Treating depression in a mother of five: What to do when the first step fails

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ABSTRACT

What should one do with a depressed patient who does not get better? If depression does not respond to an antidepressant given in adequate doses for an adequate time, logical next steps include increasing the dose, adding a different medication, or adding a nonpharmacologic therapy. Or one can reconsider the diagnosis.

OCTOBER 25, 2001. A 34-year-old woman visits her primary care physician and says that she is overwhelmed by stress: she has five children, aged 2 to 8 years, her husband has had a recent recurrence of Hodgkin disease and is undergoing chemotherapy, and her house is being remodeled and is in disarray.

She reports fatigue, loss of her usual motivation and enthusiasm, trouble concentrating, trouble getting out of bed, and tearfulness without provocation. She denies thoughts of suicide, symptoms of mania or psychosis, or alcohol and drug abuse.

Her general health is good except for recurrent sinusitis and viral syndromes. She is taking fluoxetine (Sarafem) 20 mg daily as needed, usually before menses.

Physical examination: heart rate 72, blood pressure 130/80 mm Hg, heart and lungs normal. She is pleasant, appropriate, and calm, but tearful.

This paper discusses therapies that are experimental or that are not approved by the US Food and Drug Administration for the use under discussion.

WHAT IS THE DIAGNOSIS?

1 Which diagnosis from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)[1] is supported by the available information?

- ❑ Reactive depression
- ❑ Major depression, recurrent: moderate
- ❑ Major depression, single episode: moderate
- ❑ Adjustment disorder with depressed mood
- ❑ Cannot make a DSM-IV diagnosis

The last answer is correct. "Reactive depression" is an outdated term, and not enough information is given to choose any of the other DSM-IV diagnoses with certainty. Although she has enough symptoms for major depression, we do not know how long this episode has lasted, nor do we know about her past psychiatric history. Another consideration is seasonal affective disorder because of the time of year.

It is also important to ask about family psychiatric history, since depression is often familial.

Treatment depends on the type of depression diagnosed. Adjustment disorder with depressed mood means that the depressed individual does not fulfill the symptom-and-time criteria of a major depressive episode, and that while psychotherapy may be indicated, antidepressant medication is not. Recurrent major depressive episodes typically call for treatment beyond the 4 to 6 months of the continuation phase.

Diagnosing depression: five of nine symptoms

To qualify for a diagnosis of major depression, a patient must have a problem for at least 2

She reports fatigue, loss of motivation, trouble getting out of bed, and tearfulness

weeks in five of nine areas, which can be remembered with the mnemonic SIGECAPS:

- Sleep
- Interest (or motivation)
- Guilt (or poor self-esteem)
- Energy
- Concentration
- Appetite
- Psychomotor activity
- Suicidal ideation.

A patient with uncharacteristically low self-esteem who is suicidal is likely to have a major depressive disorder. Without those two factors, the problem is more likely to be a reaction to stress or a medical disorder that mimics depression.

For those with recurrent major depression or with a depressive diathesis, depression can occur spontaneously, without a seemingly adequate stress trigger. Depression itself makes life seem more stressful, creating a vicious cycle that perpetuates depression. People who are depressed also tend to ruminate about past losses and have negative thoughts. The diagnosis of depression, however, is made exclusive of whether stress is present or absent.

All instructions to depressed patients should be specific, concrete, and in writing

Five axes

Psychiatrists use five axes to formulate psychiatric diagnoses.

Axis I: Primary psychiatric syndrome (such as schizophrenia or a mood or anxiety disorder)

Axis II: Personality disorder (includes developmental disorders or mental retardation)

Axis III: Medical disorders that may be relevant to axis I (such as acquired immunodeficiency syndrome, stroke, or Parkinson disease)

Axis IV: Stressors (type and severity)

Axis V: Global assessment of function (a scale included in the DSM-IV-TR).[1] Scores range from 1 (persistent danger of severely hurting self or others) to 100 (superior functioning without symptoms).

