The Argument for the Primary Care Physician's Involvement in Depression Management

Depression often accompanies many ailments seen in the primary care setting.[12] Depressive complaints are common in patients with chronic pain, sleep disorders, diabetes, arthritis, cerebrovascular accident (stroke), and heart disease.[12-15] In addition, numerous medical conditions, such as malignancies and thyroid or adrenal disorders, may initially present as depression.[16,17] Comorbid or primary substance abuse disorders (particularly alcohol dependence) must also be considered and ruled out.

When depression has a late onset (after age 45 years) or occurs in the absence of personal or family history, the PCP should be especially vigilant for undetected medical illness (Table 1). Routine laboratory testing, including complete blood cell count, electrolytes, B12, folate, and thyroid-stimulating hormone, may help pinpoint the underlying medical condition (eg, depression due to hypothyroidism).[18]

Table 1. Medical Disorders Commonly Presenting With Depression [18]

Viral illness (mononucleosis, HIV)	**Malignancies** (gastrointestinal, pancreatic)
Endocrine (thyroid, adrenal dysfunction)	**Hematologic** (anemia due to decreased B12, folate)
Cerebrovascular (poststroke)	**Collagen-vascular** (SLE, rheumatoid arthritis)
Degenerative CNS (Parkinson's, Huntington's disease)	**Drugs/toxins** (corticosteroids, antihypertensives)
Sleep disorders (obstructive sleep apnea)	*SLE = systemic lupus erythematosus; CNS = central nervous system*

In many cases, successful treatment of the medical disorder will alleviate or eliminate the depression; however, in some instances, concomitant treatment of the depression is necessary. Sometimes medications cause or exacerbate symptoms of depression (Table 2). Corticosteroids, calcium channel blockers, antihypertensive agents, and possibly beta blockers have all been implicated as causes of depressive symptoms; hence, a careful review of both prescribed and over-the-counter medications is essential.[19] The PCP can serve as the overall coordinator of such medication assessment, while seeking consultation with psychiatrists in selected cases.

Table 2. Medications That May Cause or Worsen Depression [18]

Beta-blockers	Calcium channel blockers

Interferons	Histamine-2-blockers
Clonidine, other antihypertensives	Corticosteroids
Procainamide	Indomethacin
Barbiturates	Narcotics
Phenytoin	Anabolic steroids

Finally, several studies have demonstrated that early recognition and treatment of depression in the primary care setting can have a positive effect on social, physical, and mental functioning. Increased productivity and decreased absenteeism in the work place could result from timely treatment. [20, 21] Conversely, the failure of PCPs to detect depression and its causes can delay potentially life-saving treatment.

Pathophysiology

In the fourth century BCE, Hippocrates hypothesized that "melancholy" was due to an excessive accumulation of "black bile."[2] The term "melancholia" is used today in the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, (DSM-IV) to describe an especially severe form of major depression, but the precise biologic causes of depression are still not fully understood, though research has uncovered important new leads. For the past 40 years, theories of depression have focused on abnormalities in the monoamine neurotransmitters, serotonin (5-HT), norepinephrine (NE), and dopamine (DA). Iproniazid, an agent used in the treatment of tuberculosis, was also found to help with symptoms of depression. This agent inhibits the breakdown of monoamines, similar to the action of monoamine oxidase (MAO) inhibitors (see below). Conversely, reserpine, a medication once used in the treatment of hypertension, has been shown to induce depression. Reserpine causes depletion of catecholamines, specifically NE, within the central nervous system. Based on these 2 pharmacologic mechanisms, both 5-HT and NE have been implicated in depression.[22-24] Currently, all antidepressants with approval from the US Food and Drug Administration (FDA) affect one or both of these neurotransmitters. Most conventional antidepressants block the reuptake of neurotransmitters, leading to greater availability in the synaptic cleft (see below).

A more sophisticated "permissive hypothesis" suggests that low levels of both 5-HT and NE are associated with depression, whereas low 5-HT and high NE may induce mania.[25] This theory is an important heuristic concept. Unipolar and bipolar depression must be managed differently, since antidepressant agents could induce mania in a person with bipolar disease.

