Diurnal Variation in the Direction of Mood Switches in Patients With Rapid-Cycling Bipolar Disorder

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Background: We assessed diurnal variation in the direction of mood switches in a sample of outpatients with rapid-cycling bipolar disorder who were on stable medication regimens. We predicted that patients would be more likely to switch from depression into mania or hypomania during the daytime hours and from mania/hypomania into depression overnight.

Method: Fifteen patients with rapid-cycling bipolar disorder completed self-rated mood scales twice a day: once shortly after awakening and once at bedtime. Using 3 months of data for each patient, we performed categorical analyses (McNemar chi-square) to study the direction of mood switches between each day's morning and evening rating and between each evening rating and the subsequent morning rating.

Results: As predicted, switches that occurred between the morning and evening ratings were more likely to be from depression into mania/hypomania or euthymia (64.3%) than in the opposite direction (35.6%; $p < .0001$). Similarly, switches that occurred between the evening rating and the next morning's ratings were more likely to be from mania/hypomania or euthymia into depression (64.8%) than in the opposite direction (35.2%; $p < .0001$).

Conclusion: Extended wakefulness, exposure to light, increased activity, and/or endogenous rhythms could contribute to the elevation of mood during the course of the day. Sleep, darkness, reduced activity, and/or endogenous rhythms could contribute to the tendency to switch into depression overnight. Clinicians should attend to the time of day that clinical assessments are performed in patients with rapid-cycling bipolar disorder. Potential therapeutic implications include the use of light or activity during depression and use of induced sleep or exposure to darkness during mania/hypomania.

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Several clinical observations suggest that disorders in diurnal regulation may play a role in the pathogenesis of affective disorders.[1] These observations include disturbances in the sleep-wake cycle that occur in patients with mood disorders, the observation that mood may vary systematically throughout the day (diurnal variation), the antidepressant effects of sleep deprivation, and the reversal of these effects by recovery sleep.[2] All of these phenomena have received considerably more attention in unipolar than bipolar patients, despite the fact that bipolar patients show marked variation in their sleep-wake cycle as their mood shifts between hypomania or mania and depression.[3,4]

When the concept of diurnal variation is applied to unipolar patients, it is usually conceptualized as a continuous variable. That is, patients with typical diurnal variation (i.e., mood improvement during the course of the day) are described as being less depressed in the evening than in the morning. When the concept is extended to bipolar patients, the possibility of categorical change also arises. Like the depressed unipolar patient, the depressed bipolar patient may experience a gradual lifting of his or her depression as the day wears on. However, the possibility also exists that, by the end of the day, the bipolar patient's mood may have lifted so much that he or she has actually switched into mania/hypomania. Therefore, in examining diurnal mood changes in bipolar patients, it is possible to ask not only whether mood improves (or worsens) in a predictable way throughout a 24-hour period, but also whether switches from one mood state to another are more likely to occur at particular times of day or night.

Indeed, the literature contains several lines of investigation suggesting that the diurnal distribution of mood switches in bipolar patients is not random. Specifically, studies show an association between extended wakefulness and mania/hypomania, on the one hand, and between sleep and depression, on the other. The fact that sleep loss, or extended wakefulness, can precipitate mania/hypomania is most clearly demonstrated in sleep deprivation

experiments. Sleep deprivation, which has antidepressant properties in unipolar depressives, is capable of inducing mania/hypomania in depressed bipolar patients.[3] In addition, the association between sleep loss and the switch into mania/hypomania has been noted in studies of bipolar inpatients,[3,5,6] and in case reports of patients who have 48-hour mood cycles.[5,7–12]

When extrapolating these findings of an association between extended wakefulness and mania/hypomania to medicated bipolar outpatients, it is important to note that sleepless nights are relatively rare in this population. Medicated bipolar outpatients, like normal subjects, are likely to experience their most extended period of wakefulness during the day. Therefore, we predicted that bipolar outpatients whose mood cycles are attenuated (but not eliminated) by medication would tend to exhibit decreasing depression and increasing mania/hypomania as the day progresses, so that the switch from depression into mania/hypomania would tend to occur during the daytime hours.

