Negative Effects of Melatonin on Depression

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In order to test the efficacy of the pineal neurohumor melatonin on depression, the hormone was administered in varying doses to six moderately to severely depressed patients and two patients with Huntington's chorea in a double-blind crossover study. Melatonin exacerbated symptoms of dysphoria in these patients, as well as causing a loss of sleep and weight and a drop in oral temperature. Melatonin increased cerebrospinal fluid 5-hydroxyindoleacetic acid and calcium in three of four patients studied. The authors discuss the implications of this finding.

PREVIOUS REPORTS (1–3) of mood improvement in parkinsonian patients and normal human subjects receiving the pineal neurohumor melatonin prompted our group to undertake a therapeutic trial of melatonin in depression. (Table 1 reviews studies reporting the psychological effects of melatonin.) Melatonin has been shown to increase brain serotonin in animals (11, 12) and urinary 5-hydroxyindoleacetic acid (5-HIAA) in parkinsonian patients (9) and to induce and prolong sleep in human subjects (1, 3, 7–9) and animals (13–15). These properties of melatonin led to our interest in this neurohumor as a possible therapeutic agent in depression, since sleep is frequently reduced in depressive illness and brain serotonin has been hypothesized to be decreased in some forms of depression.

Further rationale for such a trial came from observations that melanocyte-stimulating hormone (MSH), an antagonist of melatonin (7), produces in animals an exaggerated response to noxious stimuli (16, 17). Conversely, a double-blind study reported low-dose oral melanocyte-stimulating-hormone-release-inhibiting-factor (MIF) a more effective antidepressant than placebo in four of five patients (18).

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METHOD

Six patients with major primary depressive illness, defined according to the criteria of Spitzer and associates (19), and two patients with Huntington's chorea were hospitalized on research wards at the National Institute of Mental Health. Informed consent was obtained after the nature of the treatment and procedures was fully explained. The patients received varying amounts of melatonin either orally, divided into four equal doses daily, or by intravenous infusion once or twice daily for varying periods of time. The course of active oral melatonin was preceded and followed, for at least one week, by administration of placebo capsules identical in appearance, in a double-blind crossover design. Similarly, intravenous infusions of the active hormone were randomized with placebo infusions on a double-blind basis.

Behavioral ratings were obtained twice daily by consensus of a trained nursing research team (who were blind to all medications) using a modification of the Bunney-Hamburg Mood and Behavior Rating Scale (20), including ratings, on a 15-point scale, of such global items as depression, mania, psychosis, anxiety, and anger (21). The mean values for each item during the 7 days immediately preceding administration of melatonin, the variable number of days at the peak dose, and the placebo week following discontinuation of melatonin were employed in assessing the significance of drug-associated changes by analysis of variance.

An estimate of each patient's total nighttime sleep was determined by nurses making 30-minute checks between midnight and 8 a.m., and oral temperature by electronic thermometer and fasting weight were measured daily at 8 a.m. Blood samples were drawn twice weekly at 8:30 a.m. to monitor endocrine, metabolic, renal, hepatic, and hematologic status. Before melatonin administration and at peak dose, lumbar punctures were performed, in three patients at 9 a.m. without probenecid, and in patient 2 at 3 p.m. following oral administration of probenecid (100 mg/kg) (22) and 15 hours of bed rest.

Cerebrospinal fluid (CSF) 5-HIAA was measured by spectrofluorometric techniques as previously described (22). CSF and serum total calcium and magnesium were measured by atomic absorption spectrometry (23).