Although the monoamine hypothesis has generated many useful research strategies, it does not fully account for the etiology of depression or for the effects of antidepressants. For example, monoamine reuptake inhibitors exert their biochemical effects almost immediately. Their antidepressant effects, however, may not be seen until after 4 or more weeks of therapy.[23] Moreover, drugs without known monoamine activity, such as substance-P inhibitors, have demonstrated antidepressant activity in some animal models.[26] Hence, recent hypotheses have focused on more fundamental mechanisms of antidepressant action, such as the neuroprotective effects of these agents. For example, brain-derived neurotrophic factor (BDNF) is considered neuroprotective and may increase nerve growth in the hippocampal area.[27] Some depressed individuals have been found to have neuronal atrophy in the hippocampus. Thus, in theory, increasing BDNF levels might affect mood in symptomatic individuals. Long-term antidepressant therapy (ie, over several weeks) increases BDNF and prevents its "down-regulation," possibly explaining the well-documented lag phase, prior to antidepressant response. Recently, exposure to antidepressants has been linked with protection against gray matter loss in depressed elderly patients.[28] Similar neuroprotective effects may also explain the efficacy of some mood stabilizers and electroconvulsive therapy (ECT).

Finally, a number of neuroendocrine mechanisms have been explored as contributing factors in certain types of depression. For example, psychotically depressed patients frequently demonstrate one or more abnormalities in the hypothalamic-pituitary-adrenal axis, such as abnormally high levels of 24-hour urinary-free cortisol, higher rates of dexamethasone nonsuppression, and high postdexamethasone cortisol levels.[29] High levels of glucocorticoids are believed to have deleterious effects in several brain regions, including the frontal cortex and hippocampus, and several antiglucocorticoid agents are being investigated in the treatment of psychotic depression.[29]

Making the Diagnosis of Depression

Differential Diagnosis

The DSM-IV, text revision, describes 2 main types of clinically significant unipolar depressive disorders: major depressive disorder (MDD) and dysthymia.[30] The term "major depressive episode" is not itself a diagnosis, but rather a "building block" for both MDD and bipolar disorder. In the DSM-IV, a major depressive episode is conceptualized as a severe disturbance in mood lasting at least 2 consecutive weeks, characterized by one or more alterations in sleep, appetite, interest, pleasure, energy, and thinking. The main DSM-IV criteria for a major depressive episode are summarized in Table 3. For example, type I bipolar disorder consists of periods of

mania alternating with major depressive episodes. The umbrella term "major depression" is often used to encompass the terms "major depressive episode" and "major depressive disorder."

Table 3. Major Depressive Episode: Typical Signs and Symptoms[30]

Loss of interest, satisfaction, or pleasure in almost all activities, lasting at least 2 weeks	Appetite and sleep disturbance (early morning awakening is "classic")
Decreased energy, concentration, or libido	Low self-esteem or excessive guilt
Recurrent thoughts of death or suicide	Psychomotor agitation or retardation
Sometimes psychotic features (delusions, hallucinations)	Atypical features may be present in elderly, children/adolescents

The actual presentation of a major depressive episode is quite heterogeneous. For example, patients may present with insomnia or hypersomnia, weight loss or weight gain, psychomotor agitation or retardation, etc. The term "atypical depression" is sometimes used to describe depression characterized by weight gain rather than weight loss; hypersomnia rather than insomnia; reactive mood rather than constant depression; a sensation of "leaden paralysis"; significant anxiety; and marked rejection sensitivity. Atypical depression may have an earlier onset and greater prevalence in women than other types of depression, and appears to be particularly responsive to MAO inhibitors, as discussed below.[31] Marked psychomotor retardation, weight gain, and hypersomnia, however, are sometimes a clue to undiagnosed bipolar depression, which requires a different treatment approach.[32] Anxiety disorders are highly comorbid with major depressive episodes and are often difficult to tease out from depression. Fortunately, the management of anxiety and depression have nearly converged in recent years. Children and adolescents may present with less classic features of depression, such as poor school performance, irritability, or "acting out." Elderly depressed patients may present with a more "somatized" picture in which depressed mood is minimized or even denied.

By definition, the symptoms of a major depressive episode cannot be due directly to substances known to induce depression, such as reserpine, barbiturates, and alcohol, or to known medical disorders, such as hypothyroidism. Of course, such disorders are sometimes comorbid with a pre-existing major depressive episode or disorder. A major depressive episode should also be distinguished from uncomplicated grief or bereavement (Table 4), which theoretically should resolve within 2 months after a major loss, such as the death of a spouse.[29] In practice, however, the boundary between severe, unresolved bereavement and major depression is not always sharp.

