symptoms persist another week, he indicates that he will either resume venlafaxine or begin another seronotergic agent to help with the withdrawal. Within a week, the symptoms begin to improve, and they resolve completely in 2 weeks.

DULOXETINE

This new antidepressant is a pure norepinephrine reuptake inhibitor. As such, it is a modern version of desipramine. Its manufacturer included physical symptom assessment in its clinical trials, leading to permission from the FDA to market this agent for the treatment of depression, along with the physical symptoms associated with depression. This has led to the clinical conception that this agent may be especially useful for patients with depression and associated physical symptoms. Of course, most patients with depression also have associated physical symptoms. What is scientifically relevant is that one would need studies directly comparing duloxetine with other antidepressants for physical symptoms before one could say that duloxetine is preferentially more effective than other antidepressants for depression-related physical symptoms. We await such data. This is simply a noradrenergic antidepressant; as such, it may have utility as an alternative to SRIs or bupropion in patients who do not respond to those other agents or who have serotenergic-associated side effects. This role is no different from the potential benefits of desipramine, with the difference that duloxetine appears not to be associated with any risk of cardiac arrhythmia.

Serotonin Reuptake Inhibitors

Essential Concepts

- Serotonin reuptake inhibitors (SRIs) are not more effective than other antidepressants; their main advantage is tolerability.
- Fluoxetine has the longest half-life and the most noradrenergic effects.
- Sertraline has mild to moderate dopaminergic effects.
- Paroxetine has mild to moderate anticholinergic effects and, in higher doses, mild to moderate noradrenergic effects.
- Fluvoxamine is most used in obsessive-compulsive disorder.
- Citalopram is the most purely serotinergic of the SRIs and is especially well tolerated in the elderly.
- Sertraline and citalopram have the fewest drug interactions, fluoxetine the most, and paroxetine and fluvoxamine an intermediate amount.
- SRIs have a small but real risk of increased suicidality, especially related to causing mixed states in misdiagnosed bipolar depression or to causing akathisia.

EFFICACY AND SAFETY

SRIs have not been proven to be more effective than the tricyclic antidepressants (TCAs); rather, their advantage seems to be improved tolerability and patient acceptability. This is a strong point worth emphasizing. Many clinicians in the United States use SRIs almost exclusively, often going through all medications in this class, occasionally trying some of the newer atypical antidepressants, and rarely if ever using TCAs or monoamine oxidase inhibitors (MAOIs). This approach assumes that SRIs have equal or better efficacy than the other agents. In fact, TCAs, MAOIs, and venlafaxine are more effective than SRIs in specific populations, especially hospitalized and melancholic patients. Safety is an important

matter, though, and the popularity of SRIs is not without reason. Sometimes clinicians confuse pharmacologic safety with clinical safety. In other words, since SRIs are not lethal owing to direct physiologic effects, clinicians act as if they are safe and nonlethal in any clinical circumstance. This is not the case for certain situations, the most important of which are bipolar depression and akathisia. In bipolar depression, SRIs can induce a mixed manic state highly associated with suicide. There is also the possibility that SRI-induced akathisia also can result in suicide. Therefore, the pharmacologic safety of SRIs does not imply that clinicians can use them with impunity regardless of the clinical circumstances. Since I made these comments in the first edition, at that time somewhat controversial, the Food and Drug Administration (FDA) has required a black box warning for such SRI-related suicidality specifically in relation to children; this important topic is discussed further below.

MECHANISMS OF ACTION

All SRIs share a common mechanism of serotonin reuptake blockade, and this effect is essential to the antidepressant effect of this class. Yet they differ significantly in the amount of serotonin reuptake blockade they produce, and they differ in their other biochemical effects. Thus I am consciously not using the more common acronym, SSRIs (selective SRIs), to emphasize the point that these agents are not, in fact, particularly selective to the serotonergic system (Table 11.1).

DRUG INTERACTIONS

Perhaps no other class of psychotropic medication has heightened our interest in and knowledge of hepatic cytochrome enzymes. Differences among SRIs in effects on hepatic metabolic

TABLE 11.1. Mechanisms of Action of SRIs

1. Noradrenergic effects: fluoxetine, paroxetine (at higher doses)
2. Dopaminergic effects: sertraline
3. Highest serotonin reuptake blockade potency: citalopram, fluvoxamine, paroxetine

TABLE 11.2. Drug Interactions with SRIs

Serotonin syndrome: MAOIs, possibly trazodone
Neuroleptics: Akathisia
Hepatic cytochrome inhibition (detailed in Chapter 12): Increased levels of neuroleptics, TCAs, valproate, carbamazepine
Absolute contraindication: Fluvoxamine with ketoconazole, terfenadine, or astemizole (cardiac arrhythmias owing to elevated levels via cytochrome P450 3A4 inhibition)

enzymes are also essential to understanding how to use these various medications. Throughout the course of this chapter, I will emphasize these effects, as summarized in Table 11.2.

SEXUAL DYSFUNCTION

Sexual dysfunction is probably the most common side effect of SRIs. Despite low reports in early controlled clinical trials, later experience indicates that about 50% of patients treated for the long term with SRIs develop sexual dysfunction. Dysfunction varies from decreased libido to inability to obtain orgasm and erectile difficulty. This effect may be due in part to stimulation of 5HT-2 receptors because agents that block this receptor (such as nefazodone and mirtazapine) produce less sexual dysfunction. Weekend drug "holidays," particularly with sertraline, as noted below, are sometimes used to minimize this side effect. It is a clinical reality that sexual dysfunction is underreported if it is not specifically examined for by clinicians; patients often will not report sexual side effects owing to embarrassment or perhaps lack of recognition of those symptoms as medication-related.

TIP

You must specifically ask patients about SRI-induced sexual dysfunction. Many patients are too embarrassed to volunteer such information.

This problem is especially common in SRI treatment of depression because many depressed patients experience sexual dysfunction as part of the depressive syndrome, and it may be difficult to recognize further impairment owing to the medications. A clinician should be suspicious if most depressive

symptoms improve except for sexual function. Again, the clinician needs to consistently query about sexual function to pick up on such lack of improvement.

OTHER SIDE EFFECTS OF THE CLASS

Other side effects common to the entire class are gastrointestinal side effects and disruption of sleep architecture. Gastrointestinal side effects usually involve diarrhea and nausea. It is an often underrecognized fact that there are more serotonin receptors in the enteric nervous system of the gut than in the brain. The gut's enteric nervous system is an independent peripheral nervous system consisting mostly of serotonergic connections using 5HT-3 receptors. Mirtazapine, a 5HT-3 blocker, produces fewer gastrointestinal side effects. Another way to manage such side effects can be to add ondansetron, a selective 5HT-3 receptor antagonist indicated by the FDA for the treatment of chemotherapy-related nausea, to the offending SRI.

The effect of SRIs on sleep architecture (progression from one sleep stage to another) is also common. Sleep stages are highly influenced by serotonergic neurons in the raphe nuclei of the medulla and pons. Progression from one stage of sleep to another is disrupted by SRIs. Clinically, patients experience midcycle awakenings in the middle of the night, as well as vivid dreaming. Trazodone regularizes the transitions between sleep stages, resulting in its popularity as an antiinsomnia adjunct in polypharmacy with SRIs. Nefazodone and bupropion also appear to improve sleep architecture.

Because of these sleep effects, SRIs generally should be dosed in the morning, with the exception of some persons who experience sedation with paroxetine and occasionally fluoxetine, which should be dosed in the evening in such individuals.

THE BETTER THAN WELL SYNDROME ("LISTENING TO PROZAC")

Prozac (fluoxetine) and SRIs have become famous for possibly making people "better than well," a concept introduced by Peter Kramer that such SRIs may alter what used to be called *melancholic personality*, a mixture of dysthymic and anxious chronic symptoms. Such persons seemed to become less anxious and more extroverted with SRIs. This topic has generated much controversy both as to whether it really occurs and, if so, what it means ethically and clinically. After a decade of discussion, my impression is that some patients indeed have such responses to SRIs, which are partly changes in personality and partly improvements in depressive syndromes that had been excluded from DSM-III, such as *neurotic depression* (as discussed in chapter 8). On the other hand, these effects of SRIs are not apparently frequent and always should be distinguished from the common occurrence of misdiagnosed bipolar depression with resulting hypomania or mania.

THE APATHY SYNDROME (LISTENING TO PROZAC TOO MUCH)

What is insufficiently appreciated is that the opposite effect can occur as well. Some individuals with a baseline personality low in anxiety and highly extroverted (often hyperthymic) will experience the anxiety-reducing effects of SRIs as restrictive. SRIs appear to induce an apathy syndrome in such persons. This effect is not clearly understood, but it is speculated that SRIs might reduce frontal lobe activity in some patients (although most SRIs increase frontal lobe activity). This effect results in a flattening of affect, sometimes described by patients as a decreased ability to "feel" experiences or an attenuation of normal fluctuations in mood. In other words, patients may not be able to be appropriately sad when they should be, or appropriately happy when they should be, compared with the manner in which most nondepressed persons would react in those circumstances. This apathy syndrome can be a subtle effect for patients or clinicians to recognize. It can be mistaken as a continuation of depressive anhedonia or possibly seen as a recurrence of depression. In patients who recover from most of their neurovegetative symptoms except anhedonia, the apathy syndrome should be suspected. In such persons, I recommend reducing the dose of the SRI or changing treatment to a nonserotonergic agent (such as bupropion).

KEY POINT

The apathy syndrome is a side effect of SRIs but can be confused with depression. Suspect its presence if all depression symptoms improve except for anhedonia.

SUICIDE AND AKATHISIA

An unavoidable topic in relation to the SRIs is the risk of suicide. This issue is raised most frequently in relation to fluoxetine, but this relationship probably reflects the longer availability of fluoxetine relative to other SRIs. Legal cases arguing for an association with suicide have been raised with most SRIs, and now the FDA has instituted a black box warning of SRI-induced suicidality in children.

The FDA warning is based on a meta-analysis of multiple randomized clinical trials in children, many of which are unpublished, that demonstrated a more than 50% increased relative risk of suicidality (attempts or increased suicidal ideation) in a total sample of about 5,000 children studied. While this is important, indicating a real risk, it also should be borne in mind that the absolute rates of suicidality were about 4% with SRIs versus about 2% with placebo, meaning that this increased risk probably occurs in about 5% or less of treated children. Nonetheless, this fact, as well as the absence of completed suicides in those studies, should not engender false complacency. As with all randomized clinical trials, the subjects who enter are carefully chosen to be low risk and highly compliant; suicidal ideation of any significance was an exclusion criterion for almost all those studies. If anything, therefore, the FDA meta-analysis underestimates the true risk in the general population of children. Further, there are nuisance side effects, and there are fatal side effects. A 5% risk of nausea is irrelevant, but a 5% risk of death is unacceptable, even if the drug also saves lives (which has not yet been proven with SRIs in relation to preventing suicide).

Thus the consequence of the FDA ruling should be what the FDA intended and what has, in fact, happened: Prior indiscriminate use of SRIs has been replaced by a greater exercise of clinical judgment, which always should have been the case. The opposite extreme, of never using SRIs, is also inappropriate.

KEY POINT

There is little doubt now that SRIs cause a small but real increase in suicide risk, at least in children. The most likely causes are misdiagnosed bipolar depression, leading to induction of mixed states, and akathisia.

If we now accept that SRI-induced suicidality occurs, the next question is, Why? Some critics seem to believe that there is something inherently dangerous about these medications; this claim has not been substantiated. Two other potential causes seem, in my view, much more likely and are also preventable.

