

# Unrelenting depression: 'I would rather be dead than feel this way'

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## How would you handle this case?

Answer the challenge questions at [MDedge.com/psychiatry](http://MDedge.com/psychiatry) and see how your colleagues responded

Mr. J, age 56, presents to the ED with suicidal ideation. He reports that his current depressive episode is the most severe he's ever experienced. How would you approach his treatment?

### **CASE** Suicidal ideation, flare-up of ulcerative colitis

Mr. J, age 56, who has a history of major depressive disorder (MDD), generalized anxiety disorder (GAD), and ulcerative colitis (UC), presents to the emergency department (ED) with suicidal ideation and a plan to overdose on his medications. He reports no current emotional or financial stressors in his personal life. Home medications documented at the time of his arrival to the ED include sertraline, 100 mg/d, bupropion, 150 mg/d, buspirone, 10 mg 3 times daily, diazepam 10 mg 3 times daily, as needed, adalimumab, 40 mg IM every 2 weeks, and diphenhydramine, 50 mg every night.

A recent flare-up of UC resulted in Mr. J being placed on a 15-week prednisone taper, beginning at 80 mg/d and decreasing by 5 mg weekly, which was completed 2 weeks before he presented to the ED. After completing the prednisone taper, Mr. J went to his primary care physician (PCP) on 3 separate occasions due to episodes of severe depression. Although the PCP prescribed multiple medications to target Mr. J's depressive symptoms, he continued to decline.

Subsequently, Mr. J came to the ED and is admitted to the psychiatric unit for safety and stabilization. Upon admission, Mr. J becomes bedridden, and reports that his current depressive episode is the most severe

that he has ever experienced in his more than 30 years of having MDD. He says that neither bupropion nor buspirone are helping with his depression, anxiety, or any related symptom.

### Which of Mr. J's medications, histories, or previous diagnoses could contribute to the onset of a depressive episode?

- a) UC
- b) diazepam
- c) adalimumab
- d) prednisone discontinuation

### The authors' observations

At admission, all of Mr. J's home medications, except sertraline and adalimumab, which had been prescribed to treat UC (*Box*,<sup>1,2</sup> page 49), were discontinued. His diazepam was discontinued because the clinician felt it may have been contributing to Mr. J's inability to walk or get out of bed. Diazepam was not tapered because it was initiated 7 days prior to admission and was

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thought to be exacerbating his depression and suicidal ideation. Bupropion and buspirone, which were initiated 2 weeks prior, were discontinued because Mr. J reported that neither medication was helping with his depression, anxiety, or any related symptom.

### **EVALUATION** Poor appetite, anxiety, and continued suicidality

During evaluation, vital signs, laboratory findings, and diagnostic testing are found to be unremarkable. Mr. J's presentation and complaints are entirely subjective, and include poor appetite, fatigue, difficulty sleeping, sorrow, anxiety, and continued suicidality. Mr. J reports that he feels miserable, which is reflected by his poor eye contact, soft speech, and body language.

### **The authors' observations**

MDD is a mood disorder characterized by depressed mood and/or loss of interest or pleasure for more than 2 weeks.<sup>3</sup> First-line pharmacotherapy for MDD includes monotherapy with a selective serotonin reuptake inhibitor (SSRI), serotonin-norepinephrine reuptake inhibitor (SNRI), mirtazapine, or bupropion.<sup>4</sup> Medication selection is typically based on patient-specific factors, adverse effect profile, drug-drug interactions, and cost. Other treatments include electroconvulsive therapy (ECT) or cognitive-behavioral therapy (CBT).<sup>4,5</sup> Augmentation agents, such as second-generation antipsychotics, lithium, thyroid hormone supplementation, buspirone, anticonvulsants, and combinations of antidepressants, may also be considered.<sup>4</sup>

