Effects of Exogenous Melatonin Administration and Withdrawal in Five Patients With Rapid-Cycling Bipolar Disorder

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Background: The ready availability of exogenous melatonin means that its use in patients with mood disorders is probably not uncommon. Nonetheless, few controlled trials of exogenous melatonin in these patients have been conducted.

Method: Five patients with rapid-cycling DSM-III-R bipolar disorder were treated with melatonin 10 mg q.d. at 10:00 p.m. for 12 weeks. Melatonin was added to a stable regimen of medication and administered in a double-blind, placebo-controlled fashion.

Results: Melantonin administration had no positive effects. One patient developed a free-running (unentrained) sleep-wake cycle after melatonin withdrawal. In addition, in both this and a second patient, there is evidence that the administration of exogenous melatonin may have suppressed the secretion of endogenous melatonin.

Conclusion: The administration of melatonin had no significant effects on mood or sleep. However, melatonin withdrawal delayed sleep onset time and may have had some mild mood-elevating effects.

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There have been few controlled trials of exogenous melatonin treatment in patients with mood disorders, despite the fact that the use of the hormone in this population is probably now fairly widespread. In 1976, Carman et al.[1] published a study showing an exacerbation of dysphoria in six depressed patients treated with melatonin. However, the doses used in that study were high (150–1600 mg/day), and the time of administration, a critical parameter in the use of melatonin,[2] was variable. Since that time, the only published reports of melatonin treatment in patients with mood disorders have involved patients with seasonal affective disorder, in whom exogenous melatonin either had no effect[3] or may have caused relapse in those who had been treated with light therapy.[4]

Exogenous melatonin has been used in an attempt to stabilize free-running (i.e., unentrained) rhythms of the sleep-wake cycle, temperature, cortisol, and endogenous melatonin in blind[5] and sighted[6] people. While most studies show that circadian rhythms in patients with rapid-cycling bipolar disorder are not free-running,[7,8] data do indicate that rapid-cycling bipolar disorder may be associated with unstable rhythms. Specifically, there is evidence that the rhythms of temperature,[9,10] MHPG excretion,[9] and possibly nocturnal melatonin secretion[11] may shift in a systematic way as patients with rapid-cycling bipolar disorder cycle between hypomania and depression, with a tendency to be phase-advanced (shifted earlier) in hypomania compared with depression. If this instability in the timing (phase) of circadian rhythms is causally related to mood switching, then interventions that prevent such phase shifts may promote mood stability. In general, increasing the amplitude of a circadian rhythm makes it less susceptible to phase shifts.[12]

We hypothesized that administering exogenous melatonin at night, when endogenous melatonin secretion is occurring, would increase the amplitude of the nocturnal melatonin rhythm, prevent phase shifts, and thereby stabilize mood in patients with rapid-cycling bipolar disorder. In order to test this hypothesis without waking our subjects in the middle of the night, we began a double-blind, placebo-controlled trial in which melatonin 10 mg q.d. at 10:00 p.m. (2200 hours) was administered to patients with rapid-cycling bipolar disorder in combination with a stable regimen of psychotropic medications. Our experience with the first five patients, which is described here, revealed no positive effects of melatonin administration and some possible adverse consequences of melatonin withdrawal.

METHOD

All participants were drawn between April and December 1995 from an outpatient research clinic at the National Institute of Mental Health (NIMH) for patients with rapid-cycling bipolar disorder. All patients met DSM-III-R

criteria[13] for bipolar illness, as established by a Structured Clinical Interview for DSM-III-R.[14] In addition, all participants reported having had at least four affective episodes within the past year, thereby meeting the criteria for rapid-cycling bipolar disorder.[15] Of these four episodes, at least one each of hypomania or mania and major depression were required, and the episodes of major depression had to meet full DSM-III-R duration criteria. Patients with Axis I substance abuse or dependence within the past 6 months were excluded. In addition, patients who met criteria for borderline or antisocial personality disorder, as determined by the Structured Clinical Interview for DSM-III-R Personality Disorders (SCID-II),[16] were excluded.

