Agents Used for Depression

Case 21

HPI: PM is a 39-year-old woman who arrives today at her gynecologist's office for her annual examination. When asked how she has been feeling, PM mentions that she has been "kind of down in the dumps" for the past month. She says that she feels very sad, particularly when she wakes up in the morning, and has missed 3 days of work during this time frame. ("I just don't have the energy to get up out of bed some days and I don't know why.") She also says that even when she does go to work, her concentration is poor and she has a hard time making decisions. PM also complains of occasional stress headaches and has noticed that she has returned to her old habit of binging on snack foods (she has gained approximately 7 pounds in the past month). She denies suicidality but does feel like giving up sometimes. Her PMH is significant for an acute episode of depression following the breakup of a long-term relationship 1 year ago. PM was previously successfully treated with sertraline but discontinued the medication 3 months ago because "it was interfering with my sex life."

Thought Questions

- What are the treatment options for depression?
- What are the main adverse effects of the various antidepressants?

Basic Science Review and Discussion

From a pathophysiologic perspective, a decrease in certain neurotransmitters (serotonin, norepinephrine and possibly dopamine) have been causally associated with depression through the indirect evidence that all approved antidepressants will increase the activity of one or more of these chemical messengers.

All of the current antidepressants agents are equally effective in the general depressed population, generating a therapeutic response in 60% to 70% of patients given a therapeutic trial. Generally, symptoms begin to improve within the first 2 weeks of treatment, and 4 weeks (or more) are required to observe optimal treatment outcomes.

Selective serotonin reuptake inhibitors (SSRIs) are the most popular treatment option due to safety in overdose situations, low side effect burden, and ease of administration (i.e., once-daily dosing with minimal titration required). SSRIs are also effective treatment for the management of anxiety disorders, a common psychiatric comorbidity among the depressed.

In general, SSRIs are regarded as "activating antidepressants" less likely to induce sedation or sluggishness than tricyclic antidepressants or trazodone. Many patients experience mild nausea or light sleep when they first start taking an SSRI, but these side effects usually abate after a few days of continued treatment. Sexual dysfunction, most commonly presenting as a difficulty achieving orgasm, is more problematic and frequently leads to discontinuation, particularly if the patient is uncomfortable discussing this condition with his or her physician. Sweating is another common and dose-dependent phenomenon, and bruxism may present on occasion as well.

The potential of SSRIs to inhibit liver enzymes and cause drug interactions is relatively well known, but there are important differences among the SSRIs in this regard. Paroxetine and fluoxetine have a particularly strong affinity for the CYP450 2D6 isoenzyme, elevating plasma concentrations of drugs such as narcotics and beta-blockers that are metabolized via this route. Fluvoxamine and norfluoxetine (the principal metabolite of fluoxetine) have a high affinity for the CYP450 3A4 isoenzyme, responsible for the metabolism of calcium channel blockers, antifungals, certain benzodiazepines (alprazolam and triazolam), and estrogen. Although it is true that sertraline and citalopram have a lower likelihood than other SSRIs of causing drug interactions, these reactions are somewhat unpredictable, and caution should be exercised whenever other medications are prescribed with an SSRI.

Because 25% of patients will stop SSRIs due to side effects and an additional 30% to 40% will fail to achieve a therapeutic response, other antidepressant alternatives are of great importance. Venlafaxine is a dual-action antidepressant that enhances serotonin activity at low doses and norepinephrine at higher doses. Preliminary evidence suggests that these multiple actions on neurotransmitters may confer therapeutic superiority over SSRIs for the management of severe or melancholic depression, but the risk of HTN with high-dose venlafaxine should not be overlooked.

Bupropion is another second-line agent, particularly for patients who are wary of the SSRIs' negative impact on sexual dysfunction. Because it appears to relieve depression through a completely different mechanism than SSRIs, enhancing norepinephrine or dopamine, it is often administered to patients who fail SSRIs or exhibit a partial response. The most common side effects encountered with bupropion are insomnia, jitteriness, and nausea. Bupropion is contraindicated in patients with a history of seizures or eating disorders.

Mirtazapine is another antidepressant with a unique mechanism of action, enhancing serotonin and norepinephrine in a manner quite complex and distinct from venlafaxine or tricyclics. Like venlafaxine, it may be effective for severe or treatment-resistant depression, though its widespread use has been hampered by a high incidence of sedation and weight gain. Similarly, the popularity of trazodone and nefazodone has been limited by the potent sedating properties of these agents. In addition, nefazodone has been implicated rarely with the development of liver failure and it is also a potent inhibitor of the CYP450 3A4 isoenzyme.

Case Conclusion Given her favorable response to an SSRI in the past, sertraline would appear to be a logical choice for treatment of her latest episode, but her complaint of sexual dysfunction should be taken seriously, as this commonly leads to medication noncompliance. As all SSRI and venlafaxine are capable of inducing this side effect, bupropion is initiated and slowly titrated to effect. The activating properties of bupropion proved to be a notable benefit for this patient as her symptoms resolved within the first 3 weeks of receiving a therapeutic dose.

Thumbnail: Adverse Effects of Antidepressant Medications

Medication	Sedation	Agitation/ insomnia	Anticholinergic effects	Orthostasis	GI effects (nausea/diarrhea)	Sexual dysfunction	Weight gain
SSRIs							
Fluoxetine	+	++++	0/+	0/+	++++	++++	+
Sertraline	+	+++	0/+	0	+++	+++	+
Paroxetine	++	++	+	0	+++	++++	++
Citalopram	++	++	0/+	0	+++	++	+
Tricyclics							
Desipramine	++	+	++	+++	0/+	+	++
Nortriptyline	++	+	++	++	0/+	+	++
Amitriptyline	++++	0/+	++++	++++	0/+	++	+++
Imipramine	+++	0/+	+++	++++	0/+	++	++
Doxepin	++++	0/+	++++	++++	0/+	++	++
Others							
Bupropion	0	+++	+	0	+	0/+	0
Venlafaxine	++	++	+	0	+++	+++	+
Nefazodone	+++	+	+	++	++	0/+	0/+
Mirtazapine	++++	0	++	0/+	+	0/+	+++

0, negligible; +, very low; ++, low; +++, moderate; ++++, high.

Questions

1. RH is a 48-year-old man who had enjoyed an excellent response to paroxetine. Two months after starting the antidepressant, he mentions that he is no longer able to ejaculate and, though he has no interest in stopping the SSRI, wonders what can be done to preserve his marital relations. Which would be the best option at the present time?

   A. Change his paroxetine to sertraline.
   B. Reduce his paroxetine dose.
   C. Add bupropion.
   D. Add sildenafil.
   E. Encourage marital counseling.

2. EV is a 21-year-old college student suffering from an acute episode of major depressive disorder with severe symptomatology. Although her symptoms went into remission after 8 weeks of venlafaxine, she now complains of sudden dizziness, anxiety, and shooting pains in her legs. What is the most likely explanation for these complaints?

   A. Eosinophilia myalgia syndrome
   B. Serotonin syndrome
   C. SSRI withdrawal syndrome
   D. Stroke (cerebrovascular accident)
   E. Neuroleptic malignant syndrome