Case continued

This patient seems to have a major depressive episode, either single or recurrent, and possibly with a seasonal component. There is no indication of a personality disorder or significant medical illness. Her stressors at the moment are moderate, though in danger of becoming severe because of her husband's serious illness and the responsibility of parenting five young children. Her global assessment of function is around 60 (moderate difficulty).

INITIAL TREATMENT

2 What is the first step in treating this patient?

- ❑ Start a program of graded aerobic exercise
- ❑ Refer for psychotherapy
- ❑ Start light therapy
- ❑ Increase the dosage of fluoxetine
- ❑ Wait and see for a couple of weeks
- ❑ There is no single correct answer

Many primary care physicians appropriately take a wait-and-see approach for minor depressive episodes, which usually remit spontaneously.

In this case, her physician concludes that the problem is a major depressive episode and recommends that she increase her fluoxetine to 40 mg daily, start aerobic activity, "find time for herself" (admittedly hard for a mother of five small children), take a weekend get-away with her husband when his chemotherapy is finished, report back in 1 week or as needed, and, if symptoms worsen, go to an emergency department.

Because patients with depression have difficulty concentrating, all recommendations should be specific, concrete, and written.

SIX WEEKS LATER

December 6, 2001. The patient visits her physician complaining of a lingering respiratory illness. She reports that her depression resolved, and she has tapered herself off the fluoxetine.

February 28, 2002. The patient phones her physician in tears, requesting bupropion (it is unclear why she asked for this particular medicaion).

Several forms of bupropion are available. The original formulation was given three times a day because of its short half-life, but now a sustained-release (SR) formulation is available that is given twice a day, and an even longer-lasting formulation (XL) is given

once a day. Therefore, the preferred instructions for use of bupropion SR would have been to take two 100-mg tables, or one 200-mg tablet, twice daily. However, the physician prescribes it in the SR form, 100 mg four times a day.

March 28, 2002. The patient comes to her physician's office, appearing animated and cheerful. She feels fully recovered and asks if she can safely discontinue bupropion.

WHEN CAN TREATMENT BE STOPPED?

3 What do you recommend?

- ❑ Begin tapering off bupropion
- ❑ Continue bupropion for at least 4 months after full remission is achieved
- ❑ Continue bupropion indefinitely

The physician appropriately recommended that she continue bupropion for a total of 6 to 9 months before considering tapering off. It sometimes takes 3 months to achieve remission of the initial episode; the medicine should then be continued for an additional 4 to 6 months to reduce the risk of relapse.

June 3, 2002. The patient calls in to report tearfulness, fatigue, and malaise.

June 6, 2002. She visits her physician and says she is feeling well. She and her physician decide to start tapering off bupropion.

November 1, 2002. She calls and asks to resume bupropion.

November 12, 2002. She calls and reports that 1 week ago she was feeling so bad that she increased her dosage of bupropion SR back to 200 mg twice daily, but that it still does not seem to be working.

November 15, 2002. She sees her physician and reports feeling like she did the year before: tearful, sluggish, and depressed, without delusional thinking or suicidal ideation. The only suggestion of mania is that she says she is somewhat compulsive about making lists for herself, although she says she has a lot of energy and enjoys doing this. She has been trying to get an appointment with the psychiatry department, and she has had difficulty getting through: they told her she cannot be seen for 3 weeks.

TABLE 1

Maximum recommended doses of antidepressant drugs

DRUG	DOSE (MG/DAY) MAXIMUM
SSRIs	
Citalopram	60
Escitalopram	20
Fluoxetine	60
Sertraline	200
Paroxetine	50
NSSRIs	
Duloxetine	60
Venlafaxine	375
Other	
Bupropion	450
Mirtazapine	45
Nefazodone	600

SSRI = selective serotonin reuptake inhibitors
NSRIs = norepinephrine-serotonin reuptake inhibitors

DATA FROM THE PHYSICIAN'S DESK REFERENCE.

