Chronotherapy in Treatment-Resistant Depression

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CASE 1

The patient, JK, was a 20-year-old female college student with a history of major depressive disorder. She was admitted to the inpatient psychiatry unit after she was brought to an outpatient psychiatric clinic by friends who were concerned about her suicidal thoughts. On admission, the patient reported depression that had been present “for a long time” but had been worse for the previous 2 weeks. She had been sleeping only 5 hours per night, with frequent awakenings. The patient endorsed decreased energy, anhedonia, hopelessness, variable appetite, and decreased interest in socializing. She was unable to concentrate on reading for more than a few minutes, whereas she used to read “for hours at a time.” She had thoughts of cutting her wrists to commit suicide. Careful review of her medical history did not reveal periods of mania or hypomania. She did not smoke tobacco, rarely drank alcohol, and did not use illicit drugs.

The patient had been psychiatrically hospitalized once before, when she overdosed on six different medications and cut her wrists in a suicide attempt. Family history included a mother with bipolar disorder. Due to her mother’s illness, the patient frequently took responsibility for grocery shopping and paying bills, even as a young child. She never knew her biological father. Basic admission labs, including TSH, comprehensive metabolic panel, and CBC, were unremarkable. Urine drug screen and pregnancy test were negative. Cortisol level drawn at 4 p.m. (often elevated in severe depressions) was 11.8 mcg/dL (high normal range).

On admission, sertraline was started at 25 mg daily, with increases during the course of her stay to 150 mg daily. During the first 6 days on the unit, the patient showed no improvement, with ongoing dysphoric mood, intermittent periods of tearfulness, psychomotor retardation, and suicidal preoccupations. The idea of chronotherapy to augment the antidepressant effect of sertraline was introduced to her, and she consented.

On day 1 of the chronotherapy trial (see Table, page 167), the patient was kept awake throughout the night and not allowed to sleep until 5 p.m. of day 2. For
the subsequent days she followed the sleep-phase advance schedule, which gradually sets the patient back to a normal sleep pattern. She was allowed to use the computer and television on the unit during the nighttime to help stay awake, and the nursing staff provided her with pleasant company.

On day 3, JK reported an improved subjective mood, appetite, and concentration, and remission of suicidal ideation. She appeared brighter and had more animation in her facial features and gestures. During the daytime of day 4, she endorsed feeling depressed and “heavy,” although overall improved from admission. On day 5, after the completion of the sleep deprivation/sleep-phase advance trial, she was again seen to be tearful and distraught, with ongoing suicidal thoughts and a view of herself as a “failure.” Bupropion 150 mg daily was started at this time and increased to 150 mg twice daily after 2 days.

Over the next 3 days, she continued to endorse hopelessness and depression. However, over the following 2 to 3 days, her mood slowly began to improve, with remission of suicidal thoughts and an increasingly future-oriented and brighter outlook. She was subsequently discharged, 16 days after admission, with a follow-up plan for cognitive-behavioral therapy and medication monitoring through community mental health.

**Post-hospital course**

The patient experienced a month of remission post-hospitalization before slipping into a depression that was much less severe than that which led to her admission. This minor relapse was related to difficulty affording her outpatient medications, which in turn led to sporadic medication adherence. This depression was once again accompanied by thoughts of self-harm and continued until her outpatient team found a regimen of medication that she could afford and tolerate. Six months after discharge, the patient continued to receive outpatient therapy and medication monitoring, and has not required a hospitalization readmission. She applied to return to school after some time off. Looking back at the hospitalization, she found the sleep deprivation to be very helpful part of her recovery.

**CASE 2**

The patient was an 18-year-old female with a history of major depressive disorder; generalized anxiety disorder vs. social anxiety disorder; panic disorder without agoraphobia; and attention deficit disorder. She was admitted to the inpatient psychiatry unit after her parents brought her to the psychiatric emergency services for worsening depression with suicidal ideation.

The patient reported that she had had multiple episodes of depression and had been in therapy since the sixth grade. This most recent episode began approximately 1 year previously and had worsened acutely in response to the combined stressors of giving up her dog and subsequent arguments with her parents. She reported depressive mood most of her day every day, accompanied by feelings of worthlessness, helplessness, and hopelessness.

She also endorsed guilt over the effect of her depression on her siblings. In addition, she described anhedonia, and daily suicidal ideation with plans to overdose on her medications. She described anxiety with “low-grade” worrying all day and weekly panic attacks consisting of shortness of breath, hyperventilation, and tearfulness. These acute anxiety episodes generally lasted approximately 30 minutes and could be relieved with clonazepam.

The patient had been in treatment for depression for 7 years and was currently seeing a psychiatrist in her community. She had had up to 10 therapists over the years. Prior to admission, the patient was taking sertraline 100 mg daily and clonazepam 0.5 mg as

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
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</thead>
<tbody>
<tr>
<td>Kept up all night without any sleep (sleep deprivation)</td>
<td>Allowed to sleep from 5 p.m. to 12 p.m.</td>
<td>Allowed to sleep from 7 p.m. to 2 a.m.</td>
<td>Allowed to sleep from 9 p.m. to 4 p.m.</td>
<td>Allowed to sleep from 10 p.m. to 5 a.m.</td>
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Source: Casher MI et al.
needed for panic attacks. Previous medication trials included fluoxetine, bupropion, methylphenidate, dexamphetamine, lisdexamfetamine, and escitalopram, none of which led to sustained improvement. The patient had cut herself with a razor blade on one occasion 1 year prior to this admission. In addition, she had been hospitalized for depression and suicidal ideation at a community hospital for 5 days approximately 4 months prior to the current admission.