The trial had a double-blind, placebo-controlled, randomized-order design in which melatonin 10 mg at 10:00 p.m. (2200 hours) was added to a stable regimen of the patient's psychotropic medications. The melatonin and placebo legs of the trial were each 12 weeks long, with a 1-month washout period in between. The protocol was approved by the Institutional Review Board of the NIMH, and all patients gave informed consent. The melatonin was supplied by Regis Chemical, assayed for purity by the Pharmaceutical Development Section of the National Institutes of Health, and approved for use by the Food and Drug Administration under an Investigational New Drug Application.

Throughout the trial, patients completed daily mood self-ratings. Twice a day, shortly after awakening and just before bedtime, patients rated their mood on a 100-mm line with 0 mm = "most depressed I've ever felt" and 100 mm = "most manic I've ever felt." On the mood rating form, the region < 35 was labeled "depressed," from 35 to 65 "euthymic," and > 65 "manic."[17] In addition, patients completed a sleep log with 15-minute resolution every day. Since all patients enrolled in our clinic complete these daily mood and sleep forms continually, extensive baseline data were also available. During the clinical trial, patients' mood was measured weekly by clinicians with established interrater reliability using the Structured Interview Guide for the Hamilton Rating Scale for Depression (SIGH-SAD)[18] to measure typical and atypical depressive symptoms and the HIGH-SAD (Hypomania Interview Guide)[19] to measure hypomanic and manic symptoms.

In the final week of the placebo and melatonin legs of the trial, patients were admitted to the clinical research unit to obtain 24-hour melatonin profiles. Patients were admitted to the unit by 1:00 p.m. (1300 hours), and an intravenous line was inserted. At 3:00 p.m. (1500 hours), patients were put in dim (< 1 lux) light conditions to avoid the suppression of endogenous melatonin secretion by light. For 24 hours beginning at 4:00 p.m. (1600 hours), blood samples for melatonin were drawn every 30 minutes. Patients were prescribed sleep and nap times based on an average of their sleep-wake schedule over the preceding 3 days. While patients were sleeping, blood was drawn through a 12-foot intravenous line exiting the room through a port in the door. Neither exogenous melatonin nor placebo was given on the night of the procedure.

Blood samples were stored on ice and centrifuged every 3 hours. The plasma was then extracted and stored in a –30°C freezer. For one patient (whose data are shown in Figure 3A), the melatonin samples after treatment with melatonin and placebo were measured by American Laboratory Products Company, Windham, N.H.; all other samples in the study were analyzed by StockGrand Ltd. (Surrey, U.K.). Both laboratories use well-validated radioimmunoassays that are highly sensitive (detection limit ≤ 2 pg/mL) and specific (cross-reactivity with 6-sulphatoxymelatonin ≤ 0.25%).

RESULTS

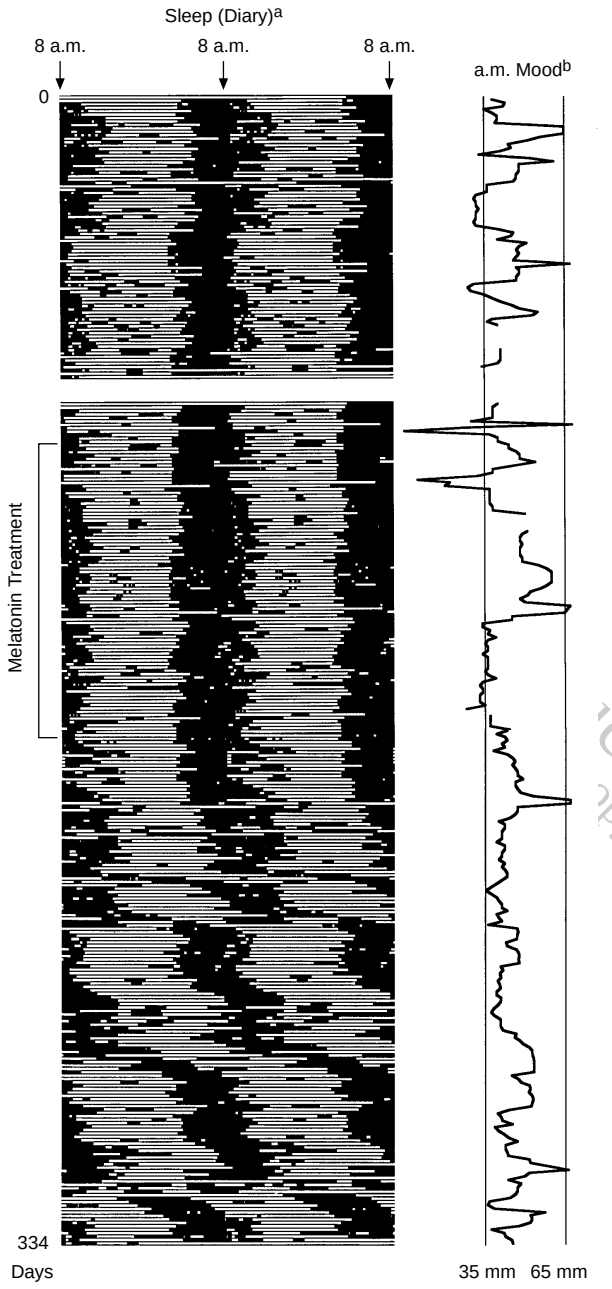
Five patients (all female) entered the trial. The mean ± SD age was 47.2 ± 3.8 years. The patients were on a variety of medications, including mood stabilizers (lithium, valproate, carbamazepine, and/or clozapine), antidepressants (fluoxetine, venlafaxine, or trazodone), benzodiazepines, thyroid hormone, and buspirone. Four patients were assigned randomly to receive melatonin first; for these patients, the placebo leg of the trial can also be viewed as a period of melatonin withdrawal. For reasons that will be described below, one patient did not complete the trial; her data are not included in Figures 2A and 2B. The clinical effects of exogenous melatonin and its withdrawal will be discussed in terms of effects on sleep, mood, and melatonin profiles.

Sleep

Mean wake and sleep onset times each differed by less than 10 minutes between the baseline and melatonin conditions. In four of the five patients, melatonin was received before placebo. There was no evidence of an advance of sleep or wake onset times in the melatonin condition, compared with baseline measures. However, both mean sleep and wake onset times showed nonsignificant delays between the melatonin and placebo conditions, i.e., melatonin withdrawal caused slight delays in these measures. Specifically, mean ± SD sleep onset was delayed from 2340 ± 0119 hours in patients taking melatonin to 0052 ± 0227 hours in those taking placebo, while mean wake onset was delayed from 0850 ± 0258 hours in patients taking melatonin to 0930 ± 0330 hours in those taking placebo. Sleep duration increased slightly from 541.9 ± 113.7 minutes at baseline to 551.8 ± 114.1 minutes on melatonin treatment, but then decreased to 515.0 ± 116.3 minutes on placebo treatment.

Melatonin withdrawal had a dramatic effect on the sleep-wake cycle of one patient. This patient had a chroni-

Figure 1. Sleep Diary of Patient Who Developed a Free-Running Sleep-Wake Cycle After Withdrawal From Melatonin 10 mg q.d. at 10:00 p.m.



[a]Self-reported sleep, double-plotted, with consecutive 24-hour (8:00 a.m.–8:00 a.m.) periods displayed in raster format.
[b]Self-reported mood as reported on a 100-mm line with 100 mm (the right pole) being "most manic I've ever felt" and 0 mm being "most depressed I've ever felt." Solid lines on the mood graph are at 35 and 65 mm, which was labeled the "euthymic" range.

cally delayed sleep-wake schedule at baseline, with a bedtime varying between midnight and 3:00 a.m. (0300 hours) (sometimes later) and a wake-up time between 9:00 a.m. (0900 hours) and 2:00 p.m. (1400 hours) (Figure 1). In addition, she tended to be hypersomnic at baseline, sleeping 10 to 12 hours a night plus afternoon naps. The hypersomnia had become particularly marked since clozapine therapy was initiated a year prior to the beginning of the melatonin trial. During the melatonin trial, her mean bedtime shifted 24 minutes earlier, and her daytime napping decreased. After the melatonin was withdrawn, however, she began to experience marked instability in her sleep-wake cycle, such as is typically seen in patients with free-running circadian rhythms. Specifically, her time of sleep onset and wake onset shifted somewhat later each day, so that in the course of an approximately 3-week period her hours of sleep rotated through the entire 24-hour cycle. This patient had never experienced a free-running rhythm before. The free-running pattern persisted for many months, showing some (but not complete) improvement after we began waking her with a telephone call every day at 10:00 a.m. (1000 hours) in an attempt to re-entrain her sleep-wake cycle. During both the melatonin trial and the free-running period, her mood remained relatively stable, varying between euthymia and mild depression.

