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 citalpram; 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.

- In patients who fail to respond to antidepressants, even short term, new data suggest that half may have misdiagnosed bipolar disorder, particularly type II. Such patients may improve with the addition of mood stabilizers.
- For the remaining patients with refractory nonbipolar depression, options include new nondrug treatments, such as vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS), and deep brain stimulation (DBS), in addition to electroconvulsive therapy (ECT).
- VNS has been proven equivalent to placebo. Its use is not supported by scientific standards, and because it is an invasive surgical treatment, the risks are not well outweighed by any purported benefits.
- TMS has not been shown effective in refractory depression and likely is less effective than ECT. DBS has potential but is still in the early stages of study.
- ECT remains the treatment of choice, after ruling out misdiagnosed bipolar disorder, in truly refractory unipolar depression. Yet it can cause cognitive impairment; thus that risk needs to be weighed against its clear short-term benefits. Long-term improvement with maintenance ECT still has not been proven compared with adequate pharmacotherapy.
- The most proven combination treatments are lithium, buspirone, thyroid hormone augmentation, and the serotonin reuptake inhibitor (SRI)–tricyclic antidepressant (TCA) combination.
- In psychotic unipolar depression, remember the 20-40-80 rule: 20% response with antipsychotic alone, 40% with antidepressant alone, and 80% with the combination.
- Often treatment resistance is really treatment intolerance. Distinguish nonresponse owing to side effects from nonresponse owing to lack of efficacy.

- Beware of the possibility that your patients are either slow or rapid metabolizers of psychotropic medications.
- If TCAs or monoamine oxidase inhibitors (MAOIs) have not been used, switching to those agents for a single-drug trial should be considered.

In Chapter 12, I discuss treatment-resistant depression (TRD) and define different stages of treatment resistance. In this chapter I will address treatment of refractory depression and compare the two main strategies of "switching" versus "adding." Switching from one agent to another is the most common strategy mainly because it entails fewer side effects. However, one can quickly run through most classes of antidepressants in refractory patients with this approach. Adding one agent to another can lead to more side effects, but it greatly multiplies the treatment options available. Recent research suggests that the adding approach increases the overall likelihood for response.

MISDIAGNOSIS

It is generally said that the first step in handling treatment resistance is to reassess diagnosis. Yet, while often mouthed, this important point is rarely practiced carefully. Beyond acknowledging the relevance of misdiagnosis, one must have a sense of which diagnoses tend to be the common ones. Surprisingly little research on TRD has tried to quantify this matter. When this limited literature is examined, an underappreciated finding emerges: About half of the cases of TRD are due to misdiagnosis of one illness—bipolar disorder. Thus, statistically, half of patients who fail to respond to unipolar depression simply do not have it; they have bipolar depression instead. Thus, without needing to get fancy or to engage in complicated medication cocktails, the wise physician will reassess the history and expect, in about half the cases, to change the diagnosis. This recent, though limited, research also suggests that most of these TRD patients who in fact have misdiagnosed bipolar disorder improve either by adding mood stabilizers to the antidepressants that failed in the past or by replacing antidepressants with mood stabilizers. Given that misdiagnosed bipolar disorder is the number one cause of TRD and that this fact has been sorely underappreciated, perhaps we now have an explanation for

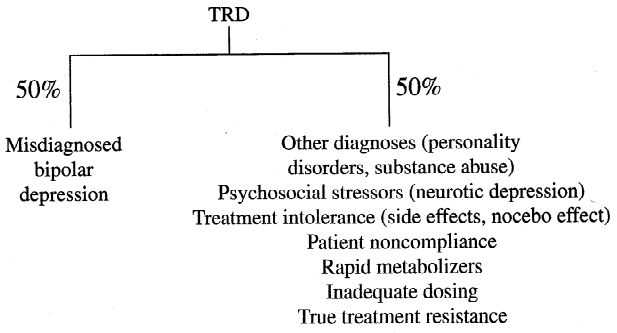

FIG. 12.1. Causes of treatment resistant depression (TRD).

lithium augmentation as the most proven treatment for TRD. Most lithium augmentation studies for TRD predate DSM-IV (1994) and thus did not even try to diagnose, much less exclude, type II bipolar disorder, the most common subtype of misdiagnosed bipolar illness found in patients with TRD.

TIP

The most common cause for TRD is misdiagnosed bipolar disorder, especially type II. About half of cases of TRD are due to this misdiagnosis. Adding mood stabilizers to antidepressants or even replacing antidepressants with mood stabilizers leads to response in most of these previously refractory depressed patients.

All other causes of TRD are more or less equivalent to bipolar misdiagnosis. These other causes are summarized in Figure 12.1.

OTHER MISDIAGNOSES

Perhaps the most common other misdiagnoses, after bipolar depression, are personality disorders and substance abuse, which can either cause or mimic depressive syndromes or indeed may co-occur with unipolar recurrent depressive disorders. In such cases, depressive symptoms may not improve markedly with antidepressant medications and instead may require individual psychotherapy or substance abuse interventions. The latter psychosocial interventions are essential to recovery for personality disorders or substance abuse, respectively, whereas antidepressant medications by themselves do not generally lead to recovery and are at best ancillary treatments.