Table 4. Normal Grief or Uncomplicated Bereavement[18]

Usually not associated with prolonged period (> 3 months) of incapacity	Usually does not entail severe "neurovegetative" signs (severe weight loss, early morning awakening, psychomotor retardation, etc.)
Rarely associated with suicidal intention/plan	Usually not associated with severe loss of self-esteem, severe guilt
Usually somewhat responsive to "positive" events	

Dysthymic disorder, or dysthymia, is qualitatively similar to MDD, but tends to be less severe and is present over a period of at least 2 years. Many dysthymic individuals have experienced nearly lifelong depression. By definition, full criteria for MDD are not met in dysthymia, and pronounced suicidal or psychotic symptoms are uncommon. However, in clinical practice, the distinction between "severe" dysthymia and "mild" MDD is more theoretical than real, particularly since treatment is similar for both disorders. Indeed, many patients suffer from so-called "double depression" (ie, comorbid MDD and dysthymia), and it is often difficult to tell precisely when each disorder "began." It is important to recognize this subgroup, since these comorbid patients tend to have a poor prognosis. Finally, the term "minor depressive disorder" appears in the Appendix of DSM-IV as a condition meriting further study. This disorder generally refers to one or more periods of depressive symptoms identical to MDD in duration, but which involve fewer symptoms and less impairment[30] (see the Patient Health Outcomes-9 Symptom Checklist, or PHQ-9, below).

Screening Questions and Instruments

In the current high-pressure practice environment, questions aimed at diagnosing MDD or dysthymia may be neglected by the busy clinician. Yet, careful inquiry into SIGECAPS -- *S*leep, *I*nterest, *G*uilt, *E*nergy, *C*oncentration, *A*ppetite, *P*sychomotor function, and *S*uicide -- are of critical importance. Remembering the mnemonic SIGECAPS can aid in proper screening for these signs and symptoms.[27] Complaints in 4 or more of these categories (feeling guilty, sleeping poorly, having low energy, etc.) point to a major depressive episode. Two or 3 complaints may suggest "minor depression," though this category should not be dismissed lightly. Left untreated, some patients with less severe depression may worsen.

Many SIGECAPS signs and symptoms are nonspecific -- difficulties in sleep may be associated not only with depression, but with obstructive sleep apnea, restless leg syndrome, chronic obstructive pulmonary disease, and a host of medical or drug-related conditions. Similarly, low energy or poor appetite might also point to an underlying medical disorder. Optimal treatment of known

medical condition(s) should generally precede use of antidepressants, so that the patient's physical and emotional baseline may be established. In cases of residual depression or comorbid depression and medical illness in optimally treated, medically ill patients, antidepressants may be useful, and even essential, agents.[33]

If time does not permit SIGECAPS questioning, the clinician may also use patient-completed questionnaires, which can often be filled out in the waiting room. The most widely used self-completed depression scale is the Beck Depression Inventory (BDI),[34] which was first introduced in 1961. The BDI consists of 21 items covering most dimensions of major depression, including suicidal ideation and plans. A more recent self-rated questionnaire is the PHQ-9, or Patient Health Outcomes-9 Symptom Checklist.[35] The usefulness and accuracy of the PHQ-9 is well documented.[35,36]

The PHQ-9 questionnaire consists of 2 parts. The first section contains 9 separate questions in which the patient circles the appropriate response for duration of the described feeling. These questions focus on experience of pleasure, sleep habits, energy, appetite, concentration, and suicidal ideation. Part 2 is a single question that assesses the functional health of the patient based on the questions in Part 1. The results are then tallied by the clinician to determine if the individual warrants treatment for depression. The total score can fall into 3 ranges. Scores less than 4 usually indicate that the patient does not require treatment, whereas scores greater than 15 would necessitate therapy. Scores between 4 and 15 are intermediate, with the decision to treat left up to the clinician and patient. The length of time the patient has experienced the symptoms and functional impairment should be considered for patients falling into this intermediate category. Scoring of the results can be completed in less than 3 minutes.[35] The PHQ-9 eliminates the need for questioning in all areas of depressive symptoms and allows the clinician to focus only on those requiring attention.