4 How would you classify this depressive episode?

- ❑ Treatment-resistant
- ❑ A relapse
- ❑ A recurrent episode

A recurrent episode is correct. Relapse pertains to reemergence of an index episode of illness, whereas recurrent describes a new episode.

TREATMENT RESISTANCE

This patient's depression is not responding to medication, but it does not qualify as treatment-resistant, which is defined as failure to achieve and sustain euthymia with adequate treatment.

Adequate dose, duration

The definition of "adequate treatment" varies: Fava and Davidson[2] define it as a standard dosage of antidepressant medication (TABLE 1) taken continuously for at least 6 weeks; others[3] define it as two trials of antidepressants

First, make sure you've prescribed adequate doses for an adequate duration

from different classes; still others define it as trials of all pharmacological treatments and electroconvulsive therapy.

Most studies indicate that a patient must take a medicine continuously for 6 weeks before response can be determined. Others suggest that 8 weeks is needed. For fluoxetine, 12 weeks may be needed to see an optimal response because of its long half-life.[2]

In practice, because depression is distressing, physicians tend to increase the dose more quickly if the patient does not seem to be responding after a few weeks.

Treatment resistance is common

Fava and Davidson[2] analyzed 36 studies and determined that over one third of participants had depression that was either partially or fully resistant to treatment.

Nearly 15% of the general population[4] and about 20% of patients in primary care[5] suffer from some kind of mental disorder, including depressive and anxiety disorders.

This, however, does not necessarily mean that a primary care physician will see many cases of treatment resistance. Out of 1,000 patients in primary care, about 135 are depressed. Of these, about 60% (81) are detected. A little more than half (43) end up being treated,[6] and only 16 adequately so. About 8 will have treatment-resistant depression.

Only about 0.8% of primary care patients have treatment-resistant depression

WHAT TO DO NEXT?

5 The patient resumed taking bupropion about 1 month ago and still feels bad. What is your next step?

- ❑ Continue the same dose
- ❑ Increase the dosage
- ❑ Switch to another antidepressant
- ❑ Augment with another medication
- ❑ Add or switch to a nonpharmacologic strategy

Nonpharmacologic strategies, such as psychotherapy, cognitive behavioral therapy, interpersonal therapy, marital therapy, family therapy, and supportive therapy, tend to be overlooked. Most of these patients need at least supportive therapy, and many would also benefit from marital therapy. Exercise is an effective antidepressant but is typically not sufficient, nor is yoga, dance, or massage therapy.

Light therapy is effective for seasonal affective disorder, and may be particularly important in northern locations in the fall and winter. Different appliances are available. It would be an appropriate choice for this patient, especially because both of her severe episodes started in the winter.

In deciding which option to use, I recommend discussing various options and leaving the decision up to the patient, who often has a good sense of what will work and knows what he or she is willing to do.

The bupropion dose could be increased to 450 mg daily, but the risk of seizures increases at higher doses.

Another medication can be added,[2,3] such as:

- Lithium 300 mg twice daily
- Liothyronine 25 μg or levothyroxine 50 μg. (The patient need not have abnormal thyroid function.)
- A second antidepressant
- An atypical antipsychotic agent (olanzapine, risperidone)[7,8]
- A central nervous system stimulant: methylphenidate, dextroamphetamine, or modafinil. Modafinil causes less cardiovascular activation and is particularly helpful for residual fatigue, but it is not approved by the US Food and Drug Administration (FDA) for this indication.[9]

Case continued

Based on the research cited above, the patient should have been encouraged to continue bupropion SR at the same dose for another 2 to 4 weeks. However, her primary care physician adds a second antidepressant, citalopram 10 mg daily, to the bupropion she is already taking.

December 9, 2002. The patient calls to report that she saw the psychiatrist and now feels great.