In addition to suggesting a relationship between wakefulness and mania/hypomania, the sleep deprivation literature also suggests a relationship between sleep and depression. Specifically, patients whose depression remits with sleep deprivation typically relapse after a night of recovery sleep.[2] However, the hypothesis that sleep is depressogenic has not been tested outside the rather specialized situation of recovery sleep. If sleep is depressogenic, one would predict that medicated, bipolar outpatients (who usually sleep at night but who may still experience mood cycles) would tend to switch out of mania/hypomania into depression at night, while they are sleeping.

Using twice-daily mood self-ratings, we tested these hypotheses in a sample of 15 outpatients with rapid-cycling bipolar disorder who were on stable medication regimens. Patients with rapid-cycling bipolar disorder are an interesting group in which to test these hypotheses, since a number of switches can be observed within a relatively short period of time. We present these data and discuss their clinical and theoretical implications.

METHOD

Subjects for the study were drawn from patients enrolled in a National Institute of Mental Health (NIMH) outpatient research clinic for patients with rapid-cycling bipolar disorder. To be enrolled in the clinic, patients had to meet DSM-III-R criteria for bipolar disorder,[13] as established by the Structured Clinical Interview for DSM-III-R, Patient Version (SCID-P).[14] In addition, each patient had to have had at least four affective episodes within the last year, including at least one episode each of major depression and hypomania, mania, or mixed state; the episodes of major depression met full DSM-III-R duration criteria. Each manic, hypomanic, or depressive episode was counted independently regardless of whether it was separated from the preceding episode by a euthymic period. Patients who met DSM-III-R criteria for borderline or antisocial personality disorder,[13] as established by SCID-II interview,[14] or alcohol or drug abuse within the preceding 6 months were excluded.

Written informed consent was obtained after a complete description of the study was given to the subjects.

All patients in the clinic were asked to rate their mood state twice each day (shortly after awakening and just before going to bed) using a 100-mm visual analogue scale (VAS) with 0 = "most depressed ever felt," 100 = "most manic ever felt," and the interval between 35 and 65 demarcated as the "euthymic or well range."[15] We used data from all patients in the clinic who had completed the self-rating forms for at least 3 months while on stable medication regimens. For those patients for whom more than 3 months of data were available, we analyzed data from the first 3 consecutive months.

Two data sets were analyzed: one including each morning mood rating and the same day's evening mood rating, and a second including each evening mood rating and the subsequent morning's mood rating. We performed categorical analyses on these data sets to examine the distribution of switches between euthymia, depression, and mania/hypomania during the course of the day and overnight. For these analyses, the categorical definitions indicated on the patient's mood rating forms were used. That is, depression was defined as a score < 35, euthymia was defined as a score between 35 and 65, and mania/hypomania was defined as a score > 65. If the patient indicated a mixed state by marking in both the depressed and manic/hypomanic range, we considered this state to be a dysphoric mania/hypomania and used only the manic/hypomanic rating in the analyses.

Data were analyzed with a McNemar chi-square test (paired data) on a 3×3 contingency table and a series of three post hoc 2×2 McNemar chi-square tests. Bonferroni corrections for multiple comparisons were performed by multiplying each of the p values by three.

RESULTS

Table 1 shows demographic and clinical data for the patients, as well as dates of the 3-month period of medication stability. The starting months for the period of medication stability range from April through August, with a peak in June and July.

