groups, using one-way analyses of variance (ANOVAs) to test for any differences among the groups with good and poor sleep quality who were treated with interpersonal psychotherapy or assigned to a medication clinic. The variables examined included measures of age, episode duration and severity, social support, chronic medical burden, personality dysfunction, and polysomnographic measures. The purposes of these analyses were to determine whether these characteristics had differential predictive effects in their own right, to uncover any possible confounding variables that might have accounted for the results of the primary survival analysis, and to develop more information about the characteristics of the four groups. The data reported refer to time 2 unless otherwise noted.

We detected two variables with possibly confounding effects: age and time 2 Hamilton depression rating. The patients whose sleep quality was good during early continuation therapy were 3 to 6 years younger on average than those whose sleep quality was poor (F=2.87, df=3, 43, p<0.05; no significant post hoc pairwise comparisons). However, age was not found to be associated with length of depression-free interval (log-rank χ^2=0.85, df=1, p=0.36).

Hamilton depression ratings during early continuation treatment, collected at the time of the sleep assessments, were significantly lower in the two groups with good sleep quality than in those with poor sleep quality. The patients with good sleep quality assigned to interpersonal psychotherapy or a medication clinic had mean Hamilton depression ratings of 4.1 (SD= 2.3) and 4.8 (SD=4.0), respectively. The patients with poor sleep quality assigned to interpersonal psychotherapy and a medication clinic had Hamilton ratings of 7.8 (SD=1.5) and 6.4 (SD=2.4), respectively. The ANOVA for the Hamilton scores showed a significant difference (F=3.15, df=3, 43, p=0.04). This difference raised the question of whether it was specifically sleep quality that distinguished patients who remained well with maintenance interpersonal psychotherapy, or whether sleep quality was a proxy for residual depressive symptoms that could account for the success or failure of maintenance interpersonal psychotherapy. We found that Hamilton depression scores (unlike scores on the Pittsburgh Sleep Quality Index) were not associated with length of depression-free interval (log-rank χ^2=0.03, df=1, p=0.86). However, the differences in Hamilton ratings were substantially related to differences in the three sleep items of the 17-item Hamilton rating scale. The mean sum of the scores on the three sleep items in the groups with good sleep quality were 0.3 (SD=0.7) for those treated with maintenance interpersonal psychotherapy and 0.7 (SD=1.1) for those in the medication clinic condition. Conversely, the mean sum of the three sleep items for those with impaired sleep quality were 2.0 (SD=1.1) for those treated with maintenance interpersonal psychotherapy and 2.3 (SD=1.5) for those assigned to a medication clinic. The ANOVA showed a significant difference (F=8.47, df=3, 43, p=0.0002). The sum of the remaining 14 items on the Hamilton scale did not differ significantly across the groups (F=0.99, df=3, 43, p=0.41).

As expected, the ANOVA for Pittsburgh Sleep Quality Index scores showed a significant difference (F= 27.30, df=3, 43, p<0.0001). Dissection of the seven component scores that make up the global sleep quality score indicated that the scores on six of the seven components were robustly different (p<0.01 or better). Only the component score measuring daytime dysfunction did not differ across the four groups (which is not surprising in view of the fact that the patients in all four

TABLE 1. EEG Sleep Measures in Relation to Subjective Sleep Quality and Maintenance Treatment Assignment for Elderly Patients With Remitted Recurrent Depression

	Pittsburgh Sleep Quality Index Score ≤5 (good sleep quality)						Pittsburgh Sleep Quality Index Score >5 (poor sleep quality)					
	Interpersonal Psychotherapy			Medication Clinic			Interpersonal Psychotherapy			Medication Clinic		
Sleep Variable	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
Before maintenance treatment	9			13			6			10		
Sleep efficiency (%)		80.1	7.0		85.0	4.6		81.4	8.5		75.3	17.0
REM latency (min)		51.4	22.1		51.7	19.7		58.6	10.9		49.6	29.1
REM activity (units)		135.5	50.9		168.6	78.9		135.2	92.8		135.2	72.2
REM density (rapid eye movements per minute of REM sleep)		1.6	0.6		1.6	0.5		1.4	0.7		1.8	0.7
REM period 1 count		133.8	102.7		219.6	242.1		330.1	643.1		350.6	247.4
Delta sleep ratio[a]		1.1	0.1		1.4	0.2		1.5	0.2		1.3	0.5
Early in maintenance treatment	10			16			9			12		
Sleep efficiency (%)		85.4	6.4		86.1	7.5		80.2	14.1		79.5	10.2
REM latency (min)		83.5	29.4		82.9	37.2		81.9	49.3		96.5	39.7
REM activity (units)		145.6	67.1		157.5	53.2		111.1	101.2		143.5	56.5
REM density (rapid eye movements per minute of REM sleep)[b]		2.3	0.5		2.3	0.5		1.6	0.8		2.6	1.1
REM period 1 count		262.6	173.1		430.5	296.1		484.2	609.2		553.6	342.9
Delta sleep ratio[a]		1.7	0.5		1.7	0.6		1.5	0.3		1.9	0.6

[a]Ratio of delta wave counts per minute in the first versus second non-REM sleep period.
[b]Significant ANOVA result ($F=3.03$, $df=3, 43$, $p<0.04$) and significant difference between interpersonal psychotherapy and medication clinic groups with poor sleep quality (post hoc comparison: $p<0.05$, Tukey's studentized range [honestly significant difference]).

groups had achieved the study criteria for remission of the index episode, with Hamilton depression ratings consistently under 10).

