Depression: A Treatment Algorithm for the Family Physician

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Unipolar depression is an illness with significant morbidity and mortality that contributes to lost work time, disrupted interpersonal relationships, substance abuse, worsening health status, and suicide.[1–4] The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV),*[5] classifies a depressive episode as a 2-week period in which the patient experiences either a depressed mood or a marked decrease in interest or pleasure gained from most activities. The patient must also complain of at least four of the following symptoms: change in appetite or weight; insomnia or hypersomnia; change in psychomotor activity; feelings of guilt or worthlessness; fatigue or loss of energy; indecisiveness or diminished ability to concentrate; and suicidal ideation or recurrent thoughts of death (**Table 1**). To warrant a diagnosis of depression, symptoms must also cause impairment or marked distress in important areas of functioning.

Although depression is a commonly encountered condition in the primary care setting,[1,6] many individuals who meet *DSM-IV* criteria do not seek treatment or are not identified by their physicians as being depressed. The patient may emphasize medical or somatic complaints (eg, fatigue, appetite changes, headache) rather than the mood component of the psychiatric illness, thus obscuring the diagnosis of depression.[7–11] In addition, if either the patient or the physician is hesitant to consider a psychiatric diagnosis, appropriate treatment may be delayed. In terms of diagnosis, a careful review of systems and the judicious use of testing can usually rule out a medical cause for the patient's symptoms. Once a diagnosis has been made, educating the patient about the validity of depressive illness can help to facilitate collaboration between physician and patient during treatment.[6,7]

There are clinical guidelines for the treatment of depression in the primary care setting. However, studies indicate that primary care physicians need to increase their efforts to correctly identify and treat depression.[6,7] The strategies presented in this article can significantly improve treatment outcomes and can be safely and effectively prescribed by primary care physicians. With patient education and careful follow-up, treatment results can closely approximate expected outcomes.[1–4,6,7]

This review presents evidence-based treatments for depression, with an emphasis on pharmacologic strategies for those patients who do not respond to first-line management. Empirically validated types of psychotherapy in the treatment of depression, as well as suggestions for a more effective collaboration between primary care providers and psychologists and psychiatrists are also discussed.

FIRST-LINE TREATMENT OPTIONS

Psychotherapy and Pharmacotherapy

Depression can be treated with either medication or psychotherapy; however, outcomes are best when patients are correctly diagnosed and education, pharmacotherapy, and psychotherapy are provided concurrently.[7] Patients with depression differ in their willingness to accept pharmacologic or psychotherapeutic treatments. If patients with mild to moderate symptoms refuse the combined approach, initial treatment with either psychotherapy or a trial of medication alone may be acceptable (**Figure 1**). For patients at risk for treatment-resistant depression or patients with severe symptoms, both psychotherapy and medication are strongly recommended from treatment outset. In patients with severe depression, medication can provide symptomatic relief, whereas psychotherapy permits an ongoing, thorough monitoring of clinical response and attention to possible concomitant interpersonal, cognitive, or behavioral

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Table 1. Criteria and Specific Severity Indicators for a Major Depressive Episode

Five or more of the following symptoms have been present during the same 2-week period and represent a change from previous functioning. At least one of the symptoms must be either (1) depressed mood or (2) loss of interest or pleasure.

1. Depressed mood
2. Diminished interest or pleasure
3. Significant weight loss or gain, or increase or decrease of appetite
4. Insomnia or hypersomnia
5. Psychomotor agitation or retardation
6. Fatigue or loss of energy
7. Feelings of worthlessness or excessive or inappropriate guilt
8. Diminished ability to think or concentrate; indecisiveness
9. Recurrent thoughts of death, suicidal ideation, suicide attempt, or specific plan for suicide

Severity indicators

Mild: few if any symptoms in excess of those required to make the diagnosis; symptoms result in only minor impairment in occupational functioning or in usual social activities or relationships with others

Moderate: symptoms or functional impairment between "mild" and "severe"

Severe (without psychotic features): several symptoms in excess of those required to make the diagnosis; symptoms markedly interfere with occupational functioning or with usual social activities or relationships with others

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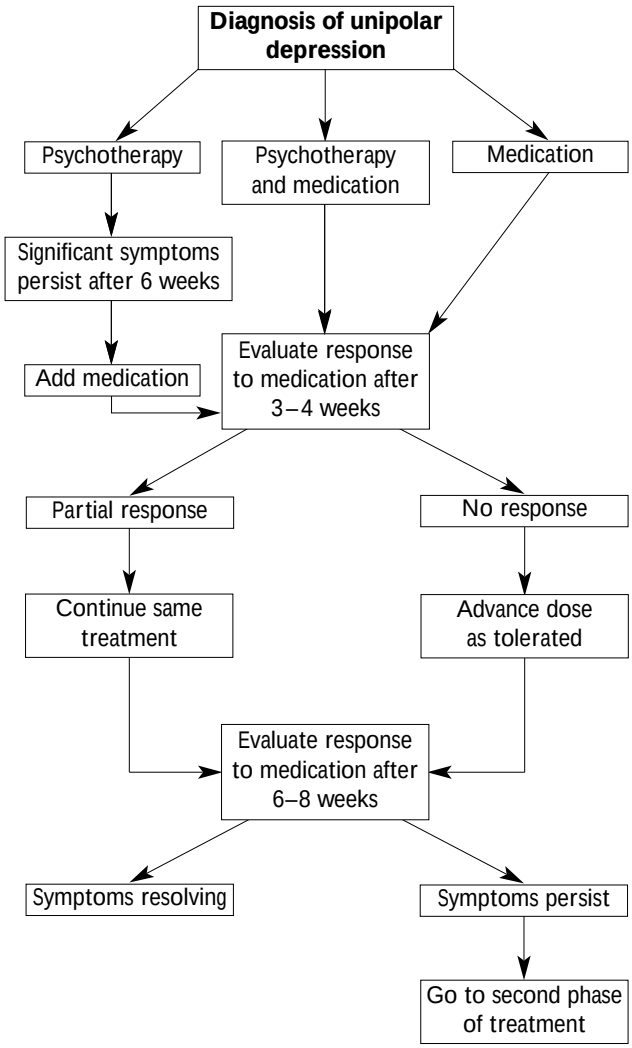

Figure 1. Initial phase of treatment for depression. When symptoms persist after first-line treatment, reevaluate the accuracy of diagnosis, the adequacy of dose, and the duration of treatment before moving to the second phase of treatment.

issues (eg, marital disputes, pattern of negative thinking, decreased work performance, social isolation).

Psychotherapeutic options. Two short-term psychotherapies (between 12 and 20 sessions) specifically target symptoms of major depression: interpersonal psychotherapy (IPT) and cognitive behavioral therapy (CBT).[12,13] According to Elkin et al,[14] patients treated with either IPT or CBT for 16 weeks experienced similar symptomatic relief when compared with patients treated with medication.

Both CBT and IPT have been empirically validated, but the two approaches address slightly different aspects of the depressive condition. CBT is directed at the negative and distorted thinking patterns and subsequent maladaptive behaviors that often accompany depressive episodes. IPT aims to help the patient learn to manage the current interpersonal relationship difficulties that are sometimes related to the development and maintenance of the depressive symptoms.

Consultation. The family physician can request a consultation from a psychologist or psychiatrist to assist in diagnosis and treatment planning for the patient who appears resistant to ongoing therapy. Certainly, consultation should be sought once the treating physician has exhausted the treatment options with which he or she feels comfortable. A formal referral is necessary when

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complicated symptoms develop (eg, psychosis, mania, suicidal tendencies, significant personality disorder). Patients with such serious symptoms require more extensive support services, such as crisis intervention, partial hospitalization, or inpatient treatment.

Pharmacologic Treatment

All antidepressants are potentially effective in the treatment of depression (**Table 2**). In addition, the advent of selective serotonin reuptake inhibitors (SSRIs) and the newer atypical antidepressants such as venlafaxine or nefazodone, which provide relatively low toxicity and ease of dosing, has significantly increased the pharmacologic treatment of depression in the primary care setting.

The choice of initial pharmacotherapy is influenced by several factors including current symptoms, potential drug toxicity and side effects, history of patient response, and cost of treatment. The patient with insomnia and weight loss, for example, might fare better with a tricyclic antidepressant (TCA), whereas the patient with concerns regarding potential sexual side effects would be better treated with nefazodone or bupropion. Potential drug interactions or underlying medical conditions that may predispose the patient to adverse effects should also be considered. Physician familiarity and comfort with medications are also considerations.

Before initiating antidepressant pharmacotherapy, the physician should educate the patient regarding potential side effects, the need to take medications regularly, and the usual time period and course necessary to achieve recovery. After the patient receives a medication at a therapeutic dose for 3 to 4 weeks, treatment response should be evaluated. If the patient does not respond, the physician should consider increasing the dose to the upper therapeutic range, as tolerated. If a partial response has occurred, the dose can be maintained for 6 to 8 weeks in anticipation of continued improvement (Figure 1).

FAILURE OF FIRST-LINE THERAPY

Some patients with depression fail to improve adequately with first-line therapy. At this point, the patient, diagnosis, and treatment plan must be reassessed, and alternative strategies must be considered. Prior to changing strategies, however, the treating clinician should consider several questions. An algorithm has been developed that outlines the following approach (**Figure 2**).

- **Is the patient failing to respond?**

The symptoms of depression often resolve gradually with intermittent remissions and exacerbations, which sometimes obscure therapeutic progress. In order to measure improvement accurately, the clinician should review and record the specific target symptoms that the patient presents at the beginning of treatment and at each follow-up visit. Progress or worsening of target symptoms can be assessed by asking the patient to note the degree of progress on a 1 to 5 scale. Empirically validated self-rating scales (eg, the Beck Depression Inventory)[15] administered at the time of initial diagnosis and at each follow-up visit can be useful in assessing treatment response. Clinicians must remember to use these types of scales as a supplement to a clinical management interview. Occasionally, improvement is noticed by family and/or friends, even before the patient recognizes change. With the patient's consent, communication between the physician, patient, and the patient's primary social supports can help to assess progress more accurately.

- **Is the patient taking the medication?**

Compliance is a significant consideration in the treatment of depression. Side effects often prompt patients to discontinue medication (Table 2). In addition, the patient's lack of understanding regarding the diagnosis or the length of time necessary to achieve a clinical response can result in frustration and noncompliance. Fear or stigma related to psychiatric treatment or the cost of medication may also contribute. Further, the symptoms of depression can interfere with the patient's motivation or ability to remember a daily medication. To enhance compliance, it is fruitful to discuss these issues early with patients and family members.

- **How long has the patient been on the current medication and dosage?**

Four to 8 weeks of antidepressant medication at a therapeutic dose may be required before symptoms begin to subside.

- **Is the medication operating at a therapeutic level?**

Research indicates that one of the most common causes of treatment failure in a primary care setting may be an inadequate or subtherapeutic dose of antidepressant.[1] The treating physician must be familiar with the typical dosing range of medications as well as potential side effects (Table 2). Collaboration with the patient's psychologist or a psychotherapist with clinical training and expertise in the treatment of depression can be helpful to the physician in many ways. Because the psychologist meets with the patient weekly, he or she may be more aware of troubling side effects that reduce compliance or the need to increase the dose due to lingering symptoms.

Table 2. Antidepressant Treatment Regimens

Drug	Dosage Range*	Starting Dose	Average Therapeutic Dose	Side Effects
Tricyclics				
Amitriptyline	50–300 mg/day	25 mg QHS	150–250 mg/day	Toxicity in overdose, anticholinergic effects, sedation, weight gain, prolonged QT interval, orthostatic hypotension
Nortriptyline	25–150 mg/day	10–25 mg QHS	75–150 mg/day	
Desipramine	50–300 mg/day	25 mg QHS	150–250 mg/day	
Clomipramine	50–250 mg/day	25 mg QHS	150–250 mg/day	
Doxepin	25–300 mg/day	25 mg QHS	150–250 mg/day	
Protriptyline	10–60 mg/day	5 mg every morning	15–40 mg/day	
Trimipramine	50–300 mg/day	25 mg QHS	150–200 mg/day	
Imipramine	50–300 mg/day	25 mg QHS	150–300 mg/day	
Selective serotonin reuptake inhibitors				
Fluoxetine	10–80 mg/day	10–20 mg/day	20–40 mg/day	Sexual dysfunction, gastrointestinal disturbance, weight changes, sedation or insomnia, anxiety, restlessness, P450 interactions
Sertraline	50–200 mg/day	25–50 mg/day	50–100 mg/day	
Paroxetine	10–80 mg/day	10–20 mg/day	20–40 mg/day	
Fluvoxamine	50–300 mg/day	25–50 mg/day	75–150 mg/day	
Citalopram	10–40 mg/day	10–20 mg/day	20–40 mg/day	
Atypical antidepressants				
Venlafaxine	75–375 mg/day	37.5–75 mg/day	75–225 mg/day	Insomnia, anxiety, hypertension
Nefazodone	50–600 mg/day	50–100 mg twice daily	150–250 mg twice daily	Nausea, mild anticholinergic effects, P450 interactions
Trazodone	200–600 mg/day	50–100 mg QHS	300–600 mg/day	Sedation, priapism, weight gain, hypotension
Bupropion	150–450 mg/day	75–150 mg/day	150 mg twice daily	Insomnia, anxiety, nausea, tremor; incidence of seizure 4% at doses greater than 450 mg/day
Monoamine oxidase inhibitors				
Phenelzine	15–90 mg/day	15 mg twice daily	30–60 mg/day	Hypertensive crisis, headache, insomnia, sexual dysfunction, weight gain, orthostatic hypotension
Tranylcypromine	10–60 mg/day	10 mg twice daily	20–40 mg/day	
Tetracyclics				
Mirtazapine	15–45 mg/day	15 mg QHS	15–30 mg/day	Sedation, weight gain (may improve at higher doses)
Amoxapine	50–300 mg/day	25–50 mg QHS	200–250 mg/day	Toxicity in overdose; can cause extrapyramidal symptoms and tardive dyskinesia
Maprotiline	50–200 mg/day	25–75 mg QHS	100–150 mg/day	Sedation, toxicity in overdose, decreased seizure threshold

*Dosage adjustment should be considered in elderly patients and patients with renal and hepatic impairment.

QHS = at bedtime.

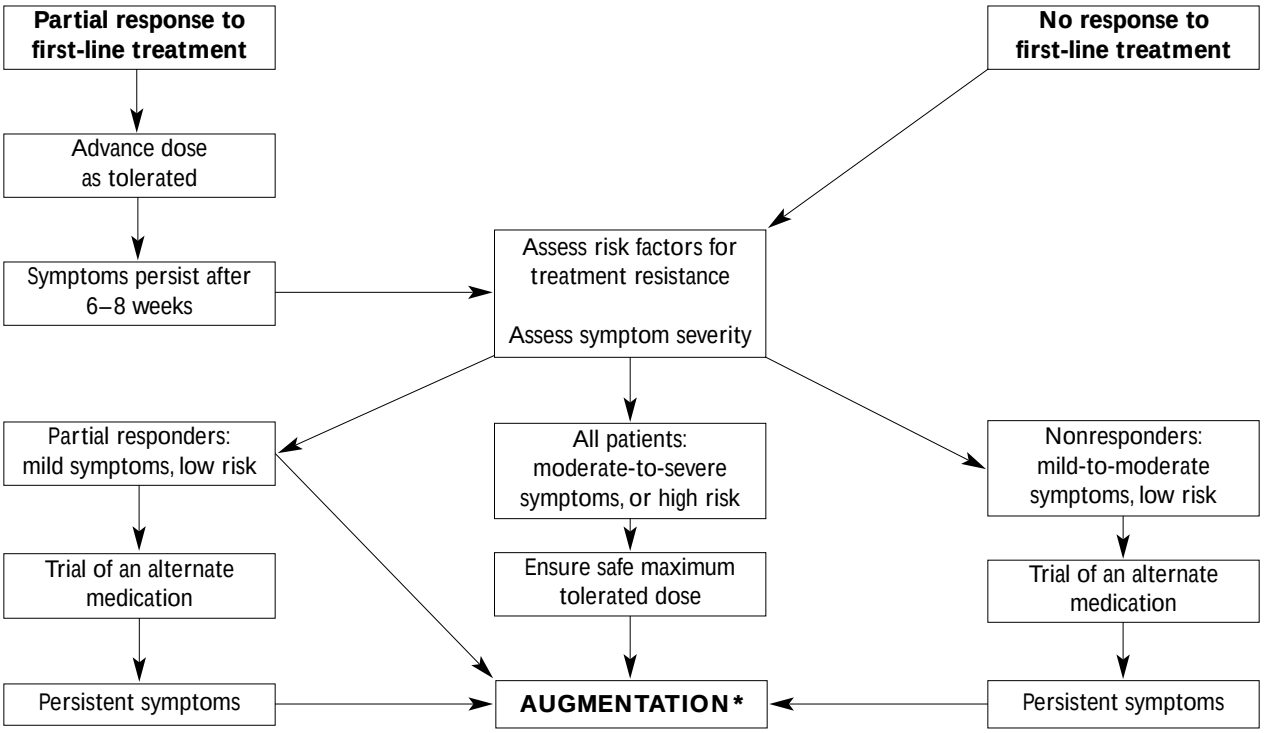

Figure 2. Second phase of treatment for depression. *Augmentation involves the use of a combination of medications to enhance the efficacy of an antidepressant.

- **Is the diagnosis correct?**

Medical conditions that may either cause or contribute to the affective syndrome (**Table 3**) must be ruled out through symptom evaluation, physical examination, and pertinent laboratory studies. Also, the presence of other psychiatric diagnoses (eg, anxiety disorders, personality disorders, substance abuse) must be considered. Each of these disorders has a high rate of comorbid depression, is difficult to assess, and requires a specific treatment approach. Because the presence of a comorbid diagnosis can interfere with the resolution of depression and is best evaluated and treated in a psychotherapeutic setting, diagnostic consultation with a psychiatrist, psychologist, or psychotherapist trained in clinical assessment and differential diagnosis can be helpful.

- **Is the patient receiving psychotherapy?**

As mentioned previously, psychotherapy can be an important part of treatment of depression. If a patient has refused psychotherapy or for some other reason has been unable to accept a referral for counseling, this option should be revisited if the psychiatric symptoms persist or worsen.

SECOND-LINE TREATMENT OPTIONS

Monotherapy

If a patient remains symptomatic after receiving a therapeutic dose of antidepressant for an adequate length of time, alternatives must be considered (Figure 2).

Dose adjustment. The physician must first determine whether the patient has had a partial response or no response to treatment. If the patient is tolerating the current medication but is not at the maximum dose, the first and perhaps simplest intervention is to increase the dose gradually to the upper therapeutic range and observe the patient for additional improvement. An increase in side effects can be a dose-limiting factor. Many side effects tend to decrease over time and many can be ameliorated. With appropriate counseling beforehand and regular discussion regarding the side effects, the patient is more likely to tolerate a full medication trial. Dosage increase, when effective, usually produces results more quickly than transition to another antidepressant. This strategy is appropriate for treatment of patients who are experiencing moderate to severe symptoms and require a more expedient intervention. If the patient fails to

Table 3. Medical Conditions Associated with Symptoms of Depression

Thyroid disorders
Parathyroid disorders
Anemia
Hypoxia
Malignancy
Disorders induced by medications (eg, β blockers, calcium channel blockers, steroids, sedatives, hormonal agents)
Dementia
Parkinson's disease
Other central nervous system diseases (eg, Huntington's chorea, multiple sclerosis, frontal lobe lesions, multi-infarct states, HIV infection)
Cushing's syndrome/corticosteroid treatment
Systemic lupus erythematosus, other connective tissue diseases

Table 4. Antidepressant Tapering Schedule*

Fluoxetine	No taper needed
Fluvoxamine	Decrease by 25 mg every 3–5 days
Paroxetine	Decrease by 5 mg every 3–5 days
Sertraline	Decrease by 25 mg every 3–5 days
Venlafaxine	Decrease by 37.5 mg every 3–5 days
Nefazodone	Decrease by 1/2 every 3–5 days to 50 mg, then stop
Bupropion	Decrease by 75 mg every 2 days
Tricyclics	Decrease by 1/2 every 3–5 days to 50 mg, then stop

*Each of these schedules can be adjusted according to each patient's sensitivity to withdrawal symptoms.

show further improvement with a maximum dose of medication, a trial of an alternate medication or augmentation, which is discussed later in this article, should be considered.

Treatment discontinuation and changing medication. When the patient does not respond to an adequate trial of initial medication, the next step can be a tapering discontinuation with subsequent initiation of a different antidepressant (Table 2). To avoid drug interactions and potentially confusing side effects, the first medication should be discontinued before initiation of the second medication.

Tapering one medication and initiating a second medication can be time consuming. No studies suggest that prior treatment with an antidepressant provides a "head start" for the subsequent agent; therefore, time from transition to potential symptom relief remains the same as with the initial therapy (ie, 4 to 8 weeks). Although this approach can be used to treat any patient with depression, patients with mild symptoms may be optimal candidates. These patients are more able to tolerate the time necessary to make the transition to another medication than patients with moderate to severe symptoms.

If tapered too quickly, almost all antidepressants can produce withdrawal syndromes. Patients may experience sleep disturbances, mood changes, anxiety, sensory disturbances, malaise, muscle aches, vertigo, sweating, fatigue, and gastrointestinal disturbances.[16,17] Agents with shorter half-lives (eg, venlafaxine, paroxetine, fluvoxamine) should be tapered more slowly, typically over 14 days (**Table 4**). Tapering is usually unnecessary with fluoxetine, which has a very long half-life. Monoamine oxidase inhibitors (MAOIs) can produce a hypertensive crisis or serotonin syndrome if administered with another antidepressant. Therefore, a 2-week washout period must be allowed between discontinuation of an MAOI and initiation of another antidepressant. If fluoxetine is being discontinued in favor of an MAOI, a 6-week washout should be allowed due to the long half-life of fluoxetine.

Before changing medication, several clinical issues must be considered. If a patient has tolerated a particular class of antidepressant (eg, an SSRI) with few side effects, another drug within this same class may be prescribed. After more than one failure within a drug class, however, a medication from a different class should be considered.

Combination Therapy (Augmentation)

Augmentation is a strategy in which a combination of medications is used to enhance the efficacy of an antidepressant. Augmentation should be considered in all patients who have had partial response to monotherapy at a maximum tolerated dose and in patients who have not experienced clinical remission despite multiple adequate drug trials. In the patient with moderate to severe symptoms or with risk factors for treatment-resistant depression, augmentation should be considered early in the course of treatment. The rationale for this more aggressive approach is twofold: first, combination therapy may provide a clinical response more quickly than transition to another antidepressant; second, for the patient at risk for treatment-resistant depression

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Table 5. Risk Factors for Treatment-Resistant Depression

Chronic depression (symptom duration > 1 year; either no treatment or inadequate treatment)
Premorbid personality disorder
Previous history of resistant depression
Comorbid axis 1 disorder (especially substance abuse, panic disorder, post-traumatic stress disorder)
Family history of affective disorder
Multiple losses (eg, death of family member or friend, divorce, loss of job)
Female gender
History of thyroid dysfunction

(**Table 5**),[18] a greater probability exists that several medication trials may be necessary to find an effective agent. The medication strategy should therefore include an attempt to rule out the efficacy of an antidepressant before moving on to another drug. Dosage should also be considered before excluding a medication in this patient group.

Lithium carbonate. Lithium has been used to treat bipolar disorder for decades. Since the early 1980s, lithium has been studied extensively and used clinically in combination with TCAs, SSRIs, and MAOIs as an augmenting agent in the treatment of unipolar depression.[19–22] The psychotropic mechanism of action has not been fully elucidated; however, lithium appears to have significant but variable enhancing effects on presynaptic serotonin turnover and norepinephrine release. Lithium may act primarily on neuronal signal transduction mechanisms that, in turn, may modulate monoamine neurotransmitter function. According to Nelson,[19] the addition of lithium may hasten the clinical response to antidepressant treatment.

Treatment initiation. Before initiating lithium therapy, baseline blood urea nitrogen, creatinine, thyroid stimulating hormone (TSH), complete blood count, and electrolyte levels should be obtained. Patients must not be pregnant while receiving lithium therapy. Patients 40 years of age or older or patients who have heart disease should first have a baseline electrocardiogram.

Dosage. When used for treatment of bipolar disorder, doses of lithium range from 900 mg/day to 2100 mg/day, with target blood levels of 0.8 to 1.2 mEq/L. As an augmenting agent in the treatment of unipolar depression, slightly lower doses may be effective, although studies have shown that blood levels below 0.4 mEq/L are significantly less effective.[22] Doses should be decreased in the elderly and in patients with reduced creatinine clearance. After 5 days of a specific regimen, serum levels should be tested prior to the next dose. Weekly or biweekly monitoring is required until levels are stabilized; thereafter, normal levels need only be checked every 3 to 4 months. As with most medications, the lowest effective dose should be used to avoid side effects and toxicity.

Side effects. Patients should be advised of the possible side effects of lithium treatment, including gastrointestinal distress, polydipsia/polyuria, acne, weight gain, mild cognitive changes, and fine hand tremor. Gastrointestinal symptoms and tremor can be reduced by prescribing lithium in divided doses. Acne can be managed with interventions such as benzoyl peroxide. Hypothyroidism may also develop, and TSH should be monitored every 6 months. Another side effect, diabetes insipidus, responds to drug discontinuation. Frequently, a benign leukocytosis may be observed; however, it does not require intervention unless evidence of another underlying problem exists (eg, infection, other hematologic disorder). T-wave flattening or inversion may develop on electrocardiography and requires no intervention unless a separate cardiac condition is evident. Little evidence exists that prolonged lithium use causes renal damage. Low salt intake or dehydration can result in enhanced renal reabsorption of lithium, producing toxicity. In turn, the patient should be counseled to maintain adequate salt and water intake.

Serotoninergic and noradrenergic combinations. There is evidence that modulation of both serotonin and norepinephrine activity in the central nervous system underlies the efficacy of antidepressants.[23,24] Whereas the SSRIs have the advantage of greater safety and tolerability, some data suggest that medications with a broader spectrum of monoamine receptor affinity (eg, venlafaxine, mirtazapine, clomipramine) may be more effective in certain patients. Following this observation, researchers have studied the combination of SSRIs with several noradrenergic antidepressants.

One of the best studied combinations is fluoxetine with desipramine, a TCA with very specific norepinephrine reuptake inhibition.[23,24] TCA blood levels are significantly increased by medications that inhibit P450 enzymes, such as fluoxetine, paroxetine, and fluvoxamine. As a result, when used in combination therapy, desipramine should be initiated at doses of 25 to 50 mg/day and advanced by 25 mg/day every 5 to 7 days, while the patient is monitored for TCA-related side effects. TCA blood levels can be useful in determining the appropriate dose for a specific patient or

demonstrating an adequate dosage of a TCA. Nelson et al[24] reported that doses in the 75 to 125 mg/day range are necessary to achieve a therapeutic desipramine blood level in the presence of 20 mg/day of fluoxetine. Nortriptyline, a TCA with minimum anticholinergic side effects that is also relatively specific for norepinephrine reuptake inhibition, has been used as an adjunct in doses of 25 to 75 mg/day. No adverse effects other than those that can be observed with either SSRIs or TCAs alone have been reported with combination therapy.

Combination therapy using TCAs and MAOIs has been studied, but the results have been mixed.[25] A significant risk of side effects is also evident.[25] Efficacy has been demonstrated in open trials with combination treatment with moclobemide, a reversible MAOI;[26,27] however, adverse interactions, such as severe serotonin syndrome, have also been reported. Bupropion in combination with SSRIs has some efficacy, but considerable side effects and low patient tolerance have been reported.[28] The risk of seizure increases with an elevated bupropion blood level in the presence of an SSRI.

Buspirone. Buspirone, an azapirone with affinity for 5-HT_{1A} and dopamine receptors, is approved and prescribed for the treatment of anxiety. Buspirone may be particularly useful for anxious, depressed patients. Buspirone may have antidepressant effects at doses of 40 to 60 mg/day.[29] Because of its serotoninergic properties, buspirone has been studied as an augmenting agent of SSRIs with positive results and little toxicity. When prescribed as an augmenting agent in patients with depression, buspirone is typically used in a divided dose of 30 mg/day.[29,30] Common side effects include dizziness, nausea, headache, and nervousness. Side effects can be reduced by using a lower starting dose of 5 mg two or three times daily; doses may be advanced as tolerated.

Thyroid hormone. In a randomized, double-blind study of patients who did not respond to a course of desipramine or imipramine, triiodothyronine given as an augmenting agent was compared with lithium and placebo.[31] Results indicated an equivalent efficacy of more than 50% for both triiodothyronine and lithium, with fewer than 20% of patients responding to placebo. Other studies of triiodothyronine, which was usually given in combination with TCAs, have demonstrated mixed results.[32,33] In this setting, triiodothyronine has been used in doses of 25 to 50 µg/day.

Stimulants. Methylphenidate and dextroamphetamine both have rapid and potent enhancing effects on central nervous system monoamine activity. In uncontrolled studies, both agents have proven useful in treatment of symptoms of depression, particularly in the elderly and the medically ill. No controlled studies have demonstrated long-term efficacy as monotherapy or as augmenting agents, but several case report series suggest the usefulness of methylphenidate and dextroamphetamine in previously refractory patients.[34,35] Dextroamphetamine is used in doses of 5 mg to 15 mg/day, and methylphenidate is used in doses up to 30 mg/day given in divided doses or as sustained release medication. Most studies report that patients experience a fairly rapid improvement of symptoms. The usefulness of these medications must be balanced against potential side effects and possible tolerance or abuse.

Investigational therapies. Several other pharmacologic strategies are currently being investigated. Yohimbine, a central α_2-antagonist, given in combination with fluvoxamine has been used successfully in the treatment of refractory depression. Enhanced central nervous system noradrenergic activity is believed to potentiate clinical response to an SSRI.[36] Pindolol, a β blocker with an affinity for central nervous system 5-HT receptors, antagonizes presynaptic inhibitory 5-HT_{1A} receptors, which would theoretically enhance neuronal 5-HT production. Cases using combination therapy with pindolol reportedly enhance antidepressant efficacy.[37] The role of the hypothalamic-pituitary-adrenal axis and central nervous system 5-HT function in patients with depression are being evaluated. These studies may lead to additional medical interventions.[38]

ADDITIONAL PHARMACOLOGIC THERAPIES

St. John's Wort (Hypericum perforatum)

St. John's wort, a first-line antidepressant in many European countries, has only recently gained popularity in the United States. Because herbal medicines do not undergo approval by the United States Food and Drug Administration, treatment outcomes are unpredictable. However, uses of St. John's wort include treatment of mild to moderate depressive symptoms.[39,40] St. John's wort is contraindicated in severe depression. Although previously believed to act as an MAOI, research indicates that St. John's wort acts as an SSRI. Recommended dosage is 300 mg three times daily. St. John's wort should be taken with meals to prevent gastrointestinal upset. If no clinical response occurs after 6 to 12 weeks of therapeutic treatment, another medication should be prescribed.[41]

In a meta-analysis involving 23 randomized trials and 1757 patients, St. John's wort demonstrated greater effectiveness when compared with placebo, was well tolerated by the majority of patients, and produced adverse effects less frequently than conventional

antidepressants.[42] Potential side effects of St. John's wort include headache, fatigue, nervousness, gastrointestinal irritation, itching, photosensitivity, and restlessness.[43] Initiation of a lower dosage with a gradual increase may help to avoid side effects. St. John's wort may interact with caffeine, any antidepressant, olanzapine, risperidone, theophylline, β_2 agonists, herbal agents, and over-the-counter decongestants. The herbal remedy may also worsen panic disorder.

NONPHARMACOLGIC SOMATIC TREATMENTS

Nonpharmacologic interventions for the treatment of depression include electroconvulsive therapy (ECT), light therapy, and, potentially, transcranial magnetic stimulation (TMS). These options can be used as monotherapy or in combination with medication and psychotherapy.

Electroconvulsive Therapy

ECT has long been used as an intervention for depression. Most studies demonstrate 80% to 90% efficacy of ECT in treatment of depression.[44] Studies of ECT in patients with treatment-resistant depression indicate approximately 50% efficacy.[45] With advances in brief sedation, anesthesia, airway management, and reversible neuromuscular paralysis, many of the original risks of ECT (eg, patient discomfort, fractures, hypoxia) have been eliminated. In addition, the use of unilateral electrode placement has reduced the short-term memory loss associated with bitemporal ECT. ECT can also be used as maintenance therapy for relapse prevention in patients who respond to ECT after failing prior medication trials.

Due to the development of a variety of effective medications, the use of ECT has decreased. However, ECT is useful in patients who are unable to take medications because of advanced age or heart conditions, patients who have not responded to medications, or patients who have severe symptoms requiring a more rapid antidepressant effect or are at very high risk of suicide.

Light Therapy

Light therapy, using exposure to full-spectrum light in the range of 10,000 lux, is effective in treating mild to moderate seasonal affective disorder. Various exposure schedules have been used. This intervention produces measurable alterations in central nervous system serotonin function and, as with all antidepressants, has the potential to precipitate mania in susceptible patients. Following these observations, light therapy has demonstrated some efficacy as a possible augmenting strategy in the treatment of resistant nonseasonal depression.[46] Light therapy is a relatively safe modality. Reported side effects include headache or eye irritation; however, these are generally transient and rarely result in treatment discontinuation.[47]

Transcranial Magnetic Stimulation

A few studies have evaluated rapid-rate TMS in the treatment of depression. TMS was originally developed as a noninvasive means of stimulating or inhibiting specific areas of the cerebral cortex for the purpose of studying neural pathways. In one study, Pascual-Leone et al[48] reported beneficial effects of rapid-rate TMS applied to the left prefrontal cortex in patients with medication-resistant depression. In this randomized, placebo-controlled, cross-over study, 11 of the 17 patients showed significant symptomatic improvement without significant adverse reactions. Although further research is necessary, TMS may become a useful treatment option for depression.

SUMMARY

Primary care physicians must be prepared to treat patients who present with symptoms of major depression. The diagnosis is not always obvious, as patients may complain of varied and confusing somatic ailments. However, with careful monitoring, a physician with good diagnostic and psychopharmacologic skills has the ability to relieve the patient's symptoms. Education is essential to ease fear and stigma and to guide the patient to appropriate psychologic referrals. The algorithm offered provides a rational, systematic approach for the use of antidepressants, particularly in patients with treatment-resistant depression. **HP**

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