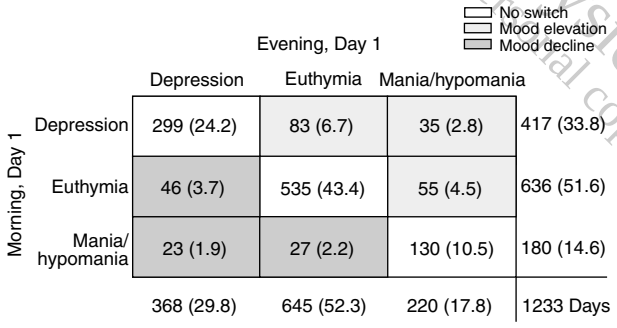
Daytime Switches

A total of 1233 days were included in the analysis of mood switches during the day (Figure 1). No mood switch was reported during 964 days (78.1%). Of the 269 days (21.8%) in which mood switches were reported,

Table 1. Clinical and Demographic Data

Patient	Sex	Age (y)	Study Dates	Bipolar I or II	Comorbid Diagnosis (DSM-III-R)	Medication
1	F	33	7/93–9/93	I	None	Valproate, bupropion
2	F	32	5/94–7/94	II	Agoraphobia, simple phobia, generalized anxiety disorder, avoidant and paranoid personality disorder	Carbamazepine, fluoxetine
3	F	43	7/93–9/93	II	Simple phobia	Lithium, phenelzine
4	F	54	6/94–8/94	I	Panic disorder, generalized anxiety disorder	Lithium, valproate, sertraline
5	F	43	6/93–8/93	II	Panic disorder, social phobia, obsessive-compulsive personality disorder	Carbamazepine, clonazepam, phenelzine, levothyroxine
6	M	47	6/93–8/93	I	None	Valproate, nortriptyline, tranylcypromine
7	M	39	7/93–9/93	I	None	Lithium, bupropion, carbamazepine
8	F	50	7/93–9/93	I	Panic disorder, social phobia, obsessive-compulsive disorder	Valproate, tranylcypromine, clonazepam, levothyroxine
9	F	40	9/93–11/93	II	Social phobia	Lithium, fluoxetine, levothyroxine
10	F	47	6/94–8/94	I	Simple phobia	Lithium, venlafaxine, clonazepam, trazodone, triiodothyronine
11	F	38	8/93–10/93	I	None	Lithium, doxepin, propranolol, lorazepam
12	M	45	5/94–7/94	II	None	Lithium
13	M	48	4/94–6/94	I	Avoidant personality disorder	Lithium, bupropion, levothyroxine, carbamazepine
14	F	40	7/93–9/93	II	None	Lithium, fluoxetine
15	F	37	6/94–8/94	I	Social phobia	Sertraline, levothyroxine, dextroamphetamine, clomipramine

Figure 1. Distribution of Mood Ratings During the Day in 15 Outpatients With Rapid-Cycling Bipolar Disorder*



*The numbers indicate the number of days on which that pattern was observed; the percentage of the total days is indicated in parentheses.

173 (64.3%) were in the direction of mood elevation (i.e., the switch was from depression into mania/hypomania [35 days] or euthymia [83 days], or from euthymia into mania/hypomania [55 days]), while 96 switches (35.7%) were in the direction of mood decline (i.e., the switch was from mania/hypomania to depression [23 days] or euthymia [27 days], or from euthymia into depression [46 days]). The chi-square statistic was significant ($\chi^2 = 17.88$, df = 2, $p < .0001$), indicating that mood switches are not randomly distributed during the day.

The three post hoc McNemar 2×2 analyses (with Bonferroni corrections) demonstrated that, between the morning and the evening ratings, patients were significantly ($p < .01$) more likely to switch from depression or euthymia into mania/hypomania than they were to switch from mania/hypomania into depression or euthymia. Specifically, in the first post hoc analysis of the daytime data, 118 (63.1%) of the switches between the a.m. and p.m. rating were from depression into euthymia (83 days) or mania/hypomania (35 days), while 69 (36.9%) of the switches were from euthymia or mania/hypomania into depression (46 and 23 days, respectively; $\chi^2 = 12.32$, df = 1, $p < .01$ with Bonferroni correction). In the second post hoc analysis, 90 (64.2%) of the switches were from depression (35 days) or euthymia (55 days) into mania/hypomania, while 50 (35.7%) of the switches were from mania/hypomania into depression (23 days) or euthymia (27 days) ($\chi^2 = 10.86$, df = 1, $p < .01$ with Bonferroni correction). However, between the a.m. and p.m. ratings, patients were equally likely to switch from euthymia into depression or mania/hypomania (46 and 55 days, respectively; 47.9%) as they were from depression (83 days) or mania/hypomania (27 days) into euthymia (52.1%) ($\chi^2 = 0.30$, df = 1, p = N.S.).