PSYCHOSOCIAL STRESSORS AND NEUROTIC DEPRESSION

Some studies show that antidepressant response for major depressive episodes appears to be lessened in the setting of marked psychosocial stressors. This observation, so common clinically, also gets back to the neurotic depression concept (see Chapter 8). Many of these persons who were previously conceptualized as having neurotic depression tend to have chronic depressive symptoms in the setting of notable psychosocial stressors. Lack of attention to these psychosocial stressors, through either psychotherapies or other means, often will lead to poor antidepressant response. Again, the psychosocial interventions in these circumstances are primary; the use of antidepressants is secondary (and sometimes not necessary). The role of psychosocial stressors in neurotic depression should be distinguished from recurrent unipolar depressive disorder, however. Neurotic depression is a clinical presentation, not a disease, in which psychosocial problems are the primary force. Recurrent unipolar depressive disorder is a disease, in which biological susceptibility is the main problem. The former requires psychotherapies, and medications are ancillary; the latter requires medications, and psychotherapies are ancillary. Thus the mere presence of psychosocial stressors should not lead to deemphasizing medications or instituting psychotherapies; rather, the key distinction is whether the psychosocial stressors happen in the setting of neurotic depression or in the setting of recurrent unipolar depressive disorder.

TIP

The presence of psychosocial stressors is neither the "cause" of depression nor an indication for psychotherapies, especially in the context of bona fide recurrent unipolar depressive disorder. However, in the setting of neurotic depression, antidepressant medication alone appears less likely to be effective than psychotherapies.

TREATMENT INTOLERANCE

Before one concludes that a lack of response to antidepressants reflects true treatment resistance, after ruling out misdiagnoses and psychosocial factors, one should assess the other factors in Figure 12.1, all of which are variations on lack of tolerability rather than lack of response. There is no treatment resistance unless full, adequate therapeutic trials have failed. Frequently, patients are dubbed "treatment resistant" even though they have not failed a single full trial of an antidepressant. Recall that in Chapter 8 I defined a full, fair trial of an antidepressant with the following rules:

1. The minimum duration of an effective trial is 4 weeks for most antidepressants, but 8 weeks is ideal.
2. The minimum effective dose of each antidepressant should be reached.
3. Patient noncompliance must be ruled out.

TIP

The three most common causes for failure to achieve a full therapeutic trial of an antidepressant are (1) patient side effects, (2) patient noncompliance, and (3) inadequate dosing.

It is very common for a patient to be sensitive to multiple medications and thus not take any single medication more than a few days to a few weeks. This type of patient can quickly try three SRIs, bupropion, venlafaxine, and nefazodone. Within 2 months, it will appear that this patient has exhausted all available pharmacologic resources. This may be the case, but it is due to intolerance, not treatment resistance. The two are not the same thing. A treatment-refractory patient must be able to tolerate at least some medications to achieve full trials of them. A treatment-intolerant patient is never able to be tested for treatment efficacy.

TIP

Treatment resistance is very different from treatment intolerance.

THE NOCEBO EFFECT

In some senses, the treatment-intolerant patient is more difficult to treat than the true treatment-refractory patient. In the case of treatment intolerance, two major factors are likely to be relevant. One factor is a possible nocebo effect.

KEY POINT

The *nocebo effect* is basically a reverse placebo effect. In other words, just as the placebo effect can make one feel better owing to one's psychological expectations, the nocebo effect can make one feel worse owing to one's psychological expectations.

In research studies, investigators often conduct what is called a *single-blind placebo lead-in*. In such cases, the investigators know that the patient is getting placebo, but the patient does not know, and this state is maintained for the first week of the study, before the patient is then treated according to the research protocol (e.g., double-blind treatment with either a drug or placebo). Not infrequently, one observes the nocebo effect in the 1-week single-blind lead-in, with patients reporting numerous side effects, such as headache, tiredness, nausea, muscle aches, and chest pain. These patients are then dropped from the study as a means of reducing the placebo effect and thus being able to detect true pharmacologic benefit with drugs more effectively. In real-life practice, one can only imagine how often this scenario occurs. In my opinion, the nocebo effect is sometimes at play in patients who are quite anxious about taking medications. Perhaps they delayed seeing a psychiatrist for a long time, or they were pushed to come to the appointment by family or friends, but deep down they do not want to be treated with medications. Even if they take medications, their underlying psychological mind-set can be so negatively predisposed to medications that numerous side effects are almost guaranteed.

Another factor that may promote the nocebo effect is excessive interest in the side effects of medications. Pharmacists often review medication side effects in some detail with patients, which is usually helpful but sometimes can promote nocebo side effects. Access to the Internet can lead to unreliable or exaggerated information about medication side-effect risks, and access to the *Physicians Desk Reference* (PDR) listing usually heightens fears about taking medications. In general, access to

more information rather than less is beneficial to medical care. If patients are more knowledgeable, treatment is usually more successful. However, in the case of individuals predisposed to the nocebo effect, a little knowledge can be quite dangerous.

In cases where I am particularly concerned about a negative mind-set on the part of the patient, I usually emphasize a few points. First, I ask patients to let me know if they have any concerns about taking the medications based on their discussions with their pharmacist. Second, I direct them toward reliable Internet sites and warn them about possible misinformation in other venues.

TIP

Research studies have demonstrated that exposure to too much information regarding side effects can increase the occurrence of side effects.

Third, I discuss the PDR listings with them and emphasize that almost any medication has a long list of side effects in the PDR because it is based on clinical trials, where any observation made by the researchers will be included. It is not until clinical experience develops that clinicians can understand the most common and severe side effects. Further, it is important to note that the PDR is not intended to be used by patients or even as a primary source for doctors beyond the initial introductory period of a medication's use. In my experience, this kind of speech, given before the first prescription is written, may help to reduce the nocebo effect.

POOR VERSUS RAPID METABOLIZERS

Besides the nocebo effect, another important contributor to treatment intolerability is poor hepatic metabolism. It is believed that about 5% to 10% of the Caucasian population are genetically poor hepatic metabolizers. Hence these persons may need to be treated with very small doses of antidepressants. Rapid metabolism is the flipside problem. Again occurring in perhaps 5% to 10% of the Caucasian population, although not apparently more frequently in non-Caucasians, rapid metabolizers are individuals whose hepatic cytochrome P450 system is overly efficient, leading to less available blood levels of psychotropic medications. Such individuals usually have a history of nonresponse to multiple full trials of

antidepressants *in the absence of any side effects*. In such persons, trials of higher than maximum doses, with appropriate informed consent and rationale, may be appropriate.

CLINICAL VIGNETTE

The patient is a 21-year-old man who has not responded to three full trials of antidepressants and has not tolerated two others. On his last trial, with the SRI sertraline, he did not respond to 200 mg per day after 2 months, at which point a blood test showed that his level was at the low end of the usual bioavailable range. Sertraline was increased to 300 mg per day, with his written consent, and laboratory tests showed that levels of that agent and its metabolites were in the middle of the usual bioavailable range. The patient then showed moderate benefit without significant side effects.

ADDING VERSUS SWITCHING

Once intolerability is ruled out, the big issue in approaching TRD is to decide between adding or switching medications. In switching, one would take patients off an ineffective antidepressant to try a completely new one. Adding would entail polypharmacy—adding another agent to augment the effect of an ineffective antidepressant. There are advantages and disadvantages to both approaches (Table 12.1). If patients tolerate the medications, the STAR-D data have now provided enough reason to generally prefer adding to switching.

TABLE 12.1. Comparison of the Switch versus Add Approach

Switch Approach	*Add (Combine) Approach*
Fewer side effects	More controlled studies
Better for initial complete nonresponse	Better for initial partial response
May identify single biochemical target	May benefit from multiple biochemical targets
Better compliance	Provides additive benefit with each drug
	Unlikely to run out of treatment options

CLINICAL VIGNETTE

The patient is a 45-year-old woman referred for TRD. She reports that she has tried "all" antidepressants, and they do not work. She has tried every single SRI singly, along with monotherapy trials of bupropion, venlafaxine, mirtazapine, and nefazodone. She has taken SRIs combined with bupropion. After referral, she is started on the TCA nortriptyline with moderate benefit. Lithium is then added with significant improvement but still some residual symptoms. At this point, low-dose sertraline is added with further improvement.

STAR-D: THE FIRST PHASES

The NIMH-sponsored STAR-D study is the largest (n = 3,671) and most expensive study ever conducted on antidepressant effectiveness in unipolar depression. This fact by itself should be sufficient to make the study results central to our clinical decision making regarding antidepressants. In the first edition of this book, most of my recommendations were based on my clinical experience as well as varied but irregular literature. Now I will be providing recommendations based on a stronger evidence base, although, as you will see, despite all this effort, STAR-D seems to have raised more questions than it has answered.

STAR-D was designed primarily to answer one question, although it also provided information on a few other questions. The primary question was, "What is the best treatment after someone fails one open trial of an antidepressant"? In this study, the initial open trial of an antidepressant was chosen to be citalopram. *Initial open response* (defined as no longer being in a major depressive episode) to that SRI was 47%, and *remission* (defined as almost no depressive symptoms after 3 months) was 33%. The results of this preliminary phase are relatively typical for previous studies of antidepressants.

The primary outcome data and later results were somewhat surprising, however (Figure 12.2): Only 31% of patients who had failed open citalopram had remission with the second phase of treatment (augmenting or switching antidepressants in a double-blind, randomized manner; there was no placebo), with not much difference among the treatment

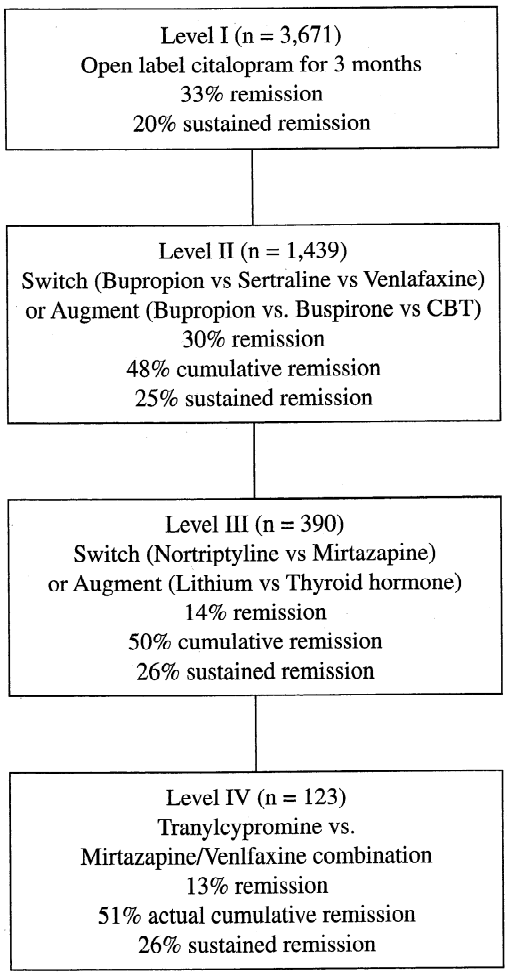

FIG. 12.2. STAR-D. (From Rush AJ, et al., *Am J Psychiatry.* 2006;163:1905-1917; Trivedi MH, et al. *N Engl J Med.* 2006;354:1243-1252; Rush AJ, et al., *N Engl J Med.* 2006; 354:1231–1242.)