Her family history is significant for multiple maternal family members with depression including her mother, as well as alcohol abuse in her maternal uncle and grandfather.

The patient had graduated from high school and was accepted to a university, but had taken a year off to cope with her depression. Currently living with her parents, she reported constant fighting in the home. Colateral information from a counselor included a description of her family as “extremely dysfunctional.”

On admission, CBC, comprehensive metabolic panel, urinalysis, and TSH were all unremarkable. Urine drug screen and pregnancy test were negative. The patient was initially continued on sertraline 100 mg daily and clonazepam 0.5 mg was scheduled twice daily.

During the course of her stay, sertraline was increased to 200 mg daily. In addition, the patient was amenable to a trial of chronotherapy as adjunctive treatment for her depressed mood. Sleep deprivation began 2 days after admission with phase shift in her sleep schedule over the course of 5 days (see Table, page 167); concurrently, lithium augmentation was begun at a dose of 300 mg in the evening, with a final dose of 450 mg in the evening.

After 3 days of chronotherapy, the patient reported 1 day of improvement in her depressed mood, a decrease in intrusive suicidal thoughts, and decreased anxiety, but noted feeling “exhausted.” On day 7, upon completion of the sleep-phase shift and with a scheduled bed time of 10 p.m., the patient stated that, aside from 1 day of improved mood, her overall state was similar to that upon admission. She reported return of suicidal ideation and hopelessness, and spoke in a monotone voice with minimal spontaneous speech or range of affect. However, on day 8, the patient stated that she felt “better” and demonstrated future-oriented thinking.

This improvement in mood was evident and sustained during the remainder of the admission. The patient was discharged to home with her parents following a 14-day admission. Her treatment plan included continued outpatient follow-up with her established psychiatrist. Her future-orientation was evidenced by her plan to seek independence by obtaining a drivers’ license, getting a job, and residing with an aunt rather than remaining at home with her parents.

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Post-hospital course
The patient did well after discharge. Within a few months, she was able to attend a study abroad program and then returned to college. Her mood was reportedly stabilized with only occasional dips that were not of the magnitude of those prior to admission and perhaps related to less than optimal compliance with outpatient meds. Her mother described her “as better than she’s been in a long time.” Reviewing the hospitalization, her mother attributed much of her daughter’s improvement to the sleep deprivation therapy. Ten months later, the patient remained in psychiatric readmission.

DISCUSSION
A challenge to working with depressed patients in an inpatient setting is the time lag between full therapeutic response to medications and the concurrent demand for rapid “turn-around” of hospitalized patients. Nonpharmacological adjuvant therapies offer the potential to speed recovery and improve remission rates.

These cases depict the use of chronotherapy (wake therapy followed by sleep-phase advance) as an adjuvant therapy for depression in the inpatient setting. In the above cases, it could be argued that improvements were due primarily to medication; however, the fact that both patients had histories of treatment resistance with multiple medications suggests that the sleep manipulations played an augmenting role.

Chronotherapy may be defined as the manipulation of sleep/wake cycles to induce improvement in psychiatric symptoms. Wake therapy — alternatively called sleep deprivation with sleep-phase advancement — is an approach to chronotherapy that has the advantage of being relatively easy.
to implement in an inpatient setting. Additional benefits that have been reported include cost-effectiveness, tolerability, and reduced inpatient hospital days.\textsuperscript{3,4}

Chronotherapy has documented effectiveness in depressed patients. For example, in a 1990 review of 61 trials encompassing 1,700 patients, 59% of patients showed a significant decrease in depressive symptoms after a night of sleep deprivation, usually within 24 hours.\textsuperscript{5} This improvement is generally short-lived. However, a gradual return to a normal sleep cycle through a sleep-phase advancement schedule can often prevent the return of depressive symptoms.\textsuperscript{6}

Additionally, chronotherapy with sleep deprivation followed by sleep-phase advancement can be combined with light therapy, and the combination of all three of these chronotherapeutic techniques can lead to even greater stability of the gains made with sleep manipulation.\textsuperscript{7}

Two recent trials have employed these combined chronotherapeutic interventions in depressed patients. Moscovici and Kotler describe the use of sleep deprivation, light therapy, and sleep-phase advance in 12 patients with moderate to severe depression.\textsuperscript{3} With this intervention, patients achieved significant improvement in levels of depression that were sustained at 4 weeks. Similarly, Wu and colleagues\textsuperscript{8} describe the use of sleep deprivation, bright light, and sleep-phase advance as ad-

junctive therapies in patients with bipolar depression. Patients were randomized to augmentation with chronotherapy vs. medication-only groups. The patients in the chronotherapy group experienced significant decreases in depression (vs. medication-only patients) that were sustained at 7 weeks.

Antidepressant medications and lithium have also been shown to reduce the relapse rates associated with wake therapy alone.\textsuperscript{6} Our two patients appear to have benefited from co-administration of medications. We speculate that the robustness of the initial improvements would have been additionally strengthened by co-administration of light therapy.

There appear to be multiple mechanisms of action for chronotherapy in depression. Sleep deprivation increases levels of neurotransmitters including serotonin, dopamine, and norepinephrine. Brain metabolism is also affected.\textsuperscript{2,9,10} Neuroimaging studies\textsuperscript{2,9,10} have documented that sleep deprivation normalizes elevated baseline metabolic rates in the cingulate cortex — a finding that parallels response to treatment and antidepressant therapy in depressed patients. Other areas implicated in response to treatment include regions of the frontal lobe, including the dorsolateral prefrontal cortex.\textsuperscript{11} Finally, alteration of the sleep architecture (disrupted in depressive episodes) constitutes another putative mechanism of action.\textsuperscript{12}

**REFERENCES**