Fourteen of the 15 patients reported mood switches during the course of the day during the 3-month period examined. Nine of the patients had > 50% of the mood switches in the hypothesized mood direction (from depression into mania/hypomania or euthymia), while 3 of the patients had > 50% of mood switches in the opposite direction, and 2 had 50% of mood switches in each direction (Table 2).

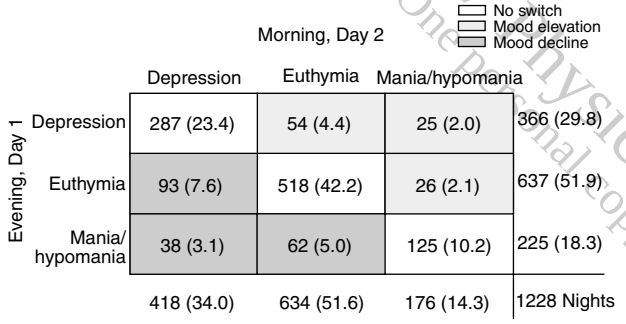
Nighttime Switches

Using each evening rating and the subsequent morning rating, we performed a set of analyses similar to those used in Figure 1 to determine the direction of mood switches occurring overnight. 1228 nights were included in the categorical analysis of overnight mood switches

Table 2. Distribution of Mood Switches During the Day and Overnight Per Patient, in 15 Outpatients With Rapid-Cycling Bipolar Disorder

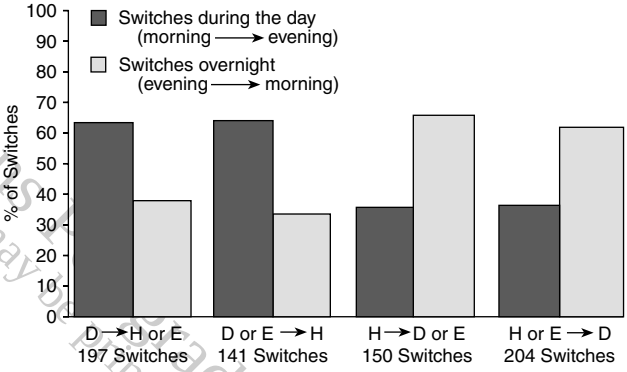
	Daytime Switches		Overnight Switches	
Patient	% Days Switched	% of Switches in Expected Direction (Evening, Day 1 > Morning, Day 1)	% Days Switched	% of Switches in Expected Direction (Evening, Day 1 > Morning, Day 2)
1	3	50	14	64
2	24	67	24	67
3	4	25	13	42
4	30	50	29	52
5	37	97	46	89
6	19	65	17	40
7	23	76	20	83
8	16	17	25	33
9	25	18	24	24
10	20	88	25	85
11	33	63	29	65
12	24	100	21	53
13	41	97	50	89
14	0	0	0	0
15	22	67	26	65

Figure 2. Distribution of Mood Ratings Overnight in 15 Outpatients With Rapid-Cycling Bipolar Disorder*



*The numbers indicate the number of days on which that pattern was observed; the percentage of the total days is indicated in parentheses.

Figure 3. Distribution of Mood Switches During the Day and Overnight in 15 Outpatients With Rapid-Cycling Bipolar Disorder*



*Abbreviations: D = depression, E = euthymia, H = mania/hypomania.

(Figure 2). Of the 298 nights (24.3%) where patients experienced a mood switch, 193 (64.8%) were in the direction of decreased activation (i.e., the switch was from mania/hypomania into euthymia [62 nights] or depression [38 nights], or from euthymia into depression [93 nights]), whereas 105 (35.2%) were in the direction of increased activation (from depression into euthymia [54 nights] or mania/hypomania [25 nights], or from euthymia into mania/hypomania [26 nights]) ($\chi^2 = 21.32$, df = 2, $p < .0001$).

The three post hoc McNemar 2×2 analyses (with Bonferroni corrections) demonstrated that overnight switches were significantly more likely to be from euthymia or mania/hypomania to depression than from depression into euthymia or mania/hypomania. Specifically, in the first post hoc analysis of the overnight data, 131 (62.4%) of the switches were from euthymia (93 nights) or mania/hypomania (38 nights) into depression, while 79 (37.6%) of the switches were from depression (54 nights) into euthymia or mania/hypomania (25 nights) ($\chi^2 = 12.4$, df = 1, $p < .01$ with Bonferroni correction). In the second post hoc analysis, 100 (66.2%) of the switches were from mania/hypomania to depression or euthymia, while 51 (33.8%) of the switches were from depression (25 nights) or euthymia (26 nights) into mania/hypomania ($\chi^2 = 15.3$, df = 1, $p < .01$ with Bonferroni correction). The third post hoc analysis of the overnight data revealed that patients were as likely to switch from euthymia to depression or mania/hypomania as they were to switch from depression and mania/hypomania to euthymia. In this group, 119 (50.6%) of the switches were from euthymia into depression (93 nights) or mania/hypomania (26 nights), while 116 (49.4%) of the switches were from depression (54 nights) or mania/hypomania (62 nights) into euthymia ($\chi^2 = 0.017$, df = 1, p = N.S.). Data from the significant post hoc analyses are presented in Figure 3.

Fourteen of the 15 patients reported mood switches during the course of the night during the 3-month period examined. Ten of the patients had > 50% of their mood switches in the hypothesized direction (from mania/hypomania or euthymia into depression), while 4 of the patients had > 50% of their mood changes in the opposite direction (Table 2).

DISCUSSION

In this sample of rapid-cycling bipolar disorder outpatients on stable medication regimens, the patients were significantly more likely to switch into a more elevated mood (i.e., from depression into euthymia or mania/hypomania), rather than into a less elevated mood (i.e., from mania/hypomania into euthymia or depression) between the morning and evening ratings. Conversely, after an overnight sleep, the patients were significantly more likely to report a switch into a less elevated mood (i.e., from mania/hypomania into euthymia or depression) rather than into a more elevated mood (i.e., from depression or euthymia into mania/hypomania). Thus, in this group of patients, mood switches were significantly more likely to occur into mania/hypomania or euthymia during the day and into depression or euthymia overnight. Since all of our patients met criteria for rapid-cycling bipolar disorder, the generalizability of these findings to non-rapid-cycling bipolar patients is unknown.

Since all of our patients were being treated, we cannot rule out the possibility that medication contributed to some of the phenomena that we observed. However, there are several reasons why medication is unlikely to account for our findings. First, in this longitudinal design, each patient was on a stable medication regimen and served as his or her control. Thus, differences that we observed over time could not be due to the patients' medications, which remain unchanged over time. Second, the diurnal pattern of mood switches that we noted was present in a sample of patients on a wide variety of medications. It is unlikely that such a wide variety of psychotropic regimens would have similar effects on the diurnal pattern of mood switches. Third, as described in the introduction, our findings are consistent with the field's current understanding of the relationship between sleep, wakefulness, and mood, and therefore have considerable face validity.

