

The bedtime solution

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Depressed and suicidal, Ms. W had not found relief after years of medication trials and electroconvulsive therapy. Then her psychiatrists tried a novel intervention.

CASE Refractory depression

Ms. W, age 38, is brought to the emergency department after her son finds her unresponsive and calls 911. Suffering from worsening depression, she wrote a note telling her children good-bye, and overdosed on zolpidem from an old prescription and her daughter's opioids. After being evaluated and medically cleared in the emergency department, Ms. W was admitted to the psychiatric unit.

Ms. W has a history of recurrent major depressive disorder that developed after she was sexually abused by a relative as a teen. She also has bulimia nervosa, alcohol dependence, and posttraumatic stress disorder. She was hospitalized twice for depression and suicidality but had not previously attempted suicide. In the mid-to-late 1990s, she had trials of paroxetine, clomipramine, lithium, and bupropion.

She was seen regularly in our outpatient psychiatry clinic for medication management and supportive psychotherapy. Since being followed in our clinic starting in early 2005, she has had the following medication trials:

- fluoxetine, citalopram, venlafaxine XR, and duloxetine for depression
- atomoxetine, buspirone, liothyronine, risperidone, and aripiprazole for antidepressant augmentation
- lorazepam, clonazepam, and gabapentin for anxiety
- zolpidem and trazodone for insomnia

- nortriptyline for migraine headache prophylaxis.

Some medications were not tolerated, primarily because of increased anxiety. Those that were tolerated were adequate trials in terms of dose titration and length. High-dose fluoxetine (80 mg/d) augmented by risperidone (0.375 to 0.5 mg/d) produced the most reliable and significant improvement.

Ms. W had 2 courses of electroconvulsive therapy (ECT) totaling 30 treatments—most recently in 2007—that resulted in significant memory loss with limited benefit. Premenstrual worsening of depression and suicidality were noted. In collaboration with her gynecologist, Ms. W was treated with a 3-month trial of leuprolide to suppress her ovarian axis, which was helpful. In 2008 she underwent bilateral oophorectomy. She has not had symptoms of mood elevation or psychosis. Family history includes schizophrenia, depression, anxiety, and alcoholism.

In the months before hospitalization, Ms. W had been increasingly depressed and intermittently suicidal, although she did not endorse a specific plan or intention to harm herself because she was concerned about the impact suicide would have on her children. Weight gain with risperidone had reac-

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Sleep deprivation is a rapid, effective treatment for depression but up to 80% of patients experience depressive relapse

tivated body image issues, so Ms. W stopped taking this medication 2 weeks before hospitalization. Her depression became worse, and she began using her husband's hydrocodone/acetaminophen prescription.

What depression treatment would you consider next for Ms. W?

- retrial of fluoxetine and an atypical antipsychotic with a lower potential for weight gain, such as aripiprazole
- lithium with a tricyclic antidepressant
- bilateral ECT
- chronotherapy utilizing sleep deprivation

The authors' observations

Approximately 40% of patients with major depression fail to respond to an initial antidepressant trial.¹ An additional 50% of these patients will be treatment-resistant to a subsequent antidepressant.¹ Patients may be progressively less likely to respond to additional medication trials.²

One of the most rapid-acting and effective treatments for unipolar and bipolar depression is sleep deprivation. Wirz-Justice et al³ found total or partial sleep deprivation during the second half of the night induced rapid depression remission. Response rates range from 40% to 60% over hours to days.⁴ Sleep deprivation also can reduce suicidality in patients with seasonal depression.⁵ This treatment has not been widely employed, however, because up to 80% of patients who undergo sleep deprivation experience rapid and significant depressive relapse.⁴

Sleep deprivation usually is well tolerated. Potential side effects include:

- headache
- gastrointestinal upset
- fatigue
- cognitive impairment.

Less often, patients report worsening of depressive symptoms and, rarely, suicidal ideation or psychosis.⁴ Mania or hypomania are potential complications of sleep loss for patients with bipolar or unipolar depression. In a review, Oliwenstein⁶ sug-

gested that rates of total sleep deprivation-induced mania are likely to be similar to or less than those reported for antidepressants. Because sleep deprivation can induce seizures, this therapy is contraindicated for patients with epilepsy or those at risk for seizures.⁴

What adjuncts could help sustain a depressed patient's response to partial sleep deprivation?

- light therapy
- lithium
- antidepressants
- sleep-phase advance
- all of the above

Researchers have successfully explored strategies to reduce the rate of depressive relapse after sleep deprivation, including coadministering light therapy, antidepressants, lithium (particularly for bipolar depression), and sleep-phase advance.⁴ Sleep-phase advance involves shifting the sleep-wake schedule to a very early sleep time and wake-up time (such as 5 PM to midnight) for 1 day, and then pushing back this schedule by 1 or 2 hours each day until the patient is returned to a "normal" sleep schedule (such as 10 PM to 5 AM). Researchers have demonstrated that sleep-phase advance can have antidepressant effects.⁷

TREATMENT Sleep manipulation

Ms. W is continued on fluoxetine, 80 mg/d. We opt for a trial of partial sleep deprivation and sleep-phase advance for Ms. W because of the severity of her depression, her multiple ineffective or poorly tolerated medication trials, and limited benefit from ECT. This treatment involves instituting partial sleep deprivation the first night and subsequently advancing her sleep phase over the next several days (*Table 1, page 96*).

Although she is sleepy the morning after partial sleep deprivation, Ms. W reports a marked improvement in her mood, decline in hopelessness, and absence of suicidal

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Table 1**Ms. W's chronotherapy protocol: Hours permitted for sleep***

	Day number				
	1	2	3	4	5
Sleep deprivation	9 PM to 2 AM				
Sleep-phase advance		5 PM to midnight	7 PM to 2 AM	9 PM to 4 AM	10 PM to 5 AM

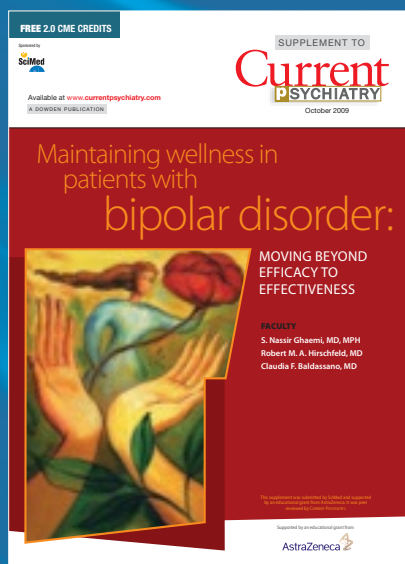
*Treatment was implemented while Ms. W was hospitalized

ideation. She continues the sleep-phase advance protocol for the next 3 nights and participates in cognitive-behavioral therapy groups and ward activities. Psychiatric unit staff support her continued wakefulness during sleep manipulation. Because Ms. W had

previously responded to antidepressant augmentation with an atypical antipsychotic we add aripiprazole and titrate the dosage to 7.5 mg/d. We also continue fluoxetine, 80 mg/d, and add trazodone, 100 mg at bedtime, and hydroxyzine, 25 mg as needed.

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The authors' observations

Chronotherapy incorporates manipulations of the sleep/wake cycle such as sleep deprivation and dark or light therapy. It may use combinations of interventions to generate and sustain a response in patients with depression. In a 4-week pilot study, Moscovici et al⁸ employed a regimen of late partial sleep deprivation, light, and sleep-phase advance to generate and maintain an antidepressant response in 12 patients. Benedetti et al⁹ used a similar regimen plus lithium to successfully treat bipolar depression and sleep-phase advance to continue that response in 50% of patients for 3 months.

Circadian rhythms affect the function of serotonin (5-HT), norepinephrine, and dopamine.^{9,10} In a manner similar to antidepressant medications, sleep deprivation may up-regulate or otherwise alter these neurotransmitters' function. In animals, sleep deprivation increases serotonin function.¹¹ Several hypothetical mechanisms of action for sleep deprivation and other types of chronotherapies have been suggested (*Table 2*).¹¹⁻¹⁴

Chronotherapies may affect function in brain pathways, as demonstrated by neuroimaging with positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). Depression has been associated with increased or decreased brain activity measured by PET or fMRI in regions of the limbic cortex (cingulate and anterior cingulate) and frontal cortex.¹²

Wu et al¹³ examined patients treated for depression with medication and total sleep deprivation therapy. Response to treatment was associated with increased function in the cingulate, anterior cingulate, and medial prefrontal cortex as measured by PET. In contrast, mood improvement was associated with reduced baseline activity in the left medial prefrontal cortex, left frontal pole, and right lateral prefrontal cortex.

Researchers have noted the convergence of sleep-wake rhythms and abnormalities seen in depression and the subsequent link

Table 2**Sleep deprivation for depression: Possible mechanisms**

Mechanism	Components
Alterations to neurotransmitter function	Serotonin, norepinephrine, dopamine ¹¹
Alterations to endogenous circadian pacemaker function	Increased gene expression ¹⁴
Changes in perfusion/activity of brain regions	Anterior cingulate, frontal cortex regions ^{12,13}

Table 3**Factors that suggest a patient might respond to chronotherapy**

Diurnal mood variation ¹⁵
Endogenous depression including insomnia and anorexia ¹⁶
Abnormal dexamethasone suppression ¹⁷
High motivation for treatment
Bipolar depression (possibly) ⁹

with improved sleep-wake cycles related to depression remission. Bunney and Potkin¹⁴ note the powerful effect of zeitgebers—environmental agents that reset the body's internal clock. They suggested that sleep deprivation may affect the function of “master clock” genes involved in controlling the biological clock. These effects on the suprachiasmatic nucleus hypothalamic pacemaker may improve mood by altering control of genetic expression through chromatin remodeling of this master clock circuit.

Certain factors may increase the likelihood that a patient may respond to chronotherapy (*Table 3*).^{9,15-17}

OUTCOME Lasting improvement

Ms. W's mood improvement is sustained during her week-long hospitalization. At discharge she

Clinical Point

Sleep-phase advance may reduce the rate of depressive relapse after sleep deprivation

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Related Resource

• Wu JC, Kelsoe JR, Schachat C, et al. Rapid and sustained antidepressant response with sleep deprivation and chronotherapy in bipolar disorder. *Biol Psychiatry*. 2009; 66(3): 298-301.

Drug Brand Names

Aripiprazole • Abilify	Leuprolide • Lupron
Atomoxetine • Strattera	Liothyronine • Cytomel
Bupropion • Wellbutrin	Lithium • Eskalith, Lithobid
Buspirone • BuSpar	Lorazepam • Ativan
Citalopram • Celexa	Nortriptyline • Aventyl
Clomipramine • Anafranil	Paroxetine • Paxil
Clonazepam • Klonopin	Risperidone • Risperdal,
Duloxetine • Cymbalta	Risperdal Consta
Fluoxetine • Prozac	Trazodone • Desyrel
Gabapentin • Neurontin	Venlafaxine XR • Effexor XR
Hydrocodone/APAP • Vicodin	Zolpidem • Ambien
Hydroxyzine • Atarax, Vistaril	

Disclosures

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is hopeful about the future and does not have thoughts of suicide.

At subsequent outpatient visits up to 4 months after discharge, her depressive symptoms remain improved. Patient Health Questionnaire scores indicate mild depression, but Ms. W is not suicidal. She maintains a sleep schedule of 10 PM to 6:30 AM and undergoes 10,000 lux bright light therapy, which she began shortly after discharge, for 30 minutes every morning. She works more productively in psychotherapy, focusing on her eating disorder and anxiety.

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Clinical Point

Chronotherapies may work by altering the function of serotonin, norepinephrine, and dopamine

Bottom Line

Deliberately altering depressed patients' sleep cycle can elevate and improve mood. Ongoing sleep manipulation, light therapy, or medications may be required to sustain response. The mechanisms of action for these treatments may include 'resetting' hypothalamic pacemaker activity and gene expression.