With respect to our second hypothesis, none of the EEG sleep measures selected (time 1 or time 2 sleep efficiency, REM latency, total REM activity count, REM density, first REM period activity count, or delta sleep ratio) was a significant covariate of time to recurrence in the survival analysis. Descriptive data for these variables are presented in table 1. Similarly, changes in these sleep measures from time 1 to time 2 were also not significant covariates of time to recurrence according to the log-rank chi-square statistic. There was a significant correlation between time 2 score on the Pittsburgh Sleep Quality Index and time 2 sleep efficiency ($r=-0.37$, $df=45$, $p<0.02$). Thus, worse subjective sleep quality (indicated by higher Pittsburgh Sleep Quality Index scores) was significantly correlated with lower sleep efficiency. The correlation was modest ($R^2=0.14$), however.

DISCUSSION

The current results confirm the first study hypothesis, namely, that patients who recovered good sleep quality by early continuation therapy had longer depression-free intervals, *provided* that they were also receiving monthly maintenance interpersonal psychotherapy, than did patients whose sleep quality did not normalize with remission of their depression. Those with persistently poor sleep quality fared no better with monthly maintenance interpersonal psychotherapy than those with good sleep quality assigned to a medication clinic. Similarly, patients with good self-reported sleep quality who were not receiving maintenance interpersonal psychotherapy also did poorly. Thus, there is a subgroup of elderly depressed patients, who can be identified on the basis of subjective sleep changes alone, who are likely to do well with once-monthly maintenance interpersonal psychotherapy after discontinuation of medication therapy.

With respect to the second hypothesis, we failed to detect a significant effect of objective polysomnographic sleep measures (sleep efficiency, REM sleep latency, REM activity, REM density, REM period 1 count, or delta sleep ratio) on the duration of the wellness interval during the first year of maintenance therapy. This latter result is a failure to replicate our findings in midlife patients, among whom patients with a high delta sleep ratio at pretreatment had a five times greater likelihood of remaining in remission over 3 years than those with a low delta sleep ratio (7). It is possible that this apparent difference between our midlife and late-life findings is a type II error and will no longer be present with a larger number of subjects and/or with completion of the 3-year maintenance phase of the late-life study.

The current finding involving scores on the Pittsburgh Sleep Quality Index should be regarded as preliminary because the final subjects entered into the study have not yet completed maintenance treatment. Nonetheless, the size of the effect noted in the primary survival analysis is encouraging, as is the fact that patients likely to do well with maintenance interpersonal

psychotherapy alone can be identified easily with a questionnaire (Pittsburgh Sleep Quality Index) taking 5 minutes to complete. The first-year 90% survival rate (percentage of patients remaining depression free) for maintenance interpersonal psychotherapy among patients with good sleep quality is all the more remarkable when viewed within the context of pharmacotherapy outcome data from the same study. Specifically, we have reported (4) that the 1-year survival rate among patients assigned to nortriptyline with or without maintenance interpersonal psychotherapy is 75%–80%. Hence, a subgroup of patients randomly assigned to once-monthly maintenance interpersonal psychotherapy, namely, those who recovered good sleep quality by early continuation therapy, achieved the same survival rate as was seen with nortriptyline taken every day at doses sufficient to maintain steady-state levels continuously in the range of 80–120 ng/ml.

Does this finding make clinical sense, and how might it be explained? The Pittsburgh Sleep Quality Index is a self-report measure of subjective sleep quality over the past month (13). Unlike most measures of sleep quality that existed before its development, it is designed to obtain a more stable and longer-term view of self-reported sleep quality, rather than an estimate for one or two nights only. Moreover, the Pittsburgh Sleep Quality Index global score reflects the patient's self-report of several different aspects of sleep, including sleep latency (i.e., the time it usually takes to fall asleep), typical sleep duration and usual sleep efficiency (i.e., the percentage of time in bed actually spent asleep), perceived disturbances of sleep at night, use of medication to promote sleep, and daytime dysfunction resulting from poor sleep and feelings of fatigue. Thus, the Pittsburgh Sleep Quality Index actually reflects dimensions of both hyperarousal at night, which could make it difficult to fall asleep and to sustain sleep, and daytime alertness and well-being. As we have suggested elsewhere (14, 15), persistently abnormal sleep quality and the associated state of central nervous system hyperarousal may make it difficult for patients to use effectively the cognitive strategies employed in psychotherapy. Hence, restoration of good sleep quality by early continuation therapy may position patients to use more effectively the strategies of interpersonal psychotherapy during the subsequent maintenance phase of therapy.

Our detailed analysis of residual depressive symptoms in early continuation therapy indicated that differences between the patients with good and poor sleep reflected primarily differences in the Hamilton depression items related to sleep and not to other symptoms, thus suggesting that poor sleep quality is not a proxy for other residual depressive symptoms. Poor self-reported sleep tends to correlate only modestly with polysomnographic measures of sleep continuity, as reported here, but is associated with daytime complaints such as poor attention, concentration, and memory and a diminished ability to cope (DSM-IV; 16). Thus, the self-reported cognitive impact associated with impaired sleep quality could diminish the maintenance efficacy of interpersonal psychotherapy, while, conversely, the absence of insomnia, impaired attention, and diminished coping ability could allow subjects to benefit from maintenance interpersonal psychotherapy. However, the absence of sleep impairment is *not* sufficient to ensure continued wellness (as evidenced by the 69% recurrence rate among the patients with good sleep who were assigned to a medication clinic), unless maintenance interpersonal psychotherapy is provided.

A final, practical note: the measurement of self-reported sleep quality by means of the Pittsburgh Sleep Quality Index is inexpensive and quick. Hence, the Pittsburgh index may be useful as a clinical measure of ultimate outcomes and valuable in both research and clinical settings.

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