The interpretation of these findings is complicated by the fact that day and night are each associated with a set of environmental and physiologic variables that could potentially affect mood. That is, day is usually associated with wakefulness, mental and physical activity, social contact, and light; while night (between bedtime and awakening) is usually associated with sleep, decreased activity, decreased social contact, and darkness. One or more of these factors could account for our findings, as could an endogenous mood rhythm. Several authors have suggested that dysregulation of an endogenous mood rhythm could account for the observation that depressed patients have more marked diurnal variation in mood than do normal subjects.[16,17] Alternatively, the sleep deprivation literature suggests that increased duration of wakefulness could account for our patients' increased activation during the day, while sleep could account for the switch into depression overnight.[2] If this hypothesis is true, then these data demonstrate that sleep is depressogenic not only when it occurs after sleep deprivation, but also in naturalistic conditions. However, as mentioned above, the data do not allow us to distinguish the effects of sleep or wakefulness from those of activity. That is, it is unclear whether sleep per se (or, rather, the lack of activity that it entails) accounts for the nighttime switch into depression, just as it is unclear whether wakefulness per se (or, rather, the mental and physical activity that generally accompanies it) accounts for the daytime switch into mania/hypomania.

The possible effects of light and darkness on mood in bipolar patients should also be considered. Light exposure could contribute to the switch into a more activated state during the day, while exposure to darkness could contribute to the switch into a less activated state overnight. Bright light treatment has been reported to trigger mania in some bipolar patients,[18,19] and preliminary data from our laboratory suggest that hypomanic patients placed in dim-light conditions tend to switch into euthymia. Indeed, Wehr et al.[20] presented data suggesting that light and sleep deprivation may have synergistic effects, raising the possibility that light exposure, sleep, mental and physical activity, and endogenous mood rhythms may all contribute to the phenomena that we observed.

We note with interest the fact that when systematically searching our patients' records for the 3-month periods of medication stability, we found that such periods were disproportionately likely to begin during the summer months. The reasons for this finding are unclear and bear future examination. Given the fact that the three major mood stabilizers are all more effective antimanic than antidepressant agents,[21] changes in the medication regimens of outpatients with rapid-cycling bipolar disorder are generally made because of severe depression. Some data indicate that bipolar patients may be less likely to become depressed in summer than winter[22]; if this is so, it may account for the increased likelihood of medication stability in the summer months. We plan to explore this question further in this and other data sets.

Our finding of diurnal variation in the direction of mood switches in patients with rapid-cycling bipolar disorder has several clinical implications. First, it suggests that both researchers and clinicians should note the time of day that mood ratings and clinical assessments are performed in rapid-cycling bipolar disorder patients (and possibly all bipolar patients), since assessments

performed later in the day are more likely to yield higher (i.e., more elevated) ratings than those performed early in the day. Second, in unipolar patients, the presence of diurnal variation may predict response to sleep deprivation,[23,24] phototherapy,[25,26] and other antidepressant treatments.[23,27] Our finding suggests that similar analyses should be performed in bipolar patients.

Studies with experimental designs could distinguish the contributions of sleep, activity, endogenous rhythms, and light to diurnal variation of mood in bipolar patients. Such studies could also elucidate the mechanisms underlying mood cycling in these patients and may suggest new therapeutic approaches. For example, these studies could provide information about the effects of light deprivation therapy and induced sleep during mania/hypomania, and about the effects of bright light therapy and increased activity during depression.

Drug names: bupropion (Wellbutrin), carbamazepine (Tegretol and others), clomipramine (Anafranil), clonazepam (Klonopin), dextroamphetamine (Dexedrine), doxepin (Sinequan and others), fluoxetine (Prozac), levothyroxine (Levothroid, Synthroid), lorazepam (Ativan and others), nortriptyline (Pamelor and others), phenelzine (Nardil), propranolol (Inderal and others), sertraline (Zoloft), tranylcypromine (Parnate), trazodone (Desyrel and others), triiodothyronine (Cytomel, Triostat), venlafaxine (Effexor).

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