



FIGURE 466-1 A guideline for the medical management of major depressive disorder. SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

for achieving remission and preventing relapse is medication, but combined treatment, incorporating psychotherapy to help the patient cope with decreased self-esteem and demoralization, improves outcome (Fig. 466-1). Approximately 40% of primary care patients with depression drop out of treatment and discontinue medication if symptomatic improvement is not noted within a month, unless additional support is provided. Outcome improves with (1) increased intensity and frequency of visits during the first 4–6 weeks of treatment, (2) supplemental educational materials, and (3) psychiatric consultation as indicated. Despite the widespread use of SSRIs and other second-generation antidepressants, there is no convincing evidence that these classes of antidepressants are more efficacious than TCAs. Between 60 and 70% of all depressed patients respond to any drug chosen, if it is given in a sufficient dose for 6–8 weeks.

A rational approach to selecting which antidepressant to use involves matching the patient's preference and medical history with the metabolic and side effect profile of the drug (Tables 466-4 and 466-5). A previous response, or a family history of a positive response, to a specific antidepressant often suggests that that drug be tried first. Before initiating antidepressant therapy, the physician should evaluate the possible contribution of comorbid illnesses and consider their specific treatment. In individuals with suicidal ideation, particular attention should be paid to choosing a drug with low toxicity if taken in overdose. Newer antidepressant drugs are distinctly safer in this regard; nevertheless, the advantages of TCAs have not been completely superseded. The existence of generic equivalents makes TCAs relatively cheap, and for secondary tricyclics, particularly nortriptyline and desipramine, well-defined relationships among dose, plasma level, and therapeutic response exist. The steady-state plasma level achieved for a given drug dose can vary more than 10-fold between individuals, and plasma levels may help in interpreting apparent resistance to treatment

and/or unexpected drug toxicity. The principal side effects of TCAs are antihistamine (sedation) and anticholinergic (constipation, dry mouth, urinary hesitancy, blurred vision). TCAs are contraindicated in patients with serious cardiovascular risk factors, and overdoses of tricyclic agents can be lethal, with desipramine carrying the greatest risk. It is judicious to prescribe only a 10-day supply when suicide is a risk. Most patients require a daily dose of 150–200 mg of imipramine or amitriptyline or its equivalent to achieve a therapeutic blood level of 150–300 ng/mL and a satisfactory remission; some patients show a partial effect at lower doses. Geriatric patients may require a low starting dose and slow escalation. Ethnic differences in drug metabolism are significant, with Hispanic, Asian, and black patients generally requiring lower doses than whites to achieve a comparable blood level. P450 profiling using genetic chip technology may be clinically useful in predicting individual sensitivity.

Second-generation antidepressants are similar to tricyclics in their effect on neurotransmitter reuptake, although some also have specific actions on catecholamine and indolamine receptors as well. Amoxapine is a dibenzoxazepine derivative that blocks norepinephrine and serotonin reuptake and has a metabolite that shows a degree of dopamine blockade. Long-term use of this drug carries a risk of tardive dyskinesia. Maprotiline is a potent noradrenergic reuptake blocker that has little anticholinergic effect but may produce seizures. Bupropion is a novel antidepressant whose mechanism of action is thought to involve enhancement of noradrenergic function. It has no anticholinergic, sedating, or orthostatic side effects and has a low incidence of sexual side effects. It may, however, be associated with stimulant-like side effects, may lower seizure threshold, and has an exceptionally short half-life, requiring frequent dosing. An extended-release preparation is available.

SSRIs such as fluoxetine, sertraline, paroxetine, citalopram, and escitalopram cause a lower frequency of anticholinergic, sedating, and cardiovascular side effects but a possibly greater incidence of gastrointestinal complaints, sleep impairment, and sexual dysfunction than do TCAs. Akathisia, involving an inner sense of restlessness and anxiety in addition to increased motor activity, may also be more common, particularly during the first week of treatment. One concern is the risk of "serotonin syndrome," which is thought to result from hyperstimulation of brainstem 5-HT_{1A} receptors and characterized by myoclonus, agitation, abdominal cramping, hyperpyrexia, hypertension, and potentially death. Serotonergic agonists taken in combination should be monitored closely for this reason. Considerations such as half-life, compliance, toxicity, and drug-drug interactions may guide the choice of a particular SSRI. Fluoxetine and its principal active metabolite, norfluoxetine, for example, have a combined half-life of almost 7 days, resulting in a delay of 5 weeks before steady-state levels are achieved and a similar delay for complete drug excretion once its use is discontinued. All the SSRIs may impair sexual function, resulting in diminished libido, impotence, or difficulty in achieving orgasm. Sexual dysfunction frequently results in noncompliance and should be asked about specifically. Sexual dysfunction can sometimes be ameliorated by lowering the dose, by instituting weekend drug holidays (two or three times a month), or by treatment with amantadine (100 mg tid), bethanechol (25 mg tid), buspirone (10 mg tid), or bupropion (100–150 mg/d). Paroxetine appears to be more anticholinergic than either fluoxetine or sertraline, and sertraline carries a lower risk of producing an adverse drug interaction than the other two. Rare side effects of SSRIs include angina due to vasospasm and prolongation of the prothrombin time. Escitalopram is the most specific of currently available SSRIs and appears to have no specific inhibitory effects on the P450 system.

Venlafaxine, desvenlafaxine, duloxetine, vilazodone, vortioxetine, and levomilnacipran block the reuptake of both norepinephrine and serotonin but produce relatively little in the way of traditional tricyclic side effects. Unlike the SSRIs, venlafaxine and vortioxetine have relatively linear dose-response curves. Patients on immediate release venlafaxine should be monitored for a possible increase in diastolic blood pressure, and multiple daily dosing is required