Finally, 2 self-completed scales aimed at detecting bipolar disorder have been validated recently, the Mood Disorder Questionnaire (MDQ) and the Bipolar Spectrum Diagnostic Scale (BSDS).[37,38] These scales may help the PCP sort out the difficult but critical issue of unipolar vs bipolar depression. Indeed, all patients with depressive complaints should be carefully screened for periods of mania, hypomania, or mood instability.[32]

The entire MDQ is available in many places, for example in the article about its development and validation by Hirschfield and colleagues,[37] while the BSDS appears here.

Assessing Suicidality

The PCP is in an excellent position to provide early, proactive screening for suicidality. The strongest risk factors for suicidal behavior include *a history of previous suicide attempt(s), presence of current severe depression, presence or history of bipolar disorder, schizophrenia, active or recent substance abuse, and aggressive/impulsive personality traits.* PCPs should be mindful that the presence of severe, chronic medical illness, especially when accompanied by pain and incapacity, also increases the risk of suicide.[39] Other risk factors are summarized in Table 5.

Table 5. Suicide Assessment[39,40]

Risk Factors for Completed Suicide (RFCS): A Provisional Assessment Tool

- ☐ *History of previous suicide attempt*
- ☐ *Presence of current severe depression*
- ☐ *Presence or history of bipolar disorder (especially current depressed or mixed features)*
- ☐ *Schizophrenia/psychosis (especially with command auditory hallucinations)*
- ☐ *Active or recent substance/alcohol abuse or dependence*
- ☐ *Aggressive/impulsive features or borderline personality disorder*
- ☐ Victim of physical or sexual abuse
- ☐ Active medical illness, especially with incapacity or pain
- ☐ Hopeless, helpless feeling
- ☐ Strong sense of shame
- ☐ Agitated, severely anxious
- ☐ Confused, delirious
- ☐ Current severe insomnia
- ☐ Socially isolated, lacks supports or living alone
- ☐ Easy access to lethal means (guns, barbiturates, etc.)
- ☐ Recent major loss or personal crisis
- ☐ Recent exposure to highly publicized suicide (esp. in adolescents)
- ☐ Giving away possessions, stockpiling pills, preparing for death
- ☐ Well-organized, detailed suicide plan
- ☐ Family history of major depression or suicide

☐ Divorced, never married, widowed
☐ Unemployed
☐ White
☐ Male
☐ Age 15-25 years, or older than 60 years

Italics indicate that greater weight should be given to these risk factors. There is no formal scoring system.

Within the last few years, considerable concern and controversy has been generated by the claim that selective serotonin reuptake inhibitor (SSRI)-type antidepressants increase the risk of "suicidality" or "suicidal behavior." These terms signify suicidal thoughts and/or self-injurious behavior, since completed suicide has not been linked with these agents. Originally the concern focused on children and adolescents. Recently, however, the FDA issued a broader warning, citing an increased risk in adults with depression.[41] All classes of antidepressants have been included in these warnings. Many experienced psychopharmacologists are skeptical of this putative association. Indeed, a preliminary report from the American College of Neuropsychopharmacology casts doubt on any significant link between SSRIs and suicidality in appropriately diagnosed and treated patients.[42] Even so, the first 2 to 3 weeks of antidepressant treatment should be carefully monitored, preferably with a follow-up appointment or phone call within a week of prescribing the medication. Any complaint of new-onset restlessness, dysphoria, akathisia, or thoughts of self-harm should immediately provoke a more detailed assessment.

When assessing the patient for suicidality, it is best to use a "pyramidal" questioning technique, which begins with broad questions at the "base" of the pyramid ("How have you been feeling these days, in terms of your mood?"), and narrows to the apex with more specific questions, if the patient's responses warrant concern ("Have you made actual plans to harm yourself? Do you have access to firearms?"). Contrary to a widespread misconception, asking patients about suicidal feelings, impulses, and plans does not "put the idea into their heads." On the contrary, most patients with such feelings are relieved to have someone finally broach the issue. While the PCP should play a key screening role in the detection and management of the suicidal patient, consultation with a psychiatrist or other mental health professional is nearly always indicated when patients show serious suicidal intent or plans.

Depression Care, Consultation, and Collaboration

General Issues of Disposition

Once the diagnosis of a depressive disorder is made, the clinician must focus on appropriate therapy. Pharmacologic treatment has become the most common regimen in primary care. When used alone, antidepressant treatment demonstrates a response rate of approximately 40%.[43] Of note, the combination of pharmacologic intervention and psychotherapy can increase response rate to 60%,[43] although the optimal "sequencing" of these treatments is still a matter of investigation.[44] Therefore, it is essential that PCPs avoid focusing solely on medication therapy, despite the ease of prescription.