### **TREATMENT** Condition worsens

On Day 2 of hospitalization, Mr. J is started on aripiprazole, 5 mg/d, clonazepam, 1 mg twice daily, and melatonin, 5 mg, each night for sleep. Aripiprazole, 5 mg/d, is initiated

### **Box**

## Ulcerative colitis and depressive episodes

Ulcerative colitis (UC) is a chronic condition associated with inflammation in the colon causing extreme abdominal discomfort during acute flare-ups. Moderate to severe UC flare-ups are commonly treated with corticosteroids due to these medications' anti-inflammatory properties. Although rare, corticosteroid withdrawal has been documented to induce episodes of depression. The pathophysiology of corticosteroid withdrawal inducing neuropsychiatric sequelae remains unclear; however, it is thought to be due to hypothalamic-pituitary-adrenocortical suppression.<sup>1</sup> Fardet et al<sup>2</sup> concluded that incident rates per 100 person-years at risk during the withdrawal period were 11.1 (95% confidence interval, 10.0, 12.3) for depression.

### **Clinical Point**

Although rare, corticosteroid withdrawal has been documented to induce episodes of depression

as an adjunct to sertraline for MDD because Mr. J reports feeling much worse and continues to report that he would "rather die than feel this way." Mr. J begins to believe that his current state is his new baseline, and that feeling better is no longer possible.

On Day 3 of hospitalization, records are obtained from a clinician at an outside facility who previously treated Mr. J; this clinician suspected Mr. J may have bipolar disorder. On Days 3 and 5 of hospitalization, aripiprazole is titrated to 10 mg/d, and then to 20 mg/d, respectively. On Day 6, sertraline is increased to 150 mg/d because Mr. J continues to report low mood and limited sleep and is less and less interactive during interviews. He remains suicidal, and because bipolar depression is suspected (although this is not a clear diagnosis in his records), a trial of divalproex sodium, 250 mg twice daily, is initiated on Day 6.

By Day 8 of hospitalization, there is no notable change in Mr. J's depressive symptoms. On Day 9, sertraline is increased to 200 mg/d, with little improvement from Mr. J's perspective. The multidisciplinary team evaluates him, and when directly asked,

### Clinical Point

The time to efficacy with mirtazapine is approximately 2 to 4 weeks, but some symptoms may improve in the first week

Mr. J cites his 4 greatest complaints to be poor sleep, fatigue, no appetite, and depressed mood. Once again, he states, "I would rather be dead than go on feeling this way."

#### What further interventions might provide relief for Mr. J's primary complaints?

- a) adjunctive thyroid hormone supplementation
- b) adjunctive ECT
- c) adjunctive mirtazapine
- d) adjunctive lithium

#### The authors' observations

Due to Mr. J's severe, unrelenting depressive episode, the treatment team obtained his informed consent to undergo ECT. On Day 9, before initiating ECT, the pharmacist recommended mirtazapine, even though the patient weighed almost 89 kg (196.21 lb) and had a body mass index of 27.8 kg/m<sup>2</sup>. The treatment team thought that mirtazapine augmentation could potentially help the sertraline work more quickly while targeting Mr. J's 4 greatest complaints.

Mirtazapine is a central alpha-2 antagonist or noradrenergic and specific serotonergic antidepressant (NaSSA) that works through antagonism of the presynaptic alpha-2 adrenergic receptors to indirectly regulate release of monoamines and increase the release of serotonin and norepinephrine.<sup>6</sup> Additionally, mirtazapine has antagonist actions at 5HT<sub>2A</sub>, 5HT<sub>2C</sub>, 5HT<sub>3</sub>, and histamine-1 receptors.<sup>6</sup> Potential adverse effects include drowsiness and increased appetite leading to weight gain.<sup>7</sup> Mirtazapine's therapeutic efficacy is similar to SSRIs for treating depression.<sup>4</sup> Mirtazapine in combination with an SNRI has been referred to as "California rocket fuel" due to the theoretical pharmacologic synergy and resulting strong antidepressant action.<sup>6</sup> It was hypothesized that similar effects could be seen by augmenting the SSRI sertraline with mirtazapine.