TABLE 1
Psychological Effects of Melatonin: A Review of the Literature

Study*	Number of Subjects	Type of Subjects	Length of Study (days)	Peak Daily Dose (mg)	Method of Administration	Psychological Effects
Lerner and Case (4)	2	Normal subjects	1	200	Intravenous	Mild sedation
Norlund and Lerner (5)	6	Normal subjects	28	1000	Oral	Sedation
Altschule (6)	2	Subjects with schizophrenia in remission	1	300	Intravenous	Marked exacerbation of symptoms almost immediately following infusion, with active hallucinations lasting 18 to 36 hours
Van Woert and Cotzias**	2	Parkinsonian patients	1	2000	Oral	Behavior not reported
Cotzias and associates (7)	1	Parkinsonian patient	51	1350	Oral	Somnolence, control of tremor
Anton-Tay and associates (1)	15	Normal subjects	1	100	Intravenous	Sleep induction, comfort, elation, subjective improvement
	5	Parkinsonian patients	28	1200	Oral	Sleep induction, comfort, elation, subjective improvement
Papavasiliou and associates (8)	11	Parkinsonian patients	35	6600	Oral	Tranquilization, somnolence
Shaw and associates (2)	4	Parkinsonian patients	28	1000	Oral	Tranquilization, relaxation, contentment
Cramer and associates (3)	15	Normal male subjects	1	50	Intravenous	Immediate sedation, decreased psychomotor activity, and shortened sleep latency with an otherwise normal sleep EEG; increased emotional stability noted on the day following bedtime infusion
Anton-Tay (9)	6	Normal subjects	6	1000	Oral	Sleep EEG effects: increased REM density, increased phase 2, and decreased phase 4
Smythe and Lazarus (10)	10	Normal male subjects	1	1000	Oral	Behavior not reported

* Studies are listed in chronological order, from 1960 to 1974.
** Cited in (5).

RESULTS

Figure 1 shows the effect of melatonin on the psychological state of the eight patients. Not only was melatonin, by either method of administration, ineffective as an antidepressant, but in every patient it caused some exacerbation of dysphoric mood. Ratings of depression and anger increased significantly for the group as a whole ($p<.01$), while psychosis emerged de novo or worsened in four patients. Anxiety increased as well, although not significantly ($p<.10$).

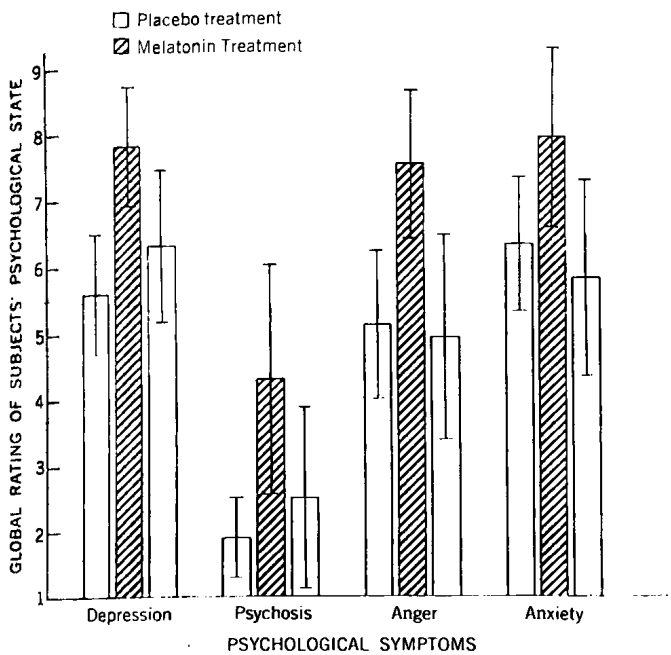
Two cardinal elements of the vegetative dysfunction characterizing endogenous depression—loss of sleep and weight—seemed specifically worsened during melatonin treatment (see table 2). Nurses' checks, although such crude estimates must be interpreted with caution (24), suggest a drop in nighttime sleep averaging 2.0 hours ($p<.01$), and the magnitude of sleep loss seemed related to the peak worsening of depression in each patient. Patients on melatonin also had an average weight loss of 1.8 kg ($p<.01$). In addition, oral temperature measured at 8 a.m. decreased by an average of 0.8C ($p<.01$) (table 2).

CSF 5-HIAA as well as CSF calcium increased markedly in three of four patients tested (table 3). The sole exception, patient 3, was also the only patient whose depression ratings did not increase on melatonin.