options chosen (augmentation with bupropion or buspirone versus switch to bupropion or sertaline or venlafaxine). This remission rate seems somewhat lower than might have been expected.

The investigators have interpreted the results in terms of the good news: Overall, one-third of patients had full remission with a first antidepressant trial, and another third had full remission with a second trial, which added up to a cumulative remission rate in about one-half of patients. This is the good news. Now for the bad news: Of those who had remission in the first two phases of STAR-D, 34% to 47% relapsed within 1 year. Thus the actual *cumulative remission rate*—meaning persons who got well and stayed well for 1 year—was only 25%.

This means that after two antidepressant treatment trials, only 25% of patients really get better in a complete and long-term way; the rest either have only partial benefit or get better for a while and then relapse, or cannot tolerate the medications owing to side effects, or fail to get any benefit at all. Indeed, this 25% long-term remission hardly budges no matter what other treatments are used, including TCAs and MAOIs.

Overall, despite the best efforts of the investigators, this is not a rosy picture.

TIP

Only about one-quarter of patients with unipolar depression experience sustained remission with antidepressants.

I used to believe that antidepressants were not very effective in bipolar disorder but that they were effective in unipolar depression. Now I have my doubts about whether they are more than moderately beneficial for only some patients with unipolar depression. This overall 25% sustained remission rate in STAR-D stands in a vacuum: We do not know if it is better than placebo or the natural history of the illness or nonspecific supportive or psychotherapeutic factors involved in any clinical treatment. One might give the drugs the benefit of the doubt and assume that this 25% rate is better than nothing (or placebo), yet even if so, the effect size is small, much smaller than most clinicians have believed.

STAR-D: THE LATER PHASES

After the initial open citalpram phase and the second treatment trial of adding or switching antidepressants, STAR-D provided exploratory results on two other phases of treatment for more refractory unipolar depression. If patients failed both open citalopram and the second treatment trial, they were double-blind, randomized to switch to more effective antidepressants (e.g., nortriptyline or mirtazapine) or more proven augmentation treatments (e.g., lithium or thyroid hormone). If they failed this treatment phase, they were randomized to either receive the most proven antidepressant class, an MAOI (i.e., tranylcypromine), or combination treatment with venlafaxine plus mirtazapine. Remission rates were quite low in both these later phases (13% to 14%) with minimal differences between drugs. Again, in the absence of placebo, we do not know if a 14% remission rate in this refractory depression is better than nothing, although it may be. Even so, it is a small benefit. In other words, after failing two antidepressants, very few patients get truly better with more antidepressants, even the most proven options, such as TCAs and MAOIs.

TIP

In TRD, after failure of two initial antidepressant treatment trials, only about 15% of patients experience sustained remission.

It should be noted that the first two phases of STAR-D also included augmentation with cognitive behavioral therapy (CBT), but not many patients agreed to this option, and thus less data are available; nonetheless, it did not seem that CBT was much better or worse than any of the other antidepressant treatment options.

Could it be that the results of STAR-D are worse than real-world results because it was, after all, a research protocol with double-blinding for most of its phases? This is often the case. However, this study was designed to mimic real-world treatment as much as possible. The initial treatment was simply open label, which is the same as real-world practice, and in later double-blind phases, after the initial 2 months or so when outcomes were assessed for the research study, patients were allowed to receive any kind of naturalistic treatments

deemed necessary, just as in standard clinical care. Thus it is possible that these results are somewhat worse than real-world practice owing to research protocol effects, but not by much.

Most of the patients in STAR-D had recurrent depressive episodes and had been treated in the past with antidepressants. Thus some would say that this is a somewhat refractory sample. However, we already know that nonrecurrent depression does not require long-term antidepressant treatment. Thus these results seem relevant to the population for which we would consider long-term antidepressant treatment.

STAR-D: WHAT TO DO?

These results of STAR-D would seem to make most of the rest of this chapter unnecessary. If not much works, why bother getting into the ins and outs of treatment for TRD? This is one lesson the reader should learn. My suggestions here are not meant to imply that all patients with TRD need to be put through all these treatment options. However, a small group may benefit, and it is important for clinicians and patients to weigh the risks carefully before trying to achieve the benefit that might be available to some patients.

COMBINATION TREATMENTS

Specific combinations for refractory depression that have been studied in that setting are listed below.