The time to efficacy with mirtazapine is approximately 2 to 4 weeks, but anxiety

symptoms and poor sleep or insomnia may improve in the first week.<sup>8</sup> Studies have suggested the possibility of a more rapid onset of efficacy with mirtazapine than with SSRIs, as well as potential response acceleration in MDD and other psychiatric illnesses such as anxiety disorders or obsessive-compulsive disorder (OCD).<sup>9,10</sup> A review that included several double-blind studies and compared mirtazapine with SSRIs found the amount of responders with persistent improvement with onset in Week 1 was more pronounced with mirtazapine.<sup>9</sup>

Augmenting an SSRI with mirtazapine is a potential therapeutic option because it can help boost the efficacy of the prescribed SSRI while enhancing appetite and blunting the activating or anxiety-like effects of some SSRIs, which may help with relaxation and sleep.<sup>4</sup> The combination of an SSRI plus mirtazapine has been studied in patients with MDD, posttraumatic stress disorder, and OCD; it was found to improve symptoms of those conditions due to the medications' complementary mechanisms of action.<sup>4,11-13</sup> Also, mirtazapine has been shown to decrease the rates of relapse after an acute phase of depression.<sup>4,14</sup>

#### OUTCOME Rapid improvement

On Day 9, Mr. J receives the first dose of mirtazapine, 7.5 mg at bedtime. On Day 10, when Mr. J wakes, his mood is notably improved. He is more interactive (sitting up in bed reading and making eye contact with the staff during an interview), and he reports improved sleep and eats most of his breakfast.

After receiving 3 doses of mirtazapine, Mr. J reports that he feels back to his normal self; he is interactive, alert, and eating well. Due to the rapid improvement in mood, ECT is discontinued, and he does not receive any ECT treatment during the remainder of his hospitalization.

On Day 11, divalproex is discontinued. Because Mr. J receives only 5 days of therapy with this agent, his divalproex level is not

checked. At this point, the treatment team feels confident in ruling out bipolar disorder.

On Day 15, Mr. J is discharged with sertraline, 200 mg/d, mirtazapine, 7.5 mg/d at 7 PM, aripiprazole, 20 mg/d, clonazepam, 1 mg twice daily as needed for anxiety, melatonin 5 mg/d, and adalimumab, 40 mg IM every 2 weeks. Discharge instructions include a follow-up in 2 weeks to evaluate continuation strategies for the discharge medications.

Ten months after his depressive episode, Mr. J has had no further admissions at the hospital where he received the treatment described here.

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## Related Resources

- Watanabe N, Omori IM, Nakagawa A, et al. Mirtazapine versus other antidepressant agents for depression. *Cochrane Database Syst Rev.* 2011;(12):CD006528.
- Kenna HA, Poon AW, de los Angeles CP, et al. Psychiatric complications of treatment with corticosteroids: review with case report. *Psychiatry Clin Neurosci.* 2011;65(6):549-560.

#### Drug Brand Names

Adalimumab • Humira	Divalproex • Depakote,
Aripiprazole • Abilify	Depakote ER
Bupropion • Wellbutrin, Zyban	Lithium • Eskalith, Lithobid
Buspiron • Buspar	Mirtazapine • Remeron
Clonazepam • Klonopin	Prednisone • Deltasone
Diazepam • Valium	Sertraline • Zoloft
Diphenhydramine • Benadryl	

## Clinical Point

**Augmenting an SSRI with mirtazapine can help boost the efficacy of the prescribed SSRI**

## Bottom Line

Evidence for the treatment of major depressive disorder induced by corticosteroid withdrawal is limited. Despite trials of agents from multiple medication classes, the depressive episode may not improve. Adding mirtazapine to a selective serotonin reuptake inhibitor or serotonin-norepinephrine reuptake inhibitor may prove successful.