CASE REPORTS

Case 1. This 66-year-old woman had an 18-year history of episodic severe unipolar depression marked by prominent anorexia, social withdrawal, psychomotor retardation, and marked morning awakening. Each of her 12 prior episodes had necessitated hospitalization and parenteral feedings and, despite numerous trials of antidepressant medication, had finally responded only to ECT. During her 24-day trial of oral melatonin (peak dose=1100 mg/day), she developed a clear and dramatically dose-related exacerbation. Figure 2 demonstrates graphically the high correlation of nurses' ratings of psychological state with the dosage of melatonin this patient

FIGURE 1
Effect of Melatonin on Subjects' Psychological State (N=8)*



*Significant differences ($p < .01$, by analysis of variance) were found for the ratings of depression and anger when melatonin treatment was compared with preceding and following placebo treatment.

received. The patient's extreme withdrawal progressed to total mutism, anorexia, rigid immobility, enuresis, and encopresis. Furiously negativistic, she closed her eyes and exhibited alarm when the staff attempted to assist her in eating, grooming, or locomotion. On melatonin the usual lessening of this patient's depressive stupor during the evening disappeared. The exacerbation in her illness lessened slowly during the week following abrupt substitution of placebo.

Case 2. This patient was a 40-year-old woman with a 6-year history of alternate episodes of mania and depression, each requiring hospitalization; her index admission was for a moderately severe retarded depression that was worse during the evenings. During her first week on oral melatonin she developed an extreme lability of mood with sudden unprovoked outbursts of tears, rage, or terror. At peak dose (1600 mg/day) she developed looseness of associations, idiosyncratic expression, bizarre and inappropriate dress and demeanor, ideas of influence and reference, and the appearance for the first time of self-accusatory auditory hallucinations, blocking, and episodes of waxy flexibility several minutes in duration. An abrupt remission of all psychotic symptoms, coupled with a considerable lessening of depression, occurred one day after substitution of placebo following a 16-day trial of melatonin. She subsequently showed further improvement in her depression during lithium carbonate administration.

Case 3. This 44-year-old man had a 10-year history of retarded bipolar depression with episodic alcoholism. While on oral melatonin at a peak dose of 1200 mg/day, no affective worsening was reflected in his global depression ratings, but this patient did report increased sadness, difficulty concentrating, early morning insomnia (although nurses' sleep checks do not reflect this), and daytime drowsiness. He became more withdrawn, developed a prominent anorexia, and for the first time in 4 years of effortless abstinence expressed a desire for alcohol. These symptoms improved a few days after he completed a 9-day trial of melatonin. Later, this patient did not show a clear response to lithium, but he did improve following administration of tricyclic antidepressants.

Case 4. This patient was a 31-year-old woman with a 3-year history of mild to moderate unipolar depression. Although early in her hospitalization she suffered from mild insomnia, anorexia, and agitation, her depression responded well to hospitalization and psychotherapy without antidepressant medication, and she was substantially improved at

TABLE 2
Effect of Melatonin on Subjects' Weight, Amount of Sleep, and Temperature

Item	Patient 1	2	3	4	5	6	7	8	Mean	SEM	F	Significance
Weight (kg)												
Predrug	50.5	80.8	78.5	52.8	38.2	57.6	56.8	59.6	59.5	5.0	—	—
Melatonin	47.0	77.9	77.0	52.8	37.3	55.2	56.0	58.4	57.7	4.8	—	—
Postdrug	48.0	78.0	77.5	53.9	38.4	57.3	56.0	59.0	58.5	4.8	—	—
Analysis	—	—	—	—	—	—	—	—	—	—	9.20	$p < .01$
Sleep (hours)												
Predrug	8.0	6.0	7.0	7.0	6.5	6.5	8.0	6.0	6.9	.3	—	—
Melatonin	6.5	3.0	7.0	5.5	1.5	6.0	6.0	4.0	4.9	.7	—	—
Postdrug	6.5	4.5	7.5	7.0	4.5	8.0	6.0	5.0	6.1	.5	—	—
Analysis	—	—	—	—	—	—	—	—	—	—	9.00	$p < .01$
Temperature (C)												
Predrug	36.4	36.8	36.1	36.0	36.4	36.8	36.2	37.0	36.5	.1	—	—
Melatonin	35.2	35.0	36.0	35.8	36.0	36.0	35.4	36.0	35.7	.1	—	—
Postdrug	36.0	36.4	36.2	36.2	36.0	36.4	36.8	36.2	36.3	.1	—	—
Analysis	—	—	—	—	—	—	—	—	—	—	9.64	$p < .01$

TABLE 3
Effect of Melatonin on CSF 5-HIAA and CSF Calcium of Four Depressed Patients

Item	Patient 1	2	3	4
CSF 4-HIAA (ng/liter)				
Predrug	24.00	129.00*	21.00	22.00
Melatonin	150.00	306.00*	22.00	177.00
CSF calcium (mEq/liter)				
Predrug	2.35	2.35	2.50	1.90
Melatonin	2.55	2.40	2.50	2.30

* In patient 2, both CSF specimens were obtained following administration of probenecid.

the time her brief trial (3 days) of oral melatonin was begun. She became increasingly tearful and drowsy on melatonin and was felt by the staff to be subtly more distant and withdrawn. She complained of easier fatigability, decreased interests and appetite, and marked morning insomnia at the peak dose of 1200 mg/day.

Case 5. This patient, a 48-year-old woman with a moderate unipolar depression who received intravenous melatonin for 7 days (peak dose=250 mg/day), experienced disturbed sleep, gloominess, argumentativeness, feelings of unreality, and increased tearfulness and reported subjective increases in depression while on melatonin.

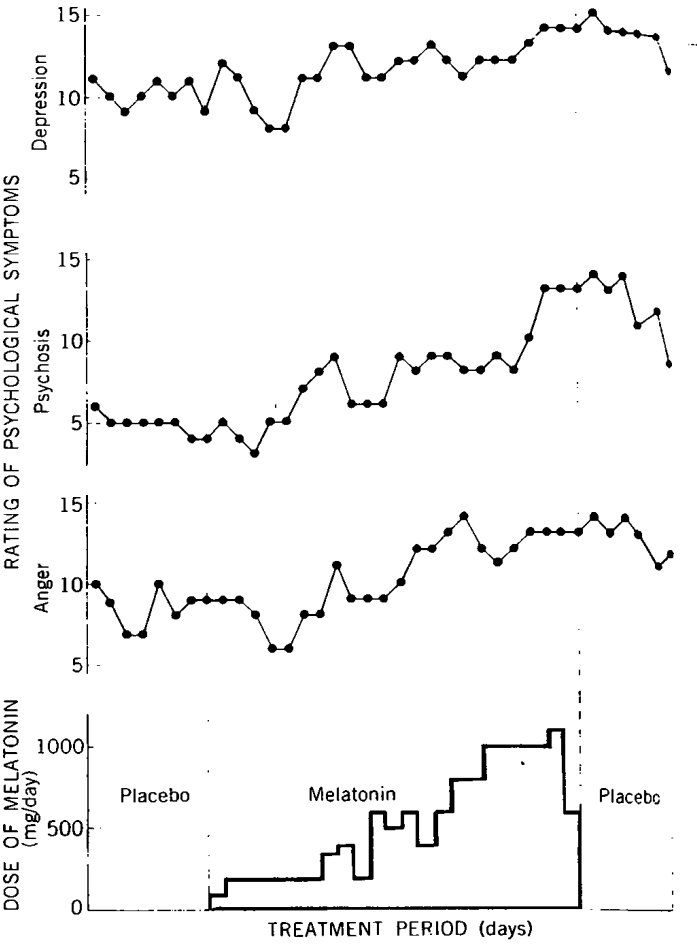
Case 6. This 47-year-old man with a moderately severe retarded bipolar depression received intravenously for 3 days the least melatonin given in this study (peak dose=150 mg/day) and showed little behavioral change other than an episode of breakthrough crying within an hour after the infusion of his highest dose. This was the only such crying in his entire hospitalization.

Cases 7 and 8. A 53-year-old woman and a 39-year-old woman had Huntington's chorea with moderate to severe motor dysfunction but only mild mental impairment. Although both were euthymic and without psychotic symptoms before the drug trial, both showed depression and psychomotor retardation during melatonin (peak dose=1200 mg/day) but no alteration in cognitive function and no emergence of psychosis. Patient 7 received melatonin for 12 days, patient 8 for 9 days.

DISCUSSION

The increased dysphoria that we observed in this small number of depressed and choreic patients was associated with sad or hopeless facial and verbal expressions and appeared to be a clear exacerbation of depression and not mere nonspecific sedation, as had been frequently reported in previous trials with human subjects (see table 1). The study was discontinued because of the evidence that melatonin was making this population of patients worse. These findings stand in striking contrast to the "elation" (1), "contentment" (2), and "increased emotional stability" (3)

FIGURE 2
Effect of Melatonin on Psychological State of Patient 1*



*During the period of active drug administration, the correlations between total daily dose of melatonin and ratings of specific psychological symptoms of patient 1 were .54 for anger, .70 for psychosis, and .57 for depression.

reported for other neurologically disordered patients and normal control subjects. Different experimental settings, closer attention to psychological effects, double-blind methodology, and the use of subjects with preexisting psychiatric morbidity or biological vulnerability could have contributed to our discrepant findings. Of possible relevance to our clinical observations are the reports that melatonin reduces spontaneous or appetitive activity in animals at doses even lower by weight than those we employed (16, 25–31).

Our results are consistent with those of Altschule (6), who noted florid exacerbation of schizophrenic symptoms following administration of intravenous melatonin to two previously recovered schizophrenic patients. The development of psychotic symptoms we saw during melatonin administration in the four most severely depressed patients is noteworthy since a variety of psychotomimetic and stimulant agents increase melatonin synthesis (dimethyltryptamine, bufotenine, mescaline, LSD, dimethoxyphenylethylamine [32], amphetamine [33], cocaine [34], and L-dopa [35]), while the neuroleptics diminish it (36)

and augment release of MSH from the pituitary (37).

It has been postulated (38–43) that endogenous or exogenous melatonin might undergo cyclic dehydration to form carbolines with either reserpine-like depressant or psychotomimetic properties. More rapid accumulation of melatonin or such metabolites or greater sensitivity to them might explain the dramatically different behavioral effects of melatonin in psychiatric patients than in normal subjects (44, 45).

Doses of exogenous melatonin administered four times a day might effectively have obfuscated the normal nocturnal, pulsatile synthesis and release of endogenous melatonin (46–49) as well as circadian variations in any behavioral characteristics referable to it. Consequently it is particularly interesting that the previously distinct diurnal differences in symptom severity of patients 1 and 2 became indiscernible at the peak dose of the hormone. If exogenous melatonin were in fact altering critical circadian rhythms, this would provide another explanation of the different effect of melatonin on normal control subjects than on psychiatric patients, who may have abnormal circadian rhythms initially (50–52). We (53) and others (54) have observed a marked, usually transient antidepressant effect of one night's sleep deprivation in severely depressed patients but not in less depressed patients or control subjects. It is an intriguing possibility that elimination of a sleep- or dark-related increase in melatonin might account for the mood improvement in sleep-deprived depressed patients.

The possible role of altered serotonin and calcium metabolism in production of the dysphoric changes observed must likewise be considered. The finding of markedly increased CSF 5-HIAA in three of four patients is consistent with earlier data from animals and human subjects. Recent evidence suggests that the increase in central serotonin turnover occurring with melatonin administration represents a compensatory response to a primary blockade of serotonin receptors by melatonin (9, 10, 55–57). Indeed, melatonin prevents release of growth hormone by serotonin (56, 57). The large increases in 5-HIAA in those patients who demonstrated the clearest worsening while receiving melatonin is consistent with studies showing that 5-HIAA in CSF decreases following various antidepressant treatments (58, 59).

Similarly, the elevation of CSF calcium associated with melatonin administration to the same three patients complements the finding that antidepressants may decrease CSF calcium (60). Several preliminary findings link the pineal to humoral calcium regulation: in rats, pinealectomy results in hyperplasia of the parafollicular (calcitonin-producing) cells of the thyroid (61) and hypofunction of the parathyroid (62), which can be restored to normal by administration of melatonin (63). In an attempt to synthesize these findings we would postulate that melatonin exerts a tonic inhibition of calcitonin release from the thyroid and other sites, possibly by blockade of serotonergic mechanisms involved in that release (64). It is also intriguing that in one patient restriction of dietary calcium, which may produce pineal atrophy (65), has been reported to lessen the duration and severity of acute episodes of periodic psychosis (66).

While this preliminary trial indicates that melatonin is ineffective as an antidepressant in this patient population and may even worsen mood in patients with moderate to severe depression, further exploration of the role of this neurohormone in affective and other psychoses appears to be indicated.

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