Lithium Augmentation

Lithium has by far the most rigorous evidence in support of its effectiveness in the polypharmacy of refractory depression, again probably owing to past nondiagnosis of type II bipolar disorder. Thirteen controlled studies in over 300 patients generally have supported the efficacy of adding lithium to TCAs and SRIs for refractory unipolar depression. Some studies find benefit with low-dose lithium (600 mg per day), whereas others report the most benefit with full-dose lithium (900 to 1,200 mg per day, level goal of 0.8 ng/dL in nonelderly adults). Blood levels are not necessary for low-dose lithium use because they will be "low," although such a level is meaningless in the setting of

clinical response. In either approach, laboratory testing for kidney and thyroid function must be done (see Chapter 14).

TIP

In my experience, it is often useful to begin with low-dose lithium in refractory unipolar depression, and if there is no response after 1 month and the medication is tolerated reasonably well, I tend to proceed to full-dose lithium before ending the trial. Lithium should be dosed once daily at night to maximize compliance and minimize renal side effects (see Chapter 14).

In my opinion, the relative underuse of lithium (in the United States) for depression is partly due to lack of knowledge on the part of clinicians and partly due to misconceptions on the part of patients. For clinicians, lithium is often viewed as a "mood stabilizer," which frequently is misinterpreted to mean that it has no utility outside bipolar disorder. The numerous misconceptions about mood stabilizers are an important topic discussed in Chapter 7.

For patients, lithium is often identified with having a severe mental illness. Since lithium is used for manic depressive illness, and since manic depressive illness is often equated in the public mind with psychosis or schizophrenia, taking lithium must mean that one has a very severe mental illness. *Depression,* on the other hand, has less severe connotations, and frequently, persons are willing to accept the diagnosis of unipolar depression but unwilling to take lithium. Part of the job of the clinician is to educate patients about these misconceptions.

Besides these issues, probably the most legitimate concern about lithium is side effects, which I discuss in detail in Chapter 14. However, many concerns about side effects are more perceived than real. For most people, lithium has no serious medical complications; only a very small minority develops serious renal problems. The thyroid effect is reversible. Most nuisance side effects are limited in most people, and many depressed persons respond to doses that are lower than those associated with most side effects. Weight gain can occur, although not as severely or consistently as is sometimes assumed.

All this being said, lithium is not as simple to take or as benign as most antidepressants. But this relative disadvantage

should be weighed against the major advantage of strong evidence regarding lithium's efficacy in refractory depression, unlike most antidepressants.

KEY POINT

As mentioned in previous chapters, antidepressants have been proven to prevent suicide; lithium has too. In refractory depression, suicide risk is often present. The addition of lithium makes sense not only for mood symptoms but also to prevent suicide.

Most of the research in refractory unipolar depression only involves acute depression. Antidepressants usually are studied in combinations for a month or two to demonstrate acute benefit. Only lithium has been studied in a controlled study for long-term benefit in refractory unipolar depression. In a double-blind, placebo-controlled study of 29 patients, lithium maintained its initial acute benefit and appeared to provide prophylactic benefit for almost 6 months.

SRIs plus TCAs

Six studies have been conducted in this setting, most of them uncontrolled and only one randomized. These studies generally support benefit with the combination, although the one randomized study failed to find benefit with this combination when compared with simply increasing the dose of the SRI (in that case, fluoxetine). In general, it is prudent to raise the dose of the first antidepressants to as high a dose as tolerated before adding a second medication.

If one starts with an SRI, as is most commonly the case these days, then one has to be careful in terms of which agents to choose owing to drug-interaction issues. SRIs interact with TCAs owing to the inhibition of the hepatic cytochrome P450 enzymes by SRIs, particularly fluoxetine and paroxetine. This inhibition will lead to higher TCA blood levels and potential toxicity. This problem can be minimized by adding TCAs in low doses and carefully checking blood levels. Another option would be to use the SRIs with the least hepatic drug interaction effects (i.e., citalopram and sertraline) when combining with TCAs. As I described in Chapter 9, my TCA of choice is nortriptyline owing to the ability to titrate that drug to therapeutic blood levels. Desipramine may be a good second choice because it is almost a purely noradrenergic agent and thus would complement SRIs well in terms of providing a completely different mechanism of action. Other TCAs, such as imipramine or amitriptyline, are less tolerable and would have less complementary benefits because they too are strongly serotonergic, like the SRIs.

Thyroid Hormone Augmentation

After lithium augmentation, there is the most amount of placebo-controlled research with thyroid hormone in refractory unipolar depression (four studies, $n = 117$). These studies involve both T_3 (triiodothyronine) and T_4 (thyroxine), usually added to TCAs for nonresponsive unipolar depressed patients. Usual doses of T_3 are 25 to 50 μg/d, and doses of T_4 are usually in the 0.05 to 0.15 ng/d range. Thyroid hormone is usually given once daily in the morning.

The relative advantages of T_3 or T_4 are unclear. In one study, T_3 was more effective than T_4, but in another study best results were found with a combination of the two. There is some endocrinologic opinion that T_3 may lead to a somewhat higher risk of osteoporosis. Sometimes it is reasoned that T_4 is the best choice because it gets converted to T_3 to some degree physiologically in any case. At this time I think clinicians should try both formulations and base their judgments on their own clinical experience.