Mood

In the group as a whole, there were no statistically significant differences in patient or observer mood ratings between the melatonin, placebo, or baseline conditions. Compared to baseline, both melatonin and placebo had mild mood-elevating effects (Figure 2A). The categorical display of the same data (Figure 2B) indicates that in the placebo condition (which in all patients but one was a period of melatonin withdrawal), there was a small increase in the number of mornings in which the patients rated their mood in the hypomanic range. This increase in hypomania was small in terms of its effects on mood ratings, but was clinically significant in that clinicians blind to the patients' treatment noticed a change and were concerned. In addition, Figure 2B shows a mild, nonsignificant accentuation of diurnal variation in the melatonin condition, so that the ratio of evening to morning hypomania is higher on melatonin than at baseline or on placebo.

One patient was withdrawn from the study after 35 days on melatonin because of an acute worsening of her mood, accompanied by suicidal ideation and an overdose on clonazepam and wine. This patient had a history of other such episodes, including one that occurred when the patient was being treated with morning light therapy.[20] Interestingly, this same patient experienced a long period of stability when treated with midday light therapy.[20]

Melatonin Profiles

Three patients had melatonin profiles drawn during the study (Figure 3, A–C). A profile was not drawn on the patient who terminated the trial prematurely, nor on

Figure 2A. Mean Daily Morning Mood Self-Ratings for Four Patients During 12 Weeks Each of Baseline, Melatonin, and Placebo

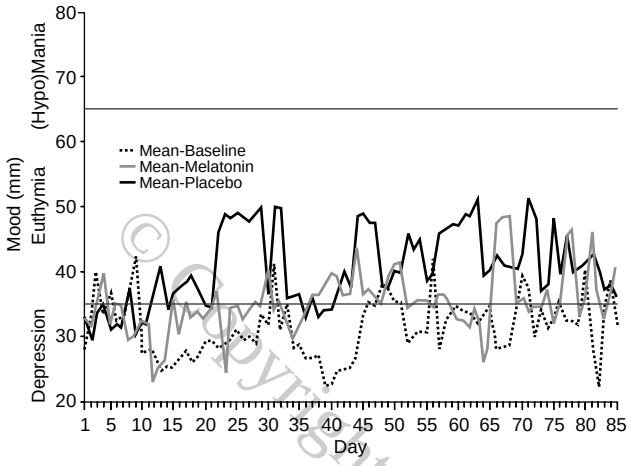
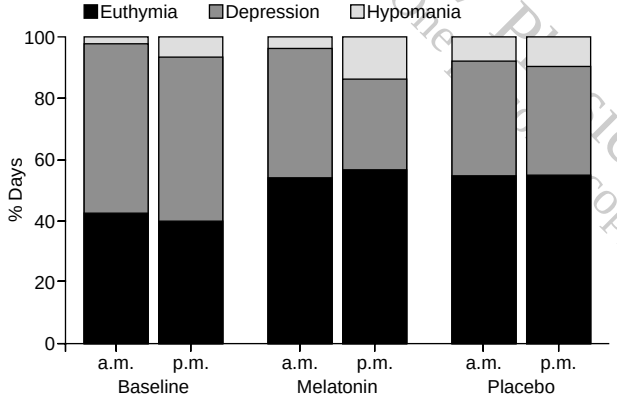


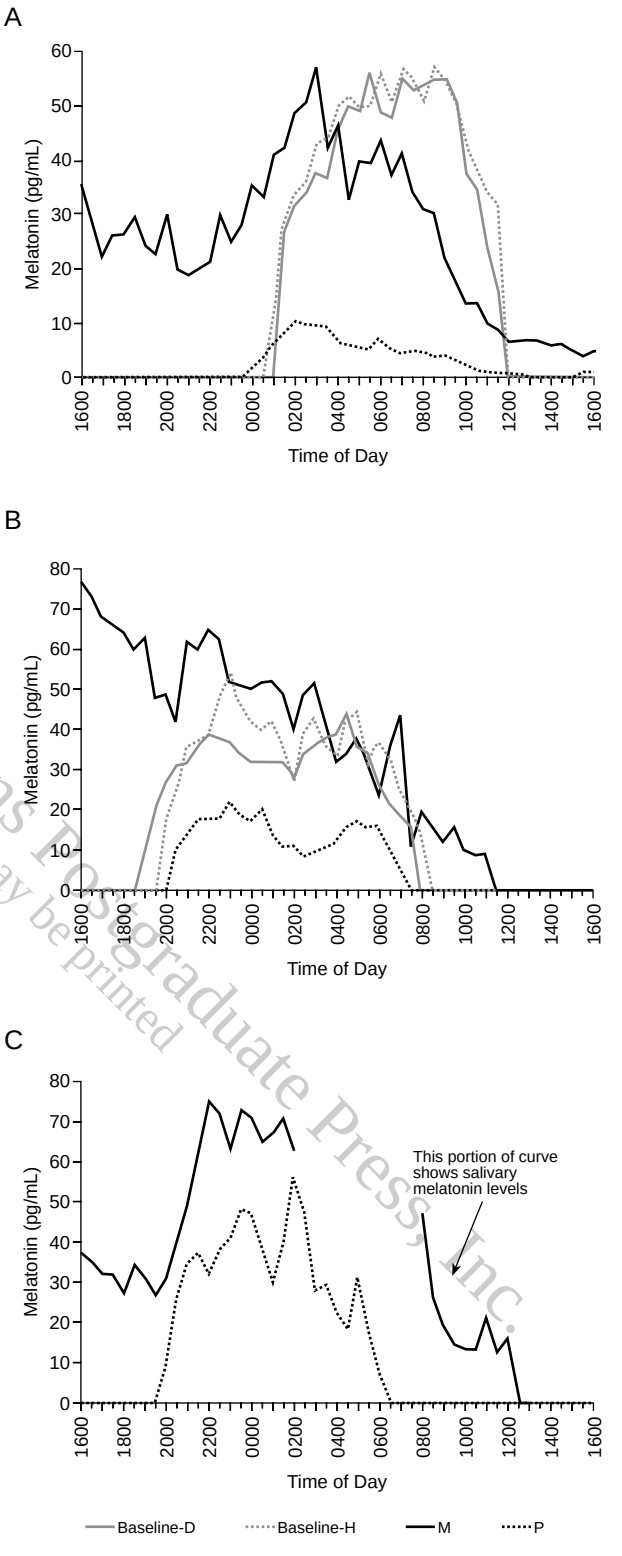
Figure 2B. Distribution Over 12 Weeks of Euthymia, Depression, and Hypomania for Four Patients as Shown in Mean Daily Morning and Evening Mood Self-Ratings*



*The daily morning mood self-ratings from Figure 2A are shown here as categorical data; the evening self-ratings (which were completed just before the patient went to bed) are also displayed.

another patient because of a history of hepatitis C. While taking exogenous melatonin, the patients' blood levels of melatonin did not fall to zero, despite the fact that the last dose of melatonin was given 17 hours before sampling began. The patients whose data are shown in Figure 3A and 3B received melatonin first; the patient whose data are shown in Figure 3C received placebo first. Baseline profiles drawn for other studies (albeit while taking different medications in the case of the patient shown in Figure 3A) show normal melatonin amplitudes for the patients whose data are displayed in Figure 3A and 3B. The data in Figure 1 and 3A come from the same patient; the patient whose data are shown in Figure 3B did not experience any remarkable changes in her sleep-wake cycle after melatonin withdrawal, despite the changes in her melatonin profile.

Figure 3. 24-Hour Melatonin Profiles for Three Patients While on Exogenous Melatonin (M), on Placebo (P), and at Baseline*



*Baseline melatonin profiles obtained while the patients were hypomanic (Baseline-H) and depressed (Baseline-D) are also shown. See text for details of data collection and analysis.

