Olanzapine Increases Slow Wave Sleep and Sleep Continuity in SSRI-Resistant Depressed Patients

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Objective: The atypical antipsychotic drug olanzapine has been employed as an augmentation treatment in depressed patients unresponsive to treatment with selective serotonin reuptake inhibitors (SSRIs). In healthy subjects, acute olanzapine administration increases sleep continuity and enhances slow wave sleep (SWS). The aim of the present study was to determine if the addition of olanzapine to SSRI treatment in depressed patients produced similar effects on sleep.

Method: We measured the effect of open-label olanzapine addition (2.5 mg/day initially) on the polysomnograms of 12 patients referred from primary care sources who met DSM-IV criteria for major depressive disorder and who had had an unsatisfactory response to therapeutic doses of an SSRI. Patients were first enrolled in November 2001; final assessment occurred in November 2003. Sleep polysomnogram recordings were made on 3 occasions: before olanzapine addition, on the first night of olanzapine treatment, and after 3 weeks of olanzapine treatment.

Results: After the first night of olanzapine treatment and during the third week, subjects showed improvements in sleep efficiency ($p < .001$), subjective sleep quality ($p < .05$), and SWS ($p < .01$). Scores on the Hamilton Rating Scale for Depression fell significantly ($p = .001$), with the majority of the decrease being apparent after the first week of treatment.

Conclusion: Olanzapine improves sleep continuity and increases SWS in patients receiving SSRI treatment. These effects are apparent after the first dose of olanzapine and are maintained for the next 3 weeks. The ability of olanzapine to increase SWS is probably attributable to 5-$HT_{2A/2C}$ receptor blockade, which has been identified as a relevant mechanism in the therapeutic effect of olanzapine in SSRI-resistant depressed patients.

(J Clin Psychiatry 2005;66:450–454)

Received June 9, 2004; accepted Sept. 13, 2004. From the University Department of Psychiatry, Warneford Hospital, Oxford, United Kingdom.

This study was supported by a research grant from Eli Lilly, Indianapolis, Ind.

Professor Cowen has received other grant/research support from manufacturers of atypical antipsychotic agents and has served on related advisory boards.

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Failure to respond to antidepressant medication is a common problem in clinical practice, and a variety of pharmacologic strategies have been adopted to deal with it. One approach, known as *augmentation*, is to add another medication to the primary antidepressant treatment.[1] The use of lithium in this situation is well documented,[2] but there has been growing interest recently in the addition of atypical antipsychotic drugs such as risperidone and olanzapine to ineffective treatment with selective serotonin reuptake inhibitors (SSRIs).[3–5] The present study also provided a preliminary opportunity to assess whether degree of 5-hydroxytryptamine-2C (5-HT_{2C}) receptor blockade, as assessed by increase in slow wave sleep (SWS), would correlate with clinical improvement. In addition, we aimed to determine whether improvement in sleep continuity with olanzapine correlated with antidepressant response, as appeared to be the case in our study of risperidone.[15]

The mechanism that might underlie the utility of atypical antipsychotic drugs in SSRI-resistant depression is unclear. However, recent suggestions have implicated 5-$HT_{2A/2C}$ receptor blockade because this might lead to increased dopamine and norepinephrine release in prefrontal cortex.[6,7] This receptor blockade would be expected to enhance the effect of SSRIs to potentiate monoamine neurotransmission.

Olanzapine is a potent 5-$HT_{2A/2C}$ receptor antagonist.[8] We have previously presented data in healthy volunteers showing that single doses of olanzapine of 5.0 mg and greater produce substantial increases in SWS in the polysomnogram, an effect likely to be mediated by 5-HT_{2C} receptor blockade.[9] The aim of the present study was to determine if a single dose of olanzapine would also increase SWS in patients who had failed to respond

satisfactorily to SSRI treatment and to determine if any increase would be sustained over the following 3 weeks of augmentation treatment.