Traditionally, PCPs have provided "low-intensity" treatments, such as brief counseling, reassurance, and short-term medication, for patients with psychological problems.[45] Indeed, historically, PCPs have referred only about 10% of patients identified as having a psychiatric disorder to mental health professionals.[45] Yet, many PCPs do not feel adequately trained in psychiatric assessment and treatment and would prefer to send patients with psychiatric problems to mental health professionals.[45] This paradox may be explained by several factors, including limited time in primary care practice to arrange for mental health referrals; patients' unwillingness to see a mental health professional; regional lack of availability of mental health professionals; the organizational structure in which the PCP works; and physicians' concerns about "stigmatizing" patients by "sending them to a shrink." Unfortunately, patients are also often concerned about such stigmatization.

While some PCPs feel quite comfortable providing counseling and medication to depressed patients, most seriously depressed patients will require more specialized care. At a minimum, consultation with a psychiatrist is indicated in cases of major depression accompanied by suicidal ideation or psychotic features, or when bipolar disorder is strongly suspected. (Valenstein provides an excellent review of various "collaborative" models for PCPs and mental health professionals.[45]) When the severely depressed patient (eg, PHQ-9 score >15) is judged to be at high risk for acting on suicidal impulses (Table 5), is floridly psychotic, or is known to have a bipolar disorder, immediate referral to a psychiatrist and/or hospitalization is recommended. We recognize, however, that in some regions of the country, such an ideal course of action may be delayed or impossible. Hence, the PCP must still be familiar with the essentials of both psychosocial and somatic treatment of depression. Indeed, in many cases, the PCP may reasonably begin treatment, while periodically reassessing the need for consultation and referral. Discussion of all viable treatment options should be addressed with the patient and be tailored to the patient's specific wishes and needs.

Psychosocial Treatments

Psychotherapy is available as psychodynamic therapy, cognitive behavioral therapy, or interpersonal therapy. Mildly to moderately severe cases of depression (eg, PHQ-9 score of 4-15) may respond well to psychotherapy alone, and this approach is often preferred by patients averse to psychotropic medication.[42] Furthermore, continuation and maintenance psychotherapy, either alone or combined

with pharmacotherapy, can reduce the risk of depressive relapse or recurrence.[46] In our view, the psychotherapeutic techniques noted above are generally best managed by mental health professionals with specialized training. However, the PCP remains a critically important source of education, counseling, and support in the treatment of the depressed patient.

Somatic Treatments

In principle, somatic treatments for depression include FDA-approved antidepressants, over-the-counter or herbal remedies (SAM-e, St. John's wort, etc.), ECT, light therapy (phototherapy), transcranial magnetic stimulation, and, in certain refractory cases, vagal nerve stimulation (recently approved by the FDA) or deep-brain stimulation.

Besides FDA-approved medications, ECT is by far the best-validated approach. It remains a safe, effective, but often underutilized treatment for severe depression, especially in cases characterized by psychosis, marked suicidality, catatonic features, and refusal to take food or liquid by mouth.[47] Due to unrealistic fears about ECT, however, as well as legitimate concern about transient cognitive side effects and numerous institutional or regulatory barriers, ECT is often (inappropriately) reserved as a "treatment of last resort."[48,49] Thus, in practice, the PCP is most likely to be managing standard antidepressant treatment, which will be the focus of our discussion. Readers are referred to several reviews of other somatic treatments.[50-53] (Although a review of over-the-counter and herbal agents is beyond the scope of this paper, the PCP should ask about the patient's use of these agents, since several may have significant side effects and drug interactions.[54,55])

Antidepressant Options

The current agents with FDA approval are thought to enhance the activities of 5-HT, NE, and/or DA. The available medications do this by: (a) blocking the reuptake of the various monoamines; (b) inhibiting the metabolism of the monoamines; and/or (c) increasing the production of the monoamines.[24] Some agents may affect more than one neurotransmitter and some may work via more than one mechanism. As noted earlier, the "ultimate" mechanism of action may lie at the level of the gene and its products.