First, in my opinion and that of others who specialize in bipolar disorder, the most likely culprit is misdiagnosed bipolar disorder. Some studies of children indicate that up to 50% of depressed children (mean age 12 years) develop manic or hypomanic episodes in a decade of follow-up. Keeping in mind that the age of onset of bipolar disorder is much earlier than that of unipolar depression (late teens versus late 20s), clinicians always should have a high index of suspicion for latent bipolar disorder in depressed children. Further, manic episodes in children are usually mixed, and about 60% of mixed states involved increased suicidality, a figure that is even higher than the occurrence of suicidality in pure depression. Statistically, if 50% of apparently depressed children are indeed bipolar, then one would easily expect that 10% of them (or more) would develop manic episodes given antidepressant monotherapy; these figures easily could explain the 5% suicidality rate observed in the FDA database.

Second, SRIs can cause the extrapyramidal symptoms of akathisia (discussed in more detail in Chapter 17). Akathisia is a very uncomfortable, dysphoric experience, often misinterpreted as agitation or worsening of depression. When unrecognized and untreated, it can increase suicidal ideation and seems to have been a factor in a number of the rare cases of fluoxetine-associated suicide. Although probably less common than SRI-induced mania, SRI-related akathisia has been reported to occur in up to 10% of treated individuals.

What should clinicians do? Carefully rule out bipolar disorder, keeping in mind that it cannot be ruled out effectively in children because they may not have yet had their first manic or hypomaniac episode. In children, therefore, the bipolar spectrum concept, including an emphasis on family history, may be especially relevant (see Chapter 4). Further, clinicians should warn patients about akathisia and carefully look for this side effect, especially in the first few months of treatment, and be prepared to reduce the SRI dose, stop the SRI, or treat with propanolol. Akathisia should never be left to fester, but needs to be terminated as soon as possible.

TABLE 11.3. Serotonin Reuptake Inhibitors

Drug	*Effective Dose (mg/day)*	*Comments*
Fluoxetine (Prozac)	20–80	Longest half-life of any antidepressant, requiring longer duration for a therapeutic trial but also producing less serotonin withdrawal, somewhat noradrenergic, marked drug interactions (all cytochromes, especially 2D6 and 3A4)
Sertraline (Zoloft)	50–200	Dopaminergic, useful in weekend "holidays" for sexual dysfunction, mild drug interactions
Paroxetine (Paxil)	20–50	Very anxiolytic, moderately anticholinergic, some weight gain, somewhat more serotonin withdrawal, multiple FDA indications, cytochrome P450 3A4 inhibitor
Citalopram (Celexa)	20–60	Most potent serotonin reuptake inhibition, most selective agent for serotonin, minimal drug interactions, especially useful in elderly
Fluvoxamine (Luvox)	50–250	Highly potent serotonin reuptake inhibition, indicated for OCD

INDIVIDUAL SRIs

See Table 11.3 for dosage guidelines and Table 11.4 for general rules of SRI treatment.

Fluoxetine (Prozac)

The groundbreaking medication in this class was fluoxetine, introduced in the United States in 1989. This agent was quickly followed by sertraline, paroxetine, fluvoxamine, and

TABLE 11.4. General Rules for SRI Treatment

1. Dose all agents once daily in the morning, with the exception of paroxetine (which can be sedating) and fluoxetine (in the minority of persons who experience sedation).
2. Fluoxetine requires a longer therapeutic trial but has less serotonin withdrawal.
3. Sertraline works well in weekend drug "holidays" for sexual dysfunction.
4. Citalopram is the most selective for serotonin reuptake.
5. Sertraline and citalopram have the fewest drug interactions.
6. Paroxetine may have the most anxiolytic effect.
7. Observe carefully for mixed states in misdiagnosed bipolar disorder, as well as akathisia, as potential risk factors for suicidality.

citalopram, in that order. Fluoxetine is also the first of these agents to become available in generic form (2001), after more than a decade of blockbusting profits. In my opinion, it is not the best SRI, but it had the major advantage of being the first on the market. Both clinicians and patients quickly became familiar, and usually comfortable, with this medication. By initiating the change in prescriptions from TCAs to newer antidepressants, fluoxetine also became the symbol of the new generation of kindler, gentler psychiatric medications. Patients and clinicians began to "listen" to it for all kinds of benefits, and it is still not unusual to see patients come to a clinician's office specifically asking for this agent.

From a sober medical perspective a decade later, however, fluoxetine has some advantages and some disadvantages that do not seem to distinguish it from its SRI compatriots. Now, perhaps its main advantage, along with citalopram and sertraline, is that it has become available in the United States in a generic formulation; cost should no longer be a limiting factor in the use of this agent.

A unique feature of fluoxetine is that it and its active metabolite, norfluoxetine, have quite long half-lives, the longest, in fact, of any major psychotropic agent. The half-life of fluoxetine is about 1 day, and that of norfluoxetine is about 3 to 5 days. Thus, on average, it takes 4 days for a dose of fluoxetine to be 50% eliminated. Since it takes three half-lives to achieve a steady-state blood level, it takes 12 days just to achieve a steady-state level of this agent. All antidepressants require about 4 to 8 weeks of time delay for their pharmacologic effects to translate into a clinical antidepressant effect.

This delay probably reflects intracellular second-messenger and genetic changes. However, this 4- to 6-week delay occurs after steady state is achieved. For most antidepressants, a steady-state blood level is achieved in 1 to 2 days. For fluoxetine, the 12-day delay, on average, means that the clinical effect of the medication may be delayed another 1 to 2 weeks. This is why fluoxetine is the only antidepressant that requires a 6- to 8-week period for a full therapeutic trial (as opposed to 4 to 6 weeks). This fact may be a partial disadvantage: If a patient is not responding to fluoxetine at 4 weeks of treatment, one cannot change to another medication knowing that a full trial has been given unless one waits another 2 weeks. This is not the case with other antidepressants, in which no response at all at 4 weeks is a sufficient therapeutic trial. On the flip side, a potential advantage to this long half-life is that fluoxetine does not leave the body quickly and thus may be less prone to causing serotonin withdrawal syndrome.

KEY POINT

Owing to its long half-life, one must wait longer to be sure of obtaining an antidepressant effect with fluoxetine. Similarly, this agent may possess less serotonergic withdrawal symptoms.

Another feature of fluoxetine is that contrary to what is sometimes assumed, it is not purely selective for serotonin. In fact, fluoxetine mildly blocks the reuptake of norepinephrine. This effect of fluoxetine is not minor and is somewhat similar to the effect of venlafaxine. This feature possibly may account for the "stimulating" effects frequently reported with fluoxetine.

As with all SRIs, fluoxetine can disrupt the sleep architecture. Combined with its potentially stimulating effects, fluoxetine can cause insomnia. (Nonetheless, a small subgroup of patients actually becomes sedated with it.)

Another major effect of fluoxetine is that it is a strong inhibitor of most hepatic cytochrome P450 enzymes, thereby increasing the blood levels and effects of many other medications, including neuroleptics, TCAs, and some mood stabilizers.

Despite its side effect of sometimes causing "stimulation," fluoxetine often has the pharmacologic effect of decreased anxiety, as do all SRIs.

Since fluoxetine has been available for the longest amount of time, it has been studied in the largest number of conditions, with reports of efficacy in bulimia nervosa, anorexia nervosa, posttraumatic stress disorder (PTSD), personality disorders, obsessive-compulsive disorder (OCD), and panic disorder. It has efficacy in these conditions, but all SRIs are likely useful in similar conditions. Fluoxetine is now indicated by the FDA (under a different trade name) for the treatment of premenstrual syndrome (late-luteal-phase dysphoric disorder).

As noted earlier, some clinicians believe that fluoxetine exerts a special beneficial effect on personality. This perspective holds that some depressed and even nondepressed individuals become "better than well" on fluoxetine; that is, not only are they no longer depressed, but they also do not return to their premorbid personality. They often become more extroverted and funloving, and a patient may feel that his or her personality on fluoxetine is his or her "real" self. When reported, this effect seems to be rare, and it seems not to be clearly specific to fluoxetine. It might be explained as an effect on personality that is separate from any antidepressant effects of the medication. Some researchers have provided evidence that some aspects of personality, especially what has been called *harm avoidance,* may be associated with serotonergic areas of the brain. By increasing serotonin availability, SRIs may alter personality by making persons less harm-avoidant, that is, less cautious or shy or introverted. As a result, this mysterious effect of fluoxetine simply may be a straightforward effect on the biochemistry of personality. At another level, however, this effect of fluoxetine needs to be balanced with an apparently equal potential for less positive effects on personality, such as the apathy syndrome.

Sertraline (Zoloft)

Sertraline, now also available as a generic agent in the United States, is an SRI with a moderate amount of dopamine reuptake blockade. It has a shorter half-life than fluoxetine, about 1 day, and causes much less inhibition of hepatic cytochrome P450 enzymes. This does not mean that it has no hepatic enzyme effect; especially at higher doses, its effect can be clinically notable. Usually, though, its hepatic effects are mild and do not lead to clinically significant drug interactions.

Sertraline shares with other SRIs a general antianxiety effect, as well as a potentially disruptive sleep effect. It is now indicated by the FDA for the treatment of PTSD. While fluoxetine possesses an FDA indication for premenstrual syndrome, sertraline is also useful in this setting and perhaps more so if an individual prefers to use the SRI for 5 days before and after the menstrual period rather than continuously. Such short-term use is effective with all SRIs except fluoxetine (again owing to the latter's long half-life). The short half-life of sertraline also may be useful in the context of drug "holidays" for sexual dysfunction.

KEY POINT

Some clinicians manage SRI-induced sexual dysfunction by stopping sertraline on Fridays and resuming it on Sundays, thereby allowing for end of the week sexual activity.

This discontinuation would not work with fluoxetine owing to its long half-life, and it might be more difficult with paroxetine or venlafaxine owing to their short half-lives and the consequent risk of serotonin withdrawal syndrome. The weekend drug "holiday" seems to work well with sertraline, however, which may reflect in part the fact that sertraline's metabolite, desmethylsertraline, has a half-life of about 3 days. As a result, in weekend drug "holidays," sertraline is short-acting enough to leave the body such that sexual function temporarily improves, but not so short-acting that serotonin withdrawal symptoms begin.

A potential disadvantage of sertraline's mild dopaminergic effect may be that in particularly susceptible individuals this biochemical property may lead to increased psychosis. This has been reported in otherwise nonpsychotic individuals, although infrequently. In bipolar disorder, sertraline has not seemed clinically useful in my experience, with quite notable mania induction, although empirical data are not available. Sometimes I am asked why I think sertraline's dopaminergic effect is a problem in terms of increased mania risk, whereas bupropion possesses less mania risk. It may be a matter of degree, because sertraline, contrary to common belief, has more dopaminergic effect than bupropion. These mechanistic issues are really a matter of speculation. The fact remains that at a clinical level, in some persons, sertraline appears prone to inducing psychosis or mania.

Paroxetine (Paxil)

Paroxetine is also short-acting, with a half-life of about 1 day, and perhaps more short-acting than sertraline (because the latter has a metabolite with a long half-life). Paroxetine is more potent than either sertraline or fluoxetine in its serotonin reuptake effect, which means that if a higher degree of serotonin reuptake is needed, then paroxetine may be useful. In other words, even strictly on the issue of serotonin reuptake effect, these SRIs are not identical. This difference may account for the clinical experience that some patients respond to one SRI and others to another SRI.

Paroxetine also possesses moderate anticholinergic effects. While prominent in vitro, in vivo studies in humans suggest that these anticholinergic effects are not marked and certainly are less severe than with TCAs. In susceptible persons, though, clinically notable anticholinergic effects may occur. These include dry mouth, sedation, constipation, and cognitive side effects.

Most SRIs are weight-neutral, with some persons losing weight and a small number of persons gaining weight. Of the SRIs, paroxetine appears to be the most liable to some amount of weight gain, although not, on the whole, to a severe degree. Some individuals will experience significant weight gain.

Among the SRIs, which all have anti-anxiety effects, paroxetine holds the reputation of having the most consistent anxiolytic effects, and it is now indicated by the FDA in the treatment of generalized anxiety disorder, panic disorder, and social phobia (social anxiety disorder).

Unfortunately, paroxetine's short half-life makes it somewhat more liable to serotonin withdrawal symptoms than other SRIs. Again, these symptoms are finite and usually tolerable with appropriate clinician support.

Paroxetine has minimal effect on the cytochrome P450 2D6 system, unlike fluoxetine, but is a strong inhibitor of the cytochrome P450 3A4 system, like fluoxetine. In terms of drug interactions, paroxetine has an intermediate effect—not as marked as fluoxetine but not as mild as sertraline.

Citalopram (Celexa)

Citalopram, now available in generic form in the United States, was used in Europe for a number of years before it was introduced into the United States in 1999. (In fact, in Europe,

it predated fluoxetine.) It is even more potent in its serotonin reuptake blockade effect than paroxetine. It is also the most purely serotonergic agent in this class, with almost no other effects on other neurotransmitter systems. It has minimal effect on hepatic enzymes and a short (but not too short) half-life of about 1 day. In many ways, then, citalopram may deserve the label of the classic SRI.

Overall, it likely has similar benefits to most SRIs as regards antianxiety and other effects. Owing to its "cleaner" biochemical profile, it may be particularly helpful in elderly patients, in whom it is less likely to cause avoidable side effects or drug interactions. Recent studies suggest some benefit also in bipolar depression (see Chapter 18).

Escitalopram (Lexapro) is the active enantiomer of citalopram; except for providing more profits to its makers and its ability to get the same effect as citalopram at lower doses, I see little need to use this expensive agent. Its maker's claims to better tolerability than citalopram have not been confirmed clinically.

Fluvoxamine (Luvox)

Fluvoxamine is indicated by the FDA for OCD but likely has benefits for depression and anxiety similar to other SRIs. As with paroxetine and citalopram, it is potent in its serotonin reuptake blockade. It has few other biochemical effects and no other real advantage over other SRIs. It is a strong inhibitor of the cytochrome P450 3A4 system, perhaps even more than paroxetine, and thus has some disadvantages in terms of drug interactions.

Treatment Strategies for Refractory Unipolar Depression

Essential Concepts

- The Sequenced Treatment Alternatives to Relieve Depression (STAR-D) trial, a major National Institute of Mental Health (NIMH)–sponsored trial of antidepressants, demonstrates that treatment-resistant depression is more often the rule than the exception in unipolar depression. The following interpretations follow from STAR-D.
- Only about a third of unipolar depressed patients get completely well (remission) with a full trial of a single antidepressant. About one-half will have acute response (75% improvement).
- Of the remaining two-thirds of patients, any change (whether switching to a new antidepressant or augmenting with another agent) leads to improvement in not more than 30% of patients.
- Augmenting with another agent added to an antidepressant may be somewhat more effective than switching to a new antidepressant.
- If one excludes dropouts owing to side effects, about half of unipolar depressed patients ultimately will get completely well short-term (acute remission) after multiple antidepressant treatments.
- If one includes dropouts owing to side effects, only about 25% of unipolar depressed patients will remain well for over a year (sustained remission) after multiple antidepressant treatments, a number that may or may not be better than improvement by natural history.
- Response rates, meaning some improvement but not full remission, are not higher than the figures just cited.