Despite this level of evidence, again better than for most antidepressants, it appears that thyroid hormone use for refractory unipolar depression is not as common as the evidence would support. Nuisance side effects are not usually the issue. Thyroid hormone sometimes can lead to some weight loss, which is usually welcomed by patients. It also can cause palpitations, sweating, or anxiety, all of which usually resolve without complications if the medication is stopped. The doses mentioned here are usually so low that a hyperthyroid state is rarely produced, and such side effects are uncommon and mild. I think that thyroid hormone may be underused because of concerns among psychiatric clinicians regarding the endocrinologic side effects, which are often highlighted by endocrinologic specialists. These include the risk of osteoporosis and the induction of hyperthyroidism. As just mentioned, hyperthyroidism is quite rare with low-dose treatment and resolves if it occurs. Osteoporosis is mainly a concern in postmenopausal women and usually a risk with excessive thyroid hormone treatment.

One way to assess whether thyroid hormone treatment is excessive is to follow thyroid-stimulating hormone (TSH) levels. This hormone reflects the feedback loop from the body to the pituitary about the amount of thyroid hormone present in the body. If too much thyroid hormone is present in the body, a negative-feedback signal is sent to the brain, and TSH levels fall. Thus low TSH levels suggest excessive thyroid hormone activity, potentially increasing the risk of osteoporosis.

With adequate attention to these potential effects, however, thyroid hormone treatment generally is quite benign and can be very effective in treating refractory unipolar depression.

OTHER TREATMENTS WITH RANDOMIZED EVIDENCE

There are a number of other treatment options supported by controlled research, although most of these options have less evidence than the three major alternatives just described. One approach is the addition of pindolol, a beta-adrenoceptor/5-HT receptor antagonist, to SRIs. Pindolol is an antagonist of both serotonin autoreceptors and beta-adrenoceptors. However, evidence more strongly suggests that pindolol use speeds up antidepressant response rather than produces benefit in refractory depression, and its use is not very popular.

Recent STAR-D data found benefit with buspirone added to SRI therapy for refractory depression. Typical buspirone dosing for depression likely needs to be above 30 mg per day, beginning at 5 mg bid and increasing by 5-mg intervals to a dosage range of 30 to 45 mg per day in bid or tid dosing.

Another major class sometimes used for refractory unipolar depression is the atypical neuroleptic class. In this setting, these agents are being used for antidepressant rather than antipsychotic effect. There is some biochemical rationale for possible antidepressant effects with these agents because they block 5HT-2 receptors, a mechanism shared with some antidepressants (e.g., nefazodone and mirtazapine). This mechanism by itself would at best lead to mild antidepressant benefit, and current clinical experience suggests that this is indeed the case with these agents.

Olanzapine is probably the most studied, with a number of double-blind, randomized studies in both nonrefractory and refractory unipolar depression, as well as bipolar depression and psychotic unipolar depression. The upshot of all these studies is that olanzapine alone repeatedly is similar to placebo; in other words, olanzapine alone likely has no antidepressant benefits. Further, olanzapine added to antidepressants was not effective in most studies when compared with antidepressant alone. The only situation where some benefit was seen was lack of acute mania induction with fluoxetine when combined with olanzapine for acute bipolar depression; that study led to an FDA indication of the olanzapine-fluoxetine combination in acute bipolar depression. This indication should not be mistaken to support any long-term use with this drug combination, nor does it prove any real antidepressant benefit to the olanzapine portion of the compound.

In contrast, two studies of queitapine (300 mg per day) showed marked benefit in acute bipolar depression. Whether such benefit extends to unipolar depression is unclear. The possibility also exists that the benefit seen was not a real antidepressant effect but rather efficacy in the depressive mixed state (see Chapter 3).

The two newest atypical neuroleptic agents, ziprasidone and aripiprazole, both have intrinsic antidepressant-like mechanisms (SRI for ziprasidone and serotonin agonism for aripiprazole), new randomized data indicate that aripiprazole is effective, when added to antidepressant, in TRD. Clinical experience suggests potential benefit for refractory depression, again, in my view, more so in the depressive mixed state than in pure depression. Lower doses may provide more of the antidepressant mechanism with less dopamine blockade (40 to 160 mg per day, given bid, for ziprasidone; 5 to 15 mg per day for aripiprazole).

The disadvantages in using most atypical neuroleptics involve weight gain (except ziprasidone and aripiprazole), metabolic syndrome risk (primarily olanzapine and clozapine), and extrapyramidal symptoms (EPS). Other specific risks apply to each agent and should be kept in mind (see Chapter 17).

CONSIDER THE USE OF TCAs OR MAOIs IF NOT USED PREVIOUSLY

Before moving on to other treatment strategies, which though often effective, are not based on controlled research, I want to reemphasize that it is also important to consider the use of TCAs or MAOIs in refractory unipolar depression. Many patients are labeled refractory because they fail a few SRIs and then begin polypharmacy with other agents. Often

such patients can receive 5 to 10 trials of antidepressants in various combinations without ever receiving a single trial of a TCA or MAOI. As discussed in Chapter 9, these antidepressant classes are very effective, and especially in SRI nonresponders, serious thought should be given to simply switching to a TCA or an MAOI before trying multiple antidepressant combinations. Side effects are obviously a concern, but the risk of side effects is frequently outweighed by the potential benefits of these agents in refractory unipolar depression.

OTHER TREATMENTS WITHOUT RIGOROUS EVIDENCE

I will mention other important options commonly used because of their safety, although double-blind, controlled studies on these combinations are lacking. Perhaps the most common combination in many circles is the combination of SRI plus bupropion. This combination has both serotonergic and dopaminergic effects, and the two types of medications do not tend to interact negatively. In fact, besides augmenting antidepressant effect, the addition of bupropion to SRIs clearly improves sexual dysfunction.

The combinations of venlafaxine plus lithium and venlafaxine plus bupropion are also sometimes used. As a serotonergic agent with some noradrenergic effects, venlafaxine may respond like SRIs in terms of being augmented in its effect by either lithium or bupropion.

Nefazodone and mirtazapine are both at least partly serotonergic, and thus the same kinds of combinations discussed earlier could be relevant to these agents. Either nefazodone or mirtazapine could be combined with TCAs, lithium, thyroid hormone, or bupropion.

MAOIs can be combined with lithium or even with TCAs, although some cases of toxic reactions with these combinations have been reported. As discussed in Chapter 9, selegiline may have some lower toxicity potential than other MAOIs. MAOIs should never be combined with SRIs or other serotonergic agents owing to the risk of serotonin syndrome.

Amphetamine stimulants can be combined with SRIs on the same reasoning as the addition of bupropion, that is, the addition of a dopaminergic mechanism. Amphetamine stimulants also can be used with venlafaxine, mirtazapine, nefazodone, and lithium.

PSYCHOTIC UNIPOLAR DEPRESSION

I will discuss psychotic unipolar depression in the setting of treatment resistance because these patients are frequently misdiagnosed as having refractory nonpsychotic unipolar depression. This happens often because patients with psychotic unipolar depression appear to need treatment with both neuroleptic and antidepressant medications. If their depression is recognized but not the psychosis (which is often the case), they will receive antidepressants alone, to which they are poorly responsive. It is very important in all depressed patients to question them carefully about delusions and hallucinations so as to rule out psychotic depression. All patients with refractory unipolar depression should be interviewed carefully for psychotic symptoms. Research studies have demonstrated that patients with psychotic depression often lack insight into their psychotic symptoms, perhaps more so than into their depressive symptoms. Hence they are more likely to describe their depressive than their psychotic symptoms.

If psychotic depression is present, the standard of care is a combination treatment with antidepressant and neuroleptic. The classic findings in one oft-cited study was that response to a traditional neuroleptic alone was 19%, to a tricyclic antidepressant alone was 41%, and to the combination was 78%.

TIP

I suggest remembering this effect as the 20-40-80 rule, with each step leading to a doubling of efficacy. Thus neuroleptic alone produces a 20% response (essentially no better than placebo); antidepressant alone produces a 40% response (only slightly better than placebo); and the combination produces an 80% response (slightly higher than standard antidepressant response in nonpsychotic depression).

CLINICAL VIGNETTE

The patient is a 60-year-old man referred for refractory depression. He has failed seven monotherapy antidepressant trials, including all SRIs, venlafaxine, bupropion, and nortriptyline. He also has failed combination treatments with SRI

plus TCA, as well as addition of lithium and thyroid hormone. On evaluation, his wife describes suspicious thinking during most of his depressive episodes. He enters into treatment and fails to respond to an MAOI trial in monotherapy, followed by lithium and thyroid hormone augmentation. A few months later, after establishing a therapeutic alliance, he confides that he sometimes hears his name called in the middle of the day. An atypical neuroleptic is added to his regimen with significant improvement. Other agents are then decreased, and ultimately he is maintained on an MAOI plus the atypical neuroleptic.

Repeated studies of olanzapine and risperidone in particular seem to indicate that these medications do not have much efficacy in monotherapy for acute unipolar psychotic depression. Thus the scenario with atypical neuroleptics does not seem to be any different from that with traditional neuroleptics, meaning that they need to be used with antidepressants, not by themselves, for optimal efficacy in unipolar psychotic depression. Future research on ziprasidone and aripiprazole may find more efficacy with those agents in this condition, but it is not yet clear whether this is the case.

ELECTROCONVULSIVE THERAPY (ECT)

ECT is an important option in the treatment of refractory unipolar depression. It could be used at any point. In practice, it is used most often in inpatient settings, usually influenced by the need (often related to managed-care restrictions) to discharge patients quickly. ECT has been shown to be the most effective treatment in psychotic depression in particular (82% overall response), edging the TCA-neuroleptic combination in recent meta-analyses.

It is worth noting, however, that ECT is not a cure-all. It is almost as much taken for granted in psychiatric circles that ECT is effective and safe as it is taken for granted in lay circles that it is not. For clinicians, it is important to recognize the limitations of ECT as well. Otherwise, all the previous strategies discussed in this chapter would be unnecessary. One limitation is that the effect of ECT is transient. ECT can be necessary for a refractory major depressive episode, which it can help resolve, but it does not confer prophylactic efficacy after an acute trial. Some recent research suggests that in patients who have refractory depression (mostly unipolar) such that they need ECT, continuation of ECT on a maintenance basis is far more effective than reversion to other medication treatments. In other words, if one resorts to ECT for refractory unipolar depression, one may need to be prepared to commit the patient to lifelong ECT treatment. Further, for bipolar depression, the evidence of efficacy of ECT is meager indeed, certainly in the long term.

Besides those caveats regarding the need for long-term ECT treatment in highly refractory patients, the other major limitation is cognitive side effects, a problem that has been long studied and is not completely resolved. Most research suggests that such side effects are short lived and mild, although many patients in my experience report a greater amount of cognitive trouble than one might expect based on the available research. The relevant factors include the type of ECT given (more problems with bilateral treatment), ECT voltage (perhaps worse with higher voltage), concurrent medications (perhaps worse with lithium or other agents that independently affect cognition), and patient factors (concurrent neurologic or medical illnesses).

Hence, while it certainly is acutely effective, the decision to use ECT needs to be made carefully, with consideration of whether long-term benefit will occur, as well as a discussion about cognitive side effects and the potential need for maintenance ECT treatment. In all these discussions, the patient's beliefs and fears need to be respected and addressed thoughtfully. In my opinion, ECT remains a near-last-resort option for most patients with refractory unipolar depression mainly because of the transience of its benefit. In someone with severe suicidality, ECT may be needed short term, but in most patients with refractory unipolar depression, it provides only a limited reprieve, often at the price of significant cognitive problems. In my practice, if I turn to ECT for refractory depression, I turn to it for acute and maintenance treatment and then obviously only if the patient agrees to such a course. In most cases, if one tries hard enough, one can find the right combination of medications to at least somewhat alleviate refractory unipolar depression. Unlike acute ECT, finding the right medications has the advantage of serving as a prophylactic treatment as well. Again, I would agree that an exception is the patient with such severe refractory acute unipolar depression with marked suicidality that short-term improvement is the primary goal of treatment initially, and long-term considerations are more secondary; in such a patient, ECT can be lifesaving.

OTHER NONMEDICATION OPTIONS: VNS, TMS, DBS

As for vagus nerve stimulation (VNS), one can be brief: The data demonstrate that it is the same as placebo. Much has been made of FDA indication granted based on observational benefit in about 20% of persons over 1 year. This kind of evidence, in the case of medications, would be irrelevant because it is so weak. The FDA has a low threshold for approval of a device, as opposed to medications, which require much more rigorous data. It seems to me that one should instead have a higher threshold to use an invasive treatment that requires surgery and results in scarring, such as VNS. Given the weakness of the data and the invasiveness involved, my own view is that it is not a scientifically supportable and clinically rational treatment option.

Transcranial magnetic stimulation (TMS) may be effective in nonrefractory depression but does not appear as powerful as ECT and thus likely will be relatively ineffective in refractory depression. It may be a viable treatment option for those with nonrefractory depression who cannot take medications, however. It has the advantage of not causing notable cognitive deficits, unlike ECT.

Deep brain stimulation (DBS), in use for neurologic syndromes, may have some potential benefit in refractory depression, but controlled evidence is lacking. Again, given the invasiveness, the risk-benefit ratio does not seem favorable at this time.

ACHIEVING REMISSION: DUAL-ACTING AGENTS OR SELECTIVE ANTIDEPRESSANTS?

In general, then, the treatment of refractory unipolar depression requires polypharmacy (see Chapter 24). Often polypharmacy involves the logical combination of antidepressants with differing mechanisms of action. Thus, if an SRI is ineffective, then a TCA adds a noradrenergic mechanism. Or perhaps bupropion augments the SRI by providing a dopaminergic mechanism. Thus there appears to be increased efficacy of treatment with polypharmacy that affects multiple neurotransmitters.

Turning this concept around, some pharmaceutical companies are marketing a single medication with multiple neurotransmitter effects as being more effective in achieving remission than drugs, such as SRIs, which only affect one neurotransmitter. This claim appears to be logical and is in fact supported by some empirical studies. One might call this "polypharmacy in one pill." For instance, venlafaxine inhibits norepinephrine as well as serotonin reuptake, and mirtazapine also affects both norepinephrine and serotonin.

Yet I would suggest a few caveats before we simply assume that all patients should take antidepressants with multiple actions. First, as discussed in Chapter 11, SRIs are not truly "selective" for serotonin reuptake, with paroxetine and fluoxetine having noradrenergic effects, and sertraline having dopaminergic effects. Second, many patients respond well to SRIs without needing dual-acting agents, often with fewer side effects. Third, some proposed that dual-acting agents are not as clearly different from SRIs in their mechanisms; for instance, fluoxetine in some animal studies has a potency of norepinephrine reuptake blockade that is similar to venlafaxine. Finally, the current rise in interest in multiple neurotransmitter effects seems ironic, since one of the major reasons SRIs had been marketed as better treatments than TCAs was the fact that they were more specific in their neurotransmitter effects. Psychopharmacology is a mixture of science and marketing, and the onus is on clinicians to be thoughtfully skeptical.

SUMMARY

In terms of a general summation, the following conclusions make sense: Assuming that one begins treatment with single-antidepressant treatment trials of SRIs or bupropion, useful next options are combinations of those two types of medications or other combinations such as an SRI plus TCAs, addition of lithium or thyroid hormone, switch to dual-acting agents such as venlafaxine or mirtazapine, or switch to other proven treatments such as TCAs or MAOIs. One also can consider adding augmenters such as atypical neuroleptics, buspirone, or pindolol. Amphetamine stimulants also can be effective. In refractory unipolar depression, the presence of psychosis also should be carefully assessed repeatedly, and if identified, atypical antipsychotic treatment is indicated, with possibly the best outcomes with ziprasidone. ECT is an option at any stage for severe suicidal depression. In other circumstances, when used after failure to respond to numerous antidepressants, serious consideration to maintenance ECT should be given. Before putting patients through all these potentially harmful tretments, however, we should make sure patients do not have bipolar depression (leading to mood stablizer use or psychotherpy as the primary treatment, respectively).