Seven different pharmacologic classes of medications are currently used to treat depression (Table 6). The oldest agents are the MAO inhibitors and the tricyclic antidepressants (TCAs). Although both types of agents are highly effective, dietary restrictions and adverse drug interactions associated with the MAO inhibitors limit their use in primary care and even in most psychiatric settings. Cardiac, anticholinergic, and hypotensive side effects, as well as the potential for severe toxicity with overdose, have also caused the TCAs to be relegated to "second-tier" or adjunctive options in most cases. Therefore, the PCP is most likely to prescribe one of the newer

agents, such as one of the SSRIs or serotonin-norepinephrine reuptake inhibitors (Table 6). These newer agents have not been proved more effective than TCAs or MAO inhibitors, but have shown superior safety and, in several respects, better tolerability.

Table 6. FDA-Approved Antidepressants[56]

Drug Classification Mechanism of Action
Amitriptyline, nortriptyline, imipramine, desipramine Tricyclic antidepressants Block the reuptake of both serotonin and norepinephrine
Phenelzine, tranylcypromine, isocarboxazid Monoamine oxidase inhibitors (nonselective) Inhibit enzymes (MAO-A, MAO-B) responsible for breakdown of serotonin, norepinephrine, and dopamine
Fluoxetine, paroxetine, fluvoxamine, sertraline, citalopram, escitalopram Selective serotonin reuptake inhibitors Relatively selective inhibition of reuptake of serotonin (though some effects on other neurotransmitters)
Bupropion Norepinephrine and dopamine reuptake inhibitor Inhibits the reuptake of norepinephrine and dopamine (possibly inhibits the reuptake of DA more than NA)
Trazodone, nefazodone Serotonin antagonist reuptake inhibitor Mainly antagonize 5-HT_2 receptors; nefazodone also modestly inhibits the reuptake of serotonin, norepinephrine, and dopamine
Mirtazapine Noradrenergic and specific serotonergic agent Antagonizes alpha$_2$ autoreceptors and heteroreceptors; also blocks 5-$HT_{2A/C}$ and 5-HT_3 receptors; stimulates 5-HT_1 receptors
Venlafaxine, duloxetine Serotonin/norepinephrine reuptake inhibitors Inhibit the reuptake of serotonin and norepinephrine (and perhaps dopamine, with very high doses of venlafaxine)

SSRIs became the mainstay of depression therapy starting in the late 1980s. The notion that these agents are completely "selective" for 5-HT is actually mistaken. Paroxetine and sertraline, for example, have significant effects on NE and DA reuptake,[57] respectively, but since the term "SSRI" is firmly entrenched in the literature, we will use it here. This class of drugs comprises 6 agents, of which only fluvoxamine lacks FDA labeling for the treatment of depression. (Fluvoxamine is labeled for use in obsessive-compulsive disorder.) Head-to-head trials comparing SSRIs to each other have generally shown little difference in efficacy and tolerability among agents.[58-62] Thus, the choice of a specific SSRI is usually governed by other concerns, such as pharmacokinetic factors, comorbid medical conditions, previous response, and cost (see below, Choosing an Antidepressant).

Although most patients tolerate SSRIs somewhat better than the older TCAs, many patients taking SSRIs complain of sexual dysfunction, gastrointestinal irritation, sleep disturbance, headaches, and other side effects. Rarely, extrapyramidal side effects or coagulopathy is associated with SSRI use.[56] Hence, the development of antidepressants with different mechanisms of action and side effect profiles has been vigorously pursued. For example, bupropion, which was developed in the 1980s, has little or no effect on 5-HT and, thus, has a markedly different side effect profile from the SSRIs. Indeed, bupropion is sometimes used to augment SSRI effects or to counteract SSRI side effects.[24,63,64]

Trazodone is rarely used now as an antidepressant. It is typically used in low doses (50 to100 mg hs) to help induce sleep, often as an adjunct to SSRIs. Controlled studies supporting this use, however, are quite limited.[65] Doses of 300 to 600 mg are often needed in the treatment of depression, but are frequently poorly tolerated (eg, the patient may be overly sedated or hypotensive). A small risk of priapism is also found with trazodone.

Nefazodone has a similar pharmacology to trazodone and appears to have a benign effect on sleep architecture, good anxiolytic effects, and a reduced rate of sexual side effects compared with SSRIs.[56] However, nefazodone now carries a "black box" warning of hepatic toxicity, which is actually quite rare, and only generic versions of the drug remain on the US market.[66]

Mirtazapine has a unique mechanism of action among the newer antidepressants. In effect, it enhances NE and 5-HT by increasing their release via action at the alpha-2 autoreceptor.[24] Doses of 15 mg or less are associated with sedation and weight gain. Acceptable antidepressant efficacy is seen in doses of 30 to 45 mg. These higher doses are said to be associated with less weight gain and sedation, perhaps due to increased noradrenergic effects; however, considerable variability is seen among patients.

Venlafaxine and duloxetine both affect the reuptake of 5-HT and NE, although at lower doses (< 200 mg/day).[57] Venlafa receptor-mediated transmission; little effect on muscarinic receptors, moderate histaminergic (H1) blockade

Very little CYP enzyme inhibition
Weight gain, sedating (possibly less at higher doses, owing to increased NE effects)
Fewer GI, sexual side effects than most SSRIs

No significant effects on hemostasis reported (vs SSRIs)

Few drug interactions due to inhibitor effect on CYP enzymes

Nefazodone (*Serzone*)*
Serotonergic, 5-HT_2 blockade
Nonlinear pharmacokinetics; strong 3A4 inhibitor
Quite sedating (and may have benign effects on sleep architecture); weight gain, sexual side effects are rare compared with SSRIs

Orthostasis and dizziness common; occasional visual abnormalities; "black box" warning re: hepatic failure, but very rare (1 per 250,000 patient years)

Dose increase leads to disproportionate rise in blood levels; interactions with triazolobenzodiazepines, quetiapine, antifungals, steroids, and other CYP 3A4 substrates
CYP = cytochrome P-450
*Serzone no longer on US market; generic nefazodone available

Table 8. Tablet Size and Maintenance Dosage for Commonly Prescribed Non-MAO Inhibitor Antidepressants[56]

Antidepressant Tablet/Capsule Sizes, Other Formulations Usual Daily Adult Dosage Range; *[Geriatric Dose*]*
Bupropion (*Wellbutrin*) **75, 100 mg** **150-450 mg [*75-225 mg*]** Bupropion SR (*Wellbutrin SR*) 100 mg, 150, 200 mg (twice-daily dosing)

150-400 mg [*100-300 mg*]
Bupropion XL
150, 300 mg (once-daily dosing)
150-450 mg [*150-300 mg*]
Citalopram (*Celexa*)
10, 20, 40 mg
10 mg/5 mL solution
20-60 mg [*10-40 mg*]
Duloxetine [*Cymbalta*]
20 mg
20-60 mg twice daily
Escitalopram [*Lexapro*]
10, 20 mg
5 mg/5 mL solution
10-20 mg [*5-10 mg*]
Fluoxetine [*Prozac*]
10, 20, 40 mg
90-mg weekly capsule
Solution: 20 mg/5 mL
20-60 mg [*5-40 mg*]
Mirtazepine [*Remeron*]
15, 30, 45 mg
15, 30, 45 mg soluble tablets
15-45 mg [*7.5-30 mg*]
Nefazodone [*Serzone*][?]
50, 100, 150, 200, 250 mg
200-500 mg
Paroxetine [*Paxil*]
10, 20, 30, 40 mg
10 mg/5 mL suspension
20-50 mg [*5-40 mg*]

Paroxetine CR (*Paxil CR*)
12.5, 25, 37.5 mg
25-75 mg [*12.5-50 mg*]
Sertraline [*Zoloft*]
25, 50, 100 mg
20 mg/mL solution
50-200 mg [*12.5-150 mg*]
Trazodone [*Desyrel*]
50, 100, 150, 300 mg
50-400 mg
Venlafaxine [*Effexor*]
25, 37.5, 50, 75, 100 mg
[twice- or 3-times-daily dosing]
75-375 mg [*50-225 mg*]
Venlafaxine XR [*Effexor XR*]
37.5, 75, 150 mg once-daily dosing
75-225 mg [*37.5-187.5 mg*]
Upper limits of the therapeutic range may sometimes exceed those shown here (eg, in extensive metabolizers). Medically ill patients (eg, those with reduced hepatic or renal function) may require dosage reduction.
*Geriatric dosing is provided only for preferred or first-line agents in elderly patients (see Jacobson et al, 2002, for detailed information).
[?]Only generic versions remain on the market in United States.