DISCUSSION

In this small sample of patients with rapid-cycling bipolar disorder, melatonin did not have statistically significant effects on either sleep or mood. However, withdrawal of exogenous melatonin after 3 months of administration induced a free-running sleep-wake cycle in one patient and, in the group as a whole, may have caused a small decrease in sleep duration accompanied by a mild increase in hypomania. In addition, the administration and subsequent withdrawal of exogenous melatonin may have caused partial suppression of endogenous melatonin secretion in the two patients for whom the relevant data are available.

The development of a free-running sleep-wake rhythm after the withdrawal of exogenous melatonin has not been reported previously. The suprachiasmatic nuclei of the hypothalamus, site of the body's endogenous clock, have melatonin receptors.[21] It is conceivable that the administration of exogenous melatonin caused a down-regulation of these receptors, with subsequent dysregulation of the circadian system when exogenous melatonin was withdrawn. The fact that this patient had delayed sleep-phase syndrome at baseline may have contributed to the occurrence of the adverse event, since other patients with delayed sleep-phase syndrome have developed free-running sleep-wake rhythms after chronobiological interventions.[22] Since patients with rapid-cycling bipolar disorder tend to have delayed circadian rhythms (Leibenluft E, Turner EH, Schwartz PJ, et al. 1996. Unpublished data), they may be at an increased risk to develop this adverse effect after melatonin withdrawal.

In the two patients in our study for whom data are available, the administration of exogenous melatonin may have caused a partial suppression of endogenous secretion that was evident 4 months after exogenous hormone was discontinued. Alternatively, exogenous melatonin may have induced liver enzyme activity in our patients (thereby increasing clearance and decreasing the blood levels of endogenous melatonin [Arendt J. July 5, 1996. Written communication]) or rendered them supersensitive to light, so that melatonin secretion was suppressed by the 1 lux of light present when the profile was drawn. No other investigators have found low endogenous levels after treatment with exogenous melatonin, but the available data are limited. In control subjects, neither 2 mg of melatonin administered for 1 month[23] nor 0.5 mg administered for 1 week[24] caused suppression of endogenous secretion. In addition, there have been reports of two blind men treated for longer periods (50 mg for 37 nights[24] and 5 mg for 10 years [Arendt J. July 5, 1996. Written communication]) in whom endogenous secretion was unaffected. Our patients differ from these others in the literature in that they were treated with a higher dose of melatonin for a longer time, received psychotropic medications concurrently, and suffer from rapid-cycling bipolar disorder. With respect to the latter characteristic, it is interesting to note that some,[25–27] but not all,[28,29] studies indicate that bipolar patients may be more sensitive than controls to light's melatonin-suppressing effects; perhaps bipolar patients are also particularly sensitive to suppressive effects of exogenous melatonin on endogenous melatonin secretion.

The effects of melatonin administration and withdrawal on the patients' sleep and mood were subtle and may reflect random variation. Melatonin administration did not appear to advance the patients' sleep onset time, perhaps because of the relatively late time of administration.[2] Somewhat surprisingly, however, melatonin withdrawal delayed sleep onset time and decreased sleep duration. It is therefore possible that the mild increase in hypomania in the placebo condition was due to the manicogenic effects of relative sleep deprivation.[30] It is also interesting to speculate about possible parallels between the mild increases in hypomania seen in the evening during the melatonin condition and during the placebo (withdrawal) condition. In both instances, hypomania may have increased at a time when melatonin levels were falling to their lowest blood levels.

Clearly, more research is needed to clarify the effects of melatonin administration and withdrawal on the clinical condition and circadian physiology of patients with rapid-cycling bipolar disorder. It is possible that the effects we observed were due to the relatively high dose that we prescribed; melatonin levels never fell to zero when the patients were taking exogenous melatonin, obliterating the "on-off" quality of the normal melatonin signal. This possibility will be explored in future studies, in which we will prescribe lower doses and follow the effect of exogenous hormone on endogenous secretion more closely.

Drug names: buspirone (BuSpar), carbamazepine (Tegretol and others), clonazepam (Klonopin), clozapine (Clozaril), fluoxetine (Prozac), trazodone (Desyrel and others), venlafaxine (Effexor).

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