METHODS AND MATERIALS

Subjects and Medication

We studied 12 patients (7 women, 5 men; mean age = 46 years; range, 29–64 years) referred from primary care sources who, on the basis of a semistructured clinical interview, met DSM-IV criteria for current unipolar major depressive disorder. Patients were first enrolled in November 2001; final assessment occurred in November 2003. None had any psychotic features. The patients had been treated with therapeutic doses of a serotonin-potentiating antidepressant for at least 4 weeks (range, 4–250 weeks, median = 8 weeks), were taking the maximum dose that they could tolerate, and required additional pharmacologic treatment as determined by their treating clinician. Of the 12 subjects, 2 had failed to respond to a single current antidepressant trial, while the remaining 10 subjects had failed to respond to 2 or 3 antidepressant medications. One had failed to respond to lithium augmentation. The length of the current episode ranged from 6 to 60 months (median = 27 months). One subject underwent polysomnography and olanzapine treatment but failed to return for the Hamilton Rating Scale for Depression (HAM-D) interviews with her treating clinician. She was excluded from the study and replaced with another subject.

The mean score of the subjects on the HAM-D[10] was 19.7 (range, 12–27) at baseline. The antidepressant treatment during the 3 study weeks was as follows: paroxetine (3 subjects: doses 30 mg, 30 mg, and 40 mg), fluoxetine (3 subjects: doses 20 mg, 20 mg, and 40 mg), venlafaxine (3 subjects: doses 75 mg, 150 mg, and 225 mg), citalopram (2 subjects: doses 30 mg and 30 mg), and sertraline (1 subject: dose 100 mg). Patients were treated with olanzapine 2.5 mg at night initially; the dose was increased to a maximum of 10 mg at the discretion of the treating clinician. Polysomnogram recordings were made on 3 occasions: at baseline, on the first night of olanzapine treatment, and following 3 weeks of olanzapine treatment. The patients were seen at baseline and then at weekly intervals by their treating clinicians. The HAM-D was administered on each occasion. Ethical approval was obtained from the local ethics committee, and informed written consent was obtained from each subject.

Olanzapine has been associated with significant increases in body weight with prolonged treatment of patients with schizophrenia. However, due to the small starting dose of olanzapine (2.5 mg) and short duration of the present study, we did not look at weight gain. It was not possible to look at rebound effects on sleep because, at the end of the study, patients returned to management with their treating clinicians.

Polysomnographic Recordings

On each of the 3 study nights, sleep polysomnograms were recorded as each subject slept at home, using the Medilog 9200-II cassette monitoring system (Oxford Instruments Medical, Surrey, U.K.). Subjects were asked to retire and rise at their usual time and to keep this time constant for each of the 3 study nights and for 1 night immediately preceding each study night. Subjects refrained from alcohol on the preceding and study nights but normal caffeine intake was maintained.

Sleep montage electrodes (2 electroencephalogram [EEG] channels: C_4-A_1, C_3-A_2, 2 electrooculogram [EOG] channels from the outer canthus of each eye referred to the mastoid and submental electromyogram [EMG]) were applied at approximately 1700 hours on each of the 3 study nights. After each study night, subjects were asked to record how well they had slept. This subjective sleep quality scale consisted of 5 points, from "much better than usual" (1) to "much worse than usual" (5). Polysomnograms were staged in 30-second epochs using the Oxford Medilog sleep stager (9200), which provides measures for all aspects of sleep architecture according to standard criteria.[11] In addition, the tapes were visually inspected and edited by a scorer blinded to treatment status according to the criteria of Rechtschaffen and Kales.[11] Sleep onset was defined as the beginning of the first 2 minutes that were not scored as wake or movement. Latencies to each sleep stage were calculated to the first 2 continuous minutes of the stage. We have previously demonstrated that the use of home sleep recordings and automatic analysis provides a reliable and valid means of detecting the effects of drugs on sleep architecture, including the effects on rapid eye movement (REM) sleep latency.[12–14]

Statistical Analysis

Data were analyzed using SPSS for Windows (version 11.5; SPSS, Inc., Chicago, Ill.) with a repeated-measures analysis of variance (ANOVA) and Huynh-Feldt correction where the assumption of sphericity was violated. For clarity, uncorrected degrees of freedom are shown. Significant effects were further assessed using the Student paired t test (2-tailed). Correlations between changes in HAM-D scores and sleep and clinical parameters were carried out using the Pearson product moment correlation (2-tailed).

RESULTS

Polysomnogram

Subjects experienced olanzapine as highly sedating and therefore found it difficult to get up at the requested time the morning after the second and third night of recording. The sleep architecture parameters were therefore calculated as percentage of total sleep time. The repeated-

Table 1. Effect of Olanzapine Addition on the Polysomnograms of 12 Depressed Patients Receiving SSRI Medication[a]

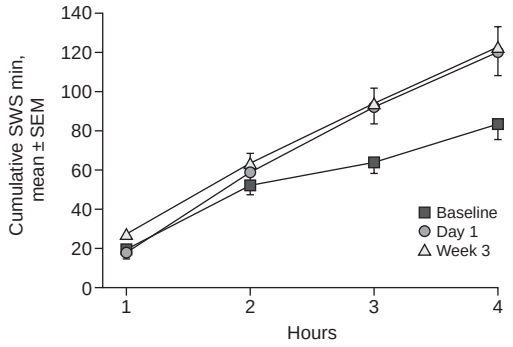
Selected Sleep Parameter	Baseline, mean ± SD	Day 1 Olanzapine, mean ± SD	Week 3 Olanzapine, mean ± SD
Sleep continuity measure			
Time in bed, min	469.1 ± 79.1	572.7 ± 76.9**	520.4 ± 76.7
Actual sleep time, %	85.8 ± 7.4	92.7 ± 4.4***	93.7 ± 3.0**
Sleep efficiency, %[b]	76.3 ± 11.4	88.4 ± 5.4***	89.9 ± 4.2***
Wake after sleep onset < 120 sec, %	2.7 ± 1.2	1.6 ± 1.1*	1.9 ± 0.9**
Wake after sleep onset > 120 sec, %	10.0 ± 7.4	4.5 ± 3.9	3.2 ± 2.5*
Total wake after sleep onset, %	12.7 ± 7.6	6.1 ± 4.8**	5.1 ± 3.0**
Sleep onset latency, min	37.9 ± 51.4	25.1 ± 24.0	18.6 ± 25.7*
Subjective sleep quality[c]	3.1 ± 0.7	4.2 ± 0.8**	3.8 ± 1.0*
Non-REM measure			
Stage 1, %	8.3 ± 3.1	8.9 ± 4.0	9.1 ± 5.1
Stage 2, %	36.4 ± 7.5	41.8 ± 9.1	33.4 ± 6.0
Slow wave sleep, %	23.0 ± 10.9	28.8 ± 10.3	33.5 ± 11.6**
Total non-REM, %	69.2 ± 8.5	80.8 ± 5.2***	77.1 ± 6.4**
REM sleep measure			
REM latency, min	152.6 ± 53.4	237.9 ± 57.3**	140.8 ± 70.8
REM sleep, %	18.2 ± 7.2	13.1 ± 5.9*	17.8 ± 4.6
No. of REM episodes	2.3 ± 1.1	2.7 ± 0.8	3.2 ± 1.1

[a]Results of post hoc paired t test, significantly different from baseline: *p < .05; **p < .01; ***p < .001.
[b]Sleep efficiency, % = actual sleep time/time in bed × 100.
[c]Sleep quality = scores 1 to 5 on subjective rating scale (from much worse than usual to much better than usual).
Abbreviations: REM = rapid eye movement, SSRI = selective serotonin reuptake inhibitor.

measures ANOVA showed a significant effect of olanzapine treatment on time in bed (min) ($F = 5.67$, df = 2,22; $p = .01$), actual sleep time (%) ($F = 12.9$, df = 2,22; $p = .001$), sleep efficiency (%) (actual sleep time as a percentage of time in bed) ($F = 22.8$, df = 2,22; $p = .00$), wake after sleep onset > 120 sec (%) ($F = 10.0$, df = 2,22; $p = .004$), total wake after sleep onset (%) ($F = 12.0$, df = 2,22; $p = .002$), SWS (%) ($F = 5.7$, df = 2,22; $p = .01$), total non-REM (%) ($F = 19.4$, df = 2,22; $p = .000$), latency to REM sleep (min) ($F = 7.8$, df = 2,22; $p = .003$), and subjective sleep quality ($F = 8.8$, df = 2,22; $p = .002$).

Post hoc testing revealed that significant changes occurred on both day 1 and week 3 of olanzapine treatment compared to baseline (see Table 1), although the pattern of changes differed somewhat between the 2 nights. Improved sleep efficiency was apparent on both occasions, but the REM changes were present only on the first night of olanzapine treatment. In contrast, effects on SWS were more robust on week 3. Because the majority of SWS occurs in the first part of the evening we also examined SWS time over the first 4 hours of sleep for each of the 3 recordings. The mean cumulative minutes of SWS for this time period are shown in Figure 1. Using this measure there were significant increases in SWS over baseline after both 1 night and 3 weeks of olanzapine treatment.