February 22 to 27, 2003. She is admitted to a psychiatric facility. The bupropion and citalopram are stopped and she is started on paroxetine and quetiapine and then released.

March 10, 2003. The patient calls to report that she is feeling terrible, as if she will "jump out of her skin." She is tearful and has psychomotor agitation, and because of this she stopped the paroxetine the day before.

She is readmitted and her medications are switched to venlafaxine and olanzapine. She recovers rapidly and is discharged after 2 days (the average psychiatric stay is 4 to 5 days).

Over the next week, her friends call to report that she seems hyperactive: she is running every morning and evening.

March 17, 2003. She is readmitted to the psychiatric unit. Her physician changes her diagnosis to bipolar affective disorder, discontinues venlafaxine, resumes quetiapine, and starts lithium.

PREDICTORS OF TREATMENT-RESISTANT DEPRESSION

The cause or causes of treatment-resistant depression are not fully understood. Many cases fitting the definition of Fava and Davidson[2] will respond, if not to further antidepressant trials, then ultimately to electroconvulsive therapy. Transcranial magnetic stimulation, vagal nerve stimulation (recently approved for treatment of depression by the FDA), magnetic seizure therapy, and deep brain stimulation are newer somatic therapies that offer promise for some types of treatment-resistant depression.[10]

Aside from yet unknown factors that prevent response to one or more therapeutic antidepressant trials, the most common cause of treatment-resistance is incorrect or incomplete diagnosis.

Bipolar disorder, for example, is an increasingly recognized cause of treatment-resistant depression.[11] Nearly one third of patients with bipolar disorder are misdiagnosed as having unipolar depression.[11] As in the case presented, the two may be hard to distinguish, since people with bipolar disorder spend more time depressed than manic, and since common comorbid disorders such as substance abuse and anxiety disorders can confuse the picture.

A patient in the depressed phase of bipolar disorder (often referred to as bipolar depression) typically requires some antidepressant medication, but an additional mood-stabilizing medication such as lithium, valproic acid, or lamotrigine, or an atypical antipsychotics such as olanzapine or quetiapine, is essential to prevent antidepressant-triggered mania or rapid cycling (four or more episodes of depression or mania in a 12-month period).

In general, disorders that mimic depression or produce a secondary depression will not respond to typical antidepressant treatment. Alcoholism and cocaine, marihuana, or opiate dependence commonly precipitate a secondary depression that remits with cessation of substance abuse.

Attention deficit disorder is another common psychiatric disorder in adult primary care patient populations that can either mimic or produce a secondary depression. A central nervous system stimulant such as methylphenidate or amphetamine or the new nonstimulant medication atomoxetine is the treatment of choice.

Common medical disorders that can mimic depression and fail to respond to antidepressant treatment alone include hypothyroidism, vascular depression, subcortical dementia (such as in Parkinson disease), vitamin B_{12} deficiency, testosterone deficiency, sleep apnea, and adverse effects from medications.[12–15]

Major depression is always harder to treat when it occurs along with a comorbid chronic medical disorder such as diabetes, an anxiety disorder such as panic or social anxiety disorder, or any of the common comorbidities listed above.

Overcoming obstacles

Resistance to treatment may be a greater barrier to high-quality care for depression and other psychiatric disorders in primary care than is *treatment resistance*. Both the patient and the physician may be reluctant to delve into these personal matters, and the physician may also want to avoid the extra time needed to deal with them adequately.[16]

Resistance to treatment may be a greater barrier to care than treatment resistance

However, treating depression and anxiety need not take too much office time. I generally see my patients only once a month but also stay in close contact by telephone and e-mail. Just having a psychiatrist available by telephone in a primary care practice can help improve the network of care. Spreading the care of depressed patients among an interdisciplinary team that collaborates with the primary care physician affords the best chance of a cost-effective outcome.[17,18]

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