Initial Choice of Antidepressant

The choice of an antidepressant should be based mainly on the unique medical-historical profile of the individual patient. If a patient has had a well-documented, favorable response to an agent in the past, that agent may be preferred for treatment of the current episode, all other things being equal. For patients with a family history of depression, the medication history of the relatives should be reviewed. If a family member has had a positive response to a particular agent, that experience should be weighed in selecting an agent for the patient.[27] Conversely, if a particular antidepressant was associated with a negative outcome in a family member, that

agent may be less appropriate for the patient, all other factors being equal. Although no convincing evidence has established that "matching" a patient's symptomatic presentation to a particular antidepressant leads to improved outcome, some clinicians do find that this helps during the initial treatment period. For example, use of a more sedating antidepressant for an extremely agitated, insomniac patient makes clinical sense, all other factors being equal, and may enhance initial adherence to treatment.

Drug safety, side effect profile, tolerability, and the potential for drug interactions are important considerations and greatly affect adherence to treatment. For example, if weight gain or sexual dysfunction are major medical concerns, bupropion might be the agent of choice, all other factors being equal. On the other hand, a patient with a history of seizures or eating disorder would not be a good candidate for bupropion, all other factors again being equal. Patients in primary care settings are often taking numerous nonpsychiatric medications, and their metabolism may be affected by antidepressants. In such cases, selecting agents with minimal effects on cytochrome enzymes (Table 7), such as citalopram or escitalopram, would be prudent.

Cost must also be reviewed. Although newer agents such as duloxetine and venlafaxine may offer enhanced pharmacology, their benefits do not often outweigh their price. Generic formulations of fluoxetine, paroxetine, fluvoxamine, citalopram, bupropion, and mirtazapine have reduced the cost of therapy substantially. Although some patients may have idiosyncratic adverse reactions to specific generic formulations (perhaps a reaction to drug excipient or unexpected variation in drug bioavailability), it is reasonable to consider generics before turning to more costly agents.

Goals of Therapy

Whether choosing psychotherapy, medication, or a combination of the 2, ongoing assessment of treatment outcome is essential. Serial use of the BDI or PHQ-9 may be helpful in assessing progress. Clinical trials generally focus on reducing depressive symptoms by 50% ("response"); however, the clinician's ultimate goal should be returning the patient to a fully functional status (ie, remission of illness) and a good quality of life.

The presence of residual symptoms (ie, failure to treat depression to remission) is associated with a high risk of later relapse. A 1995 study of a predominantly inpatient population with MDD (n=70) found that subjects with residual symptoms at the time of remission had a relapse rate of 76%, compared with 25% among subjects without such symptoms.[66a]

Many patients fail to respond to initial treatment because of inadequate dosing for an inadequate duration. For example, a patient is inappropriately said to have "failed" a 2-week trial on 25 mg of sertraline. However, only about two thirds of patients will respond to

medication, even after a 3- to 6-week trial.[69] Drug intolerance is the main reason for failure in the rest of the cases. Dosage reduction is sometimes helpful when dose-related side effects (such as sedation) are pronounced, but this maneuver may result in an inadequate dose. In such circumstances, changing to a different agent or drug class may be useful. For example, if a patient is experiencing sexual dysfunction with an SSRI, changing to an agent with lower serotonergic activity is warranted.

In those instances of inadequate response that are not due to intolerance, a variety of medication strategies have been proposed, usually described as switching, augmentation, or combination.[70,71] Switching to a different class of antidepressant may produce a response in some refractory patients. The addition of lithium or thyroid hormone to ongoing antidepressant are the best-supported augmentation strategies.[70,72] For a variety of reasons, however, these strategies are rarely used in primary care or even in many psychiatric settings. For some refractory patients, combining 2 antidepressants at therapeutic doses is required. In general, if a depressed patient fails to achieve a robust response after 2 adequate trials of antidepressant monotherapy, the PCP should arrange for consultation with, or referral to, a psychiatrist. In many instances, earlier consultation or referral is appropriate, particularly when the patient is at high risk for noncompliance, self-harm, or markedly impaired social-vocational function.

Conclusion

Depression is a highly prevalent condition with considerable morbidity and mortality. The PCP is in a unique position to diagnose and manage depression in its early stages, but this requires careful screening, differential diagnosis, and knowledge of both psychosocial and somatic treatments. The use of patient-completed questionnaires, such as the PHQ-9, can help initiate this process. Once individuals with depression are identified, the PCP may begin treatment, often working in concert with a mental health professional. Psychotherapy along with antidepressant medication can lead to remission in a large percentage of cases, as well as to a vast improvement in the patient's quality of life.

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