Figure 1. Slow Wave Sleep (SWS) in the First 4 Hours of the Polysomnograms of 12 Depressed Patients Before (baseline) and After 1 Day and 3 Weeks of Olanzapine Addition to SSRI Treatment[a]



[a]The cumulative minutes of SWS are significantly greater after both 1 day ($p = .037$) and 3 weeks ($p = .001$) olanzapine treatment (paired t tests).
Abbreviation: SSRI = selective serotonin reuptake inhibitor.

Clinical Responses

A significant decline occurred in both HAM-D total and HAM-D item 1 (depressed mood) scores (Figure 2) over the 3 weeks of olanzapine addition. Of the 12 subjects, 6 achieved remission as judged by a score of less than 8 on the total HAM-D at 3 weeks. The mean dose of olanzapine at the time of the final polysomnogram was 4.8 mg (range, 2.5–10 mg); there was a negative correlation between final dose and change in HAM-D score ($r = –0.63$; $p = .027$). There was also a significant negative correlation between length of the depressive episode and decrease in HAM-D ($r = –0.66$; $p = .021$) but not with the prior duration of SSRI treatment ($r = –.029$; $p = .3$) or number of previous antidepressant trials ($r = 0.27$; $p = .40$). Remitters had lower baseline HAM-D scores (mean ± SEM) compared with nonremitters (17 ± 1.6 vs. 23 ± 0.9; $p = .01$). There were no significant correlations between

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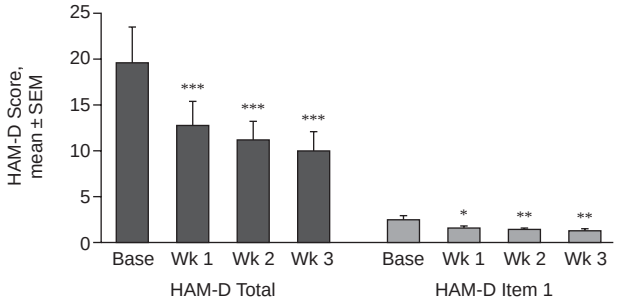
Figure 2. HAM-D Total and HAM-D Item 1 (depressed mood) Scores Before (baseline) and During Olanzapine Addition to SSRI Treatment of 12 Depressed Patients for the Following 3 Weeks



*p = .02.
**p = .01.
***p = .001.
Abbreviations: HAM-D = Hamilton Rating Scale for Depression, SSRI = selective serotonin reuptake inhibitor.

change in HAM-D and change in SWS or sleep continuity (all p values > .5).

DISCUSSION

Our findings indicate that the addition of olanzapine to SSRI treatment in depressed patients improves sleep continuity and increases slow wave sleep. These effects were maintained throughout the 3 weeks of olanzapine addition.

Assessment of the effects of olanzapine on sleep architecture in the present study is complicated by the fact that, despite encouragement to maintain a relatively stable time of rising, patients spent substantially longer periods in bed and had more time asleep following olanzapine addition. These effects were experienced by the patients as an improvement in subjective sleep quality, and, as judged by sleep efficiency measures, objective sleep quality was also better after olanzapine addition. However, because the total length of sleep was greater after olanzapine, we decided to analyze the time spent in the various sleep stages as a percentage of actual sleep time rather than an absolute measure as is our usual practice.

This analysis confirmed that olanzapine increased the proportion of SWS in the polysomnogram. There were also what appeared to be somewhat transient acute effects to decrease REM latency and REM sleep following acute olanzapine addition, but these effects had dissipated by the third week of treatment. Our findings in this respect differ somewhat from our previous SSRI augmentation study with the atypical antipsychotic agent risperidone, which did not alter SWS but lowered REM sleep after 2 weeks' treatment.[15] Like olanzapine, however, risperidone decreased wake after sleep onset and improved sleep efficiency.[15] Olanzapine is a potent histamine H_1-receptor antagonist,[8] and its ability to improve sleep efficiency and subjective quality of sleep could be attributable to this action.[9]

SWS increased over the 3 weeks of olanzapine treatment. We have previously shown that the effect of olanzapine on SWS is dose-related.[9] Plasma olanzapine levels would have risen because of both pharmacokinetic factors (achievement of steady state) and clinical dose increases. We think these 2 factors underlie the increase in SWS during the course of treatment. The main point is that there is no clear tolerance to this effect (as might be occurring with the REM sleep).

The increase in SWS following olanzapine is probably a consequence of 5-$HT_{2A/2C}$ receptor blockade,[9] and our previous studies with selective 5-HT_2 receptor antagonists such as ketanserin and ritanserin have implicated 5-HT_{2C} receptor antagonism as the likely mechanism.[16] This might explain why olanzapine but not risperidone increased SWS in SSRI-treated patients, since olanzapine is a more potent 5-HT_{2C} receptor antagonist than risperidone.[8,17]

Alterations in REM sleep may result from antagonistic effects of olanzapine at muscarinic cholinergic receptors. REM suppression is a common effect of drugs that possess clinical antidepressant activity.[14] The REM suppression noted on day 1 of olanzapine addition returned to baseline levels by week 3 of olanzapine treatment, which suggests the development of tolerance, but we are uncertain of the mechanism.

Of the 12 patients in the study, 6 achieved good responses as judged by reduction in HAM-D scores to less than 8. A previous placebo-controlled study has shown a similar response rate to olanzapine addition in depressed patients resistant to fluoxetine treatment.[5] However, the present study is difficult to assess from the point of view of the efficacy of olanzapine because it was carried out open-label and the patients were taking different SSRIs for varying lengths of time. In addition, 2 subjects had received only 4 weeks of treatment with SSRI before augmentation, so it is possible that any therapeutic response in these cases could have been due to an effect of the primary antidepressant medication. Against this is the fact that both these subjects had been resistant to at least 2 previous courses of antidepressant treatment, one of which included another SSRI. Generally, we found no correlation between length of treatment with the SSRI and response to olanzapine, although, as might be expected, the patients with more severe illness in terms of chronicity and high baseline HAM-D showed lesser response to olanzapine augmentation. As noted in the study by Shelton et al.,[5] much of the therapeutic response to olanzapine was apparent by the end of the first week of treatment. The negative correlation between final olanzapine dose and reduction in HAM-D is presumably attributable

to the tendency of clinicians to increase olanzapine dosing in patients who were not responding.

The HAM-D rating scale carries 3 sleep-related items,[10] and it is therefore possible that improvement in HAM-D ratings that followed olanzapine addition could be attributable to improved sleep. However, item 1 on the HAM-D, which measures depressed mood, showed a pattern of improvement similar to that of the total score, suggesting that olanzapine augmentation probably did produce an antidepressant effect as well as benefiting sleep in the present study. In our study with risperidone, we found that improvement in sleep (as judged by decrease in wake) correlated with improvement on the HAM-D.[15] However, this was not apparent in the present study, and, in fact, we found no correlation between any of the effects of olanzapine on the sleep polysomnogram and improvement in HAM-D. In particular, there was no trend to a relationship between the extent of the SWS increase (a putative measure of 5-HT_{2C} receptor blockade[16]) and therapeutic response.

Increase in SWS could conceivably benefit depression independent of the pharmacologic mechanism that causes the increase. Many depressed patients have low levels of SWS, which is believed to be a sleep phase during which neuronal connections in the brain are modified, with beneficial effects on cognitive performance.[18] However, there is no evidence from this study that increases in SWS per se were important in the therapeutic effect of olanzapine addition. Similar comments apply to the improvement in sleep continuity seen in this investigation. Sleep continuity improvements might be associated with clinical remission, as in our study of risperidone,[15] or attributable to the sedative effects of medication. The latter appears to be the more likely explanation in the current study.

As noted above, the lack of correlation might be due to the fact that the patient group and its treatment were clinically heterogeneous. Another possibility is that olanzapine produced effective 5-HT_{2C} receptor blockade in all subjects but that only a subgroup responded to this pharmacologic effect with clinical improvement. Finally, it is possible, of course, that 5-HT_{2C} receptor blockade does not play an important role in the ability of olanzapine to augment SSRI treatment. If olanzapine and risperidone are found eventually to be equally efficacious in this respect, it could implicate 5-HT_{2A} receptor antagonism as a relevant therapeutic mechanism.[6] Ultimately, SSRI augmentation studies with selective 5-HT_{2A} and 5-HT_{2C} receptor antagonists will be needed to resolve this question.

Drug names: citalopram (Celexa and others), fluoxetine (Prozac and others), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), paroxetine (Paxil and others), risperidone (Risperdal), sertraline (Zoloft), venlafaxine (Effexor).

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