

MOOD DISORDERS: BIPOLAR AND MAJOR DEPRESSIVE DISORDERS



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Learning Objectives

1. Articulate the differences between the clinical presentation and course of illness for unipolar and bipolar disorders.
2. Formulate appropriate treatment recommendations, including the rationale for treatment selection, for a patient experiencing an acute exacerbation of a mood disorder.
3. Provide appropriate monitoring parameters for pharmacological treatment, target symptoms, and potential strategies to minimize adverse effects.
4. Formulate recommendations for optimizing and discontinuing a given pharmacotherapy regimen.
5. Identify potential drug-drug interactions and discuss the clinical significance of these interactions.

Depressive Disorder

Epidemiology

Depression occurs in as many as one in eight individuals during their lifetime, making it one of the most prevalent of all medical illnesses. The prevalence rates for major depressive disorder (MDD) based on community samples are about 2–3% in men and 5–9% in women, with a lifetime risk for developing an episode of 5–12% and 10–25%, respectively. The disease appears to develop independent of ethnicity, education, or income.

A recent epidemiological study evaluating lifetime and 12-month prevalence rates of MDD found that of the surveyed respondents, 72% and 64%, respectively, met the criteria for at least one other Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision

(DSM-IV-TR) disorder. Anxiety disorder was the most prevalent of the psychiatric comorbidities in both groups, followed by impulse control disorder and substance abuse.

A major depressive episode (MDE) can develop at any age, with an average age of onset being the mid-20s. Epidemiological studies indicate that the age of onset is earlier for those born after 1940. Currently, the highest rates of first onset depression are in the 25–35-year-old age group. In children, rates of depression are equal between boys and girls. After puberty, these rates change drastically, and rates for women are 2–3 times higher than in men. Some studies have revealed that women are 4 times more likely to develop recurrent depression than men. Other studies have refuted these findings. Gender differences seen in depressive symptoms and severity, course of illness, personality, and treatment response are not fully understood.

Some patients may suffer from only a single episode and others may go on to have recurrent episodes, regardless of gender. Much variability in the course of recurrent depression is seen among patients. Some will have long periods of remission and others have more frequent episodes. The number of previous episodes is predictive of future episodes. At least 60% of patients with a single episode will go on to develop a second episode. Patients who have a second episode have a 70% chance of a third, and patients who have three episodes have a 90% chance of developing a fourth. About 5–10% of patients with a single depressive episode will eventually experience a manic episode.

Naturalistic studies suggest that 1 year after a diagnosis of MDD is made, 40% of patients continue to have symptoms severe enough to meet criteria for MDD. An additional 20% remain symptomatic, but do not meet the full criteria (MDD, partial remission). This is important

Kessler RC, Berglund P, Demler O, et al. The epidemiology of major depressive disorder. Results from the National Comorbidity Replication (NCS-R). *JAMA* 2003;289(23):3095–105.

Abbreviations in this Chapter

5-HT	Serotonin	MAO	Monoamine oxidase
ACTH	Adrenocorticotropin	MAOI	Monoamine oxidase inhibitor
BDI	Beck Depression Inventory	mCPP	meta-Chlorophenylpiperazine
BP	Blood pressure	MDD	Major depressive disorder
cAMP	Cyclic adenosine monophosphate	MDE	Major depressive episode
CBC	Complete blood cell	NE	Norepinephrine
CGI	Clinical Global Impressions (scale)	NK	Neurokinin
CNS	Central nervous system	ODC	Obsessive-compulsive disorder
CRF	Corticotropin releasing factor	ODV	O-desmethylvenlafaxine
CYP	Cytochrome P450	PMDD	Premenstrual dysphoric disorder
DA	Dopamine	QIDS-SR	Quick Inventory for Depressive Symptoms-Self-Report
DHEA	Dehydroepiandrosterone	REM	Rapid eye movement
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision	rTMS	Repetitive transcranial magnetic stimulation
ECT	Electroconvulsive therapy	SNRI	Serotonin noradrenergic reuptake inhibitor
EEG	Electroencephalogram	SSRI	Selective serotonin reuptake inhibitor
EKG	Electrocardiogram	T ₃	Triiodothyronine
FDA	Food and Drug Administration	T ₄	Thyroxine
HAM-D	Hamilton Rating Scale for Depression	TCA	Tricyclic antidepressant
HIV	Human immunodeficiency virus	TMAP	Texas Medication Algorithm Project
HPA	Hypothalamic-pituitary-adrenal (axis)	YMRS	Young Mania Rating Scale
IDS	Inventory of Depressive Symptoms		
MADRS	Montgomery-Asberg Depression Rating Scale		

because those patients whose symptoms do not fully remit are more likely to suffer from future episodes of depression. Furthermore, continued illness may have a negative impact on social supports. Repeated treatment failures also may influence patients' willingness to continue treatment.

Psychosocial events, such as the death of a spouse or divorce, may trigger a depressive episode. Although this trigger may play a significant role in the precipitation of a first or second episode, it is unlikely to be predictive of subsequent episodes. Chronic medical conditions or their treatments also may precipitate or exacerbate MDD. Diabetes, coronary artery disease, human immunodeficiency virus (HIV) infection, cancer, and chronic pain may contribute to depressive symptoms. Conditions, such as fibromyalgia, chronic fatigue syndrome, and irritable bowel syndrome, also are associated with symptoms of depression. Endocrine disorders, such as Cushing's disease, Addison's disease, and hypothyroidism, in particular, can cause symptoms of depression.

Economic Burden

The implications of unremitted, and possibly prolonged, depression are significant. More than 50% of completed suicides involve an episode of depression. The annual cost of depression in the United States is about \$44 billion

(1990 dollars). Seventy-two percent of that figure reflects indirect costs related to functional impairment, such as unemployment, underemployment, and total disability. Results from an epidemiological study revealed that patients with MDD in the previous 12 months, missed, on average, 35.2 days "out of role" (i.e., functioning in work, household, relationship, and social roles) because of their depression. This number is alarming. The average days "out of role" for other chronic illnesses is about 15 for every 12 months. Another study of patients between 18 and 30 years of age revealed that 33% who had depressive symptoms had new unemployment in the previous 5 years compared to 21% of patients without depressive symptoms. Both studies indicate the significant functional deficits that can be seen in patients suffering from depression.

Pathophysiology

The exact etiology of depression is unknown. Theories include genetic, environmental, and biological etiologies. More than likely, the cause of depression is multifaceted. One indication of a genetic component to depression is the fact that a person with a first-degree biological relative who has had an episode of MDD is 1.5–3 times more likely to develop the disorder than is the general population. In addition, some evidence exists that children of adults with

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MDD may be at higher risk of alcohol dependence, anxiety disorders, and/or attention deficit-hyperactivity disorder.

For the past 50 years, dysfunction in brain serotonin (5-HT) and norepinephrine (NE) have been implicated in the pathophysiology of depression. The monoamine hypothesis was initially put forth to explain the effects of monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs) to facilitate neurotransmission of the monoamines, 5-HT and NE. However, this hypothesis cannot explain why it takes antidepressant drugs 2–3 weeks of continued drug exposure to alleviate depressive symptoms when increased concentrations of NE and 5-HT occur within 1–2 days. The desensitization theory suggests that the 5-HT- and NE-receptors are desensitized after continued antidepressant therapy, which may explain the delayed onset of action. The dysregulation theory combines the monoamine and desensitization theories and suggests that insufficient 5-HT and NE are released during depression and antidepressants increase their concentration. However, the monoamine depletion theories cannot explain why drugs, such as cocaine, which enhance 5-HT and NE transmission, are ineffective in treating depression. In addition, they also do not explain how a drug that is a relatively weak dopamine (DA) and NE reuptake inhibitor, such as bupropion, is equal in efficacy to TCAs.

Although antidepressant drugs decrease depressive symptoms through enhancement of 5-HT and/or NE transmission, it does not necessarily indicate that these neurotransmitters are actually involved in the pathophysiology of depression. Four decades of research have failed to prove that patients suffering from depression differ from controls with respect to brain 5-HT and NE. The theory that mood is influenced by these neurotransmitters is based on pharmacological evidence, and for many decades, this was the only evidence available.

In more recent years, evidence has linked chronic stress and stressful life events, including childhood trauma, with increased risk for affective disorders and anxiety. It has been suggested that these events cause long-lasting changes in neurons containing corticotropin releasing factor (CRF), which would then increase the individual's vulnerability to stressors later in life. The hypothalamic-pituitary-adrenal (HPA) axis arbitrates this neuroendocrine response. The cascade of events begins in the central nervous system (CNS) through the release of CRF from the hypothalamus. The CRF stimulates the release of adrenocorticotropin (ACTH), which in turn stimulates the release of glucocorticoids (cortisol). About one-third to two-thirds of patients with depression display signs of a hyperactive HPA axis, including increased 24-hour urinary-free cortisol and elevated serum cortisol concentrations, nonsuppression by dexamethasone, adrenal hyperplasia, and blunting of ACTH release in response to CRF challenge.

Both rodent and primate models have shown hippocampal atrophy after exposure to stress and elevated levels of glucocorticoids. Chronic stress mediated by increased cortisol levels may contribute to the decreased hippocampal volume seen in patients with depression. The effectiveness of some antidepressants may actually be the result of their ability to promote neuronal growth in the hippocampus through remodeling of the neurons.

Another theory of depression involves neurokinins (NKs), specifically substance P. Initially investigated for use as an analgesic, substance P is a peptide neurotransmitter involved in the transmission of pain. Substance P also has been found in brain regions involved in emotion and stress circuits. A newly developed substance P antagonist, MK-869, has been reported to have antidepressant effects in placebo-controlled trials. Novel compounds, such as MK-869, may lead to other agents for the use as antidepressant monotherapy or adjunct therapy.

Currently, biological models of depression continue to dominate our understanding of depression. No single theory provides a cohesive explanation of the cause of depression and how antidepressant drugs work. Improvements in brain imaging techniques and advancements in the development of new compounds to treat depression may serve as catalysts for future advances in the understanding of the pathophysiology of depression.

Diagnostic Criteria

Major Depressive Disorder

The American Psychiatric Association uses the DSM-IV-TR for classification and diagnosis of mental disorders. The diagnosis of an MDD is centered on two key features. First, the patient must have depressed mood and/or lack of interest or pleasures (anhedonia) occurring almost every day for at least 2 weeks. Second, the patient also must have at least four additional symptoms, which may include the following:

- Changes in sleep, appetite, weight, and psychomotor activity
- Decreased energy or fatigue
- Thoughts of guilt or feeling of worthlessness
- Poor concentration and thinking, or indecisiveness
- Recurrent thoughts of death or suicidal ideation plan or attempt.

The symptoms must be accompanied by significant distress and/or impairment in social or occupational functioning.

A patient does not have to convey feelings of sadness or depressed mood to meet the DSM-IV-TR criteria for MDD. If a patient expresses a loss of interest or pleasures in conjunction with the additional diagnostic criteria, he or she could still be suffering from MDD. This becomes an important factor when looking at differences in symptom presentation in various cultural, ethnic, and age cohorts. For example, studies evaluating ethnic differences in depressive symptoms have shown that African-American men are more likely to express a decreased interest in pleasurable activities than they are to express feelings of sadness. Clinicians who falsely believe that depressed mood is a requirement for the diagnosis of MDD may fail to identify and treat MDD in their clinical practice.

Symptom presentation varies widely among individuals. For instance, some patients may focus primarily on somatic concerns, such as insomnia and loss of appetite, while minimizing a depressed mood. Changes in sleep are most frequently experienced as insomnia, which may present as an inability to fall asleep, intermittent nighttime awakenings, or early morning awakening. Less frequently, patients will become hypersomnic, sleeping

12–30 hours at a time. Changes in appetite are typically a loss of appetite versus an increase in appetite. Patients may feel as if they have to push themselves to eat or not eat at all. Increased carbohydrate craving or appetite also may occur, but less frequently. Changes in psychomotor activity may include agitation or retardation. Psychomotor agitation may present as an inability to sit still, pacing, or wringing of the hands. Psychomotor retardation may include slowing of physical movement, speech, or thoughts. Examples include decreased speech tone or volume, pausing between words or sentences, and even muteness.

Many patients experience thoughts of death or suicide. These may range from passive, infrequent ideas that others would be better off if the patient were not around, to distinct, reoccurring thoughts of suicide and an actual plan or attempt at committing suicide. Clinical lore has theorized that patients demonstrating an increase in energy secondary to early treatment response may be at greater risk of suicide because they have regained the energy needed to follow through with their suicide plan.

A complete review of a patient's symptoms and functioning may be difficult. Patients may exhibit poor concentration or indecisiveness, hampering the clinician's ability to fully characterize the symptomatology. The presence of general medical conditions can cloud the diagnostic picture. Certain conditions may mimic signs and symptoms of major depression. For example, weight gain or fatigue associated with untreated hypothyroidism may present like an MDE. However, somatic symptoms should not contribute to the diagnosis of MDD if they are fully and clearly accounted for by the general medical condition. Conversely, in a patient who recently has suffered a stroke, symptoms of depression, anhedonia, and guilt should count toward a diagnosis of MDD if they cannot be fully accounted for by the physiological effects of the stroke. Furthermore, according to DSM-IV-TR diagnostic criteria, an MDE cannot be due to the direct physiological effects of substance abuse, a drug side effect, or a toxin exposure. Finally, depressive symptoms are attributed to bereavement if they develop after the loss of a loved one, and do not persist for more than 2 months. Collateral information from family and friends often is useful in confirming the diagnosis.

Dysthymic Disorder

In dysthymia, a depressed mood is present more days than not for at least 2 years, during which time there is not a 2-month period that patient did not experience symptoms. In addition, at least two of the following symptoms must be present: appetite changes, sleep changes, low energy or fatigue, low self-esteem, poor concentration, difficulty making decisions, or feelings of hopelessness. If a patient has had a diagnosis of MDE during the past 2 years, he or she does not meet the criteria for dysthymia. Like MDE, all other possible medical and psychiatric causes need to be ruled out before making the diagnosis of dysthymic disorder.

Depressive Disorder, Not Otherwise Specified

Depressive disorder, not otherwise specified is a diagnosis indicating that the patient is experiencing some

depressive symptoms, but does not meet the full criteria for MDD or dysthymia. Examples of depressive disorder not otherwise specified include the following:

- Premenstrual dysphoric disorder (PMDD): symptoms usually occur in the last week of the luteal phase and remit before the onset of menses.
- Minor depressive disorder: depressive symptoms last at least 2 weeks, but the patient does not exhibit enough symptoms to be classified as MDD.
- Recurrent brief depressive disorder: depressive symptoms last 2–14 days and occur monthly but are not related to menstrual cycle. This term may be used when depressive symptoms have been identified, but medical or substance abuse causes have not been ruled out.
- Postpsychotic depressive disorder: MDD that occurs after the residual phase of schizophrenia. The MDE must include depressed mood. Loss of interest or pleasure cannot take the place of depressed mood. The MDE cannot be attributable to the effects of a substance or a general medical condition.

Episode or Course Specifiers

Once the diagnosis of major depression has been made, the severity of the episode is further characterized as mild, moderate, or severe without psychotic features or severe with psychotic features. If applicable, it should be noted if the current episode is in full or partial remission. Clinicians should note if the current episode presents with a specific feature such as melancholia or atypical features, which becomes critical for treatment decisions.

- Mild, moderate, or severe without psychotic features: the severity of the illness is assessed by the number and severity of symptoms present and the functional impairment caused by the symptoms. In mild episodes, only five to six depressive symptoms are present and are either mild in nature or the ability to function normally is obtainable, although possibly difficult. On the other hand, in severe episodes, patients are experiencing most depressive criteria and are experiencing true functional impairment (e.g., loss of job). Moderate episodes fall between mild and severe.
- Severe with psychotic features: this type of episode refers to patients who suffer from delusions or hallucinations during their current MDE. Psychotic symptoms are classified as mood congruent if they are related to depression or mood incongruent if they are unrelated to the depression. Examples of mood congruent hallucinations include hearing voices telling patients that they are worthless or command hallucinations telling them to hurt themselves. Mood incongruent psychosis may include paranoid delusions, such as a belief that someone is out to get the patients or that people are inserting thoughts into patients' heads. Whether the psychotic symptoms are mood congruent or incongruent, patients will need to be treated with both an antidepressant and an antipsychotic drug. Currently, no definitive guideline exists to assist clinicians in deciding how long an antipsychotic drug should be continued. Results from a recent study suggest that continuing the antipsychotic drug along with the antidepressant for more than 4 months provided no further benefit over

continuing only the antidepressant past 4 months. Studies such as this suggest that antipsychotic drugs in the continuation phase of treatment typically are not necessary. Many clinicians believe that the antipsychotic drug should be continued for a minimum of 3 months after remission of psychotic symptoms. Thereafter, an attempt to taper patients off the antipsychotic drug can be made, but the antidepressant drug should be continued.

- In partial remission/in full remission: patients must be free of significant symptoms of depression for a minimum of 2 months. In partial remission, some symptoms may still be present but do not meet the full criteria for an MDE, or the patient has achieved remission of symptoms but for less than 2 months.
- Chronic: this specifier refers to patients who have suffered from an MDE continuously for a minimum of 2 years. This specifier can only be used during the most current episode of MDD. Maintenance drugs should be considered for patients with chronic depression.
- Catatonic features: this specifier is used when a patient has at least two of the following: motor immobility (catalepsy or stupor), excessive motor activity, extreme negativism (maintaining a rigid posture despite all attempts to be moved) or mutism, echolalia (repeating words just spoken by another person) or echopraxia (imitating movements), or peculiar voluntary movements (bizarre postures). Patients with MDD with catatonic features typically need to be treated with an antipsychotic drug in conjunction with their antidepressant drug.
- Melancholic features: this specifier can only be applied to the current MDE. Melancholic features include loss of pleasure in all, or almost all activities or a lack of reactivity to usually pleasurable stimuli. In addition, patients can have three or more of the following: distinctly depressed mood, depression that typically is worse in the morning, early morning awakenings, marked psychomotor retardation or agitation, significant appetite decrease or weight loss, or excessive or inappropriate guilt. Patients with melancholic features often have biological markers, such as dexamethasone nonsuppression of cortisol, elevated cortisol levels, alterations in sleep electroencephalogram (EEG), and abnormal tyramine challenge test.
- Atypical features: the atypical specifier is only applied to the most recent MDE. The term “atypical depression” does not imply a rare clinical presentation, but rather a distinction from the stereotypical presentation of depression. The essential features of an atypical depression are mood reactivity and the presence of at least two of the following: increased appetite or weight, hypersomnia, leaden paralysis, or extreme rejection sensitivity. Atypical presentations of depression are more common in women.
- Seasonal pattern: a seasonal pattern refers to the onset and remission of depressive symptoms at a particular time of the year. For example, the regular appearance of an MDE in the fall or winter and resolution of the symptoms in the spring. The seasonal pattern must have occurred for at least the past 2 years, without nonseasonal episodes in between them. Winter seasonal patterns are more commonly seen in patients of younger

age, living in a higher latitude, and of the women gender. Clinicians often refer to this specifier as seasonal affective disorder. Treatment of seasonal affective disorder with phototherapy is discussed in the Non-pharmacological Therapies section.

- Postpartum onset: for this specifier, the MDD symptoms must have an onset within 4 weeks after giving birth. Symptoms often include fluctuations in mood, mood lability, and preoccupation with infant well-being, ranging from overprotectiveness to delusions. Postpartum mood episodes with psychotic features are characterized by command hallucinations to kill the infant or delusions that the infant is at increased risk of harm. Psychotic features occur in about one in 500 to one in 1000 deliveries and may be more common after the birth of the first child. The risk of psychotic features is higher in patients who have had a previous postpartum MDE, as well as those who have had prior mood disorders. Postpartum depression not only carries with it a risk for psychosis, but also the burden of risk to two lives.

About 70% of women suffer from the “baby blues” during the first 10 days postpartum. It is important to distinguish this minor mood change with that of postpartum depression. The baby blues typically are transient and do not impair functioning. Treatment of postpartum depression often requires the use of an antidepressant, and patients with psychotic symptoms also will need an antipsychotic drug in conjunction with their antidepressant.

Assessment

When a patient initially presents with symptoms of depression, a full medical history, physical examination, and appropriate laboratory testing should be conducted. Clinicians should consider the possibility that the depression may be an associated symptom of a physical illness. Although treatment of the underlying physical illness may alleviate the depressive symptoms, initiation of antidepressant pharmacotherapy may be necessary in some patients. Many clinicians obtain thyroid functioning tests as part of their baseline assessment of a patient, especially in women. The patient’s drug regimen should be reviewed to rule out drug-induced depression. Many drugs of abuse (i.e., amphetamines, marijuana, cocaine, opiates, and alcohol), certain antihypertensive agents (reserpine, propranolol, clonidine, and methyldopa), corticosteroids, and oral contraceptives have all been associated with depressive symptoms.

Currently, there are no definitive laboratory tests to assist in diagnosing depression. The diagnosis and assessment of symptom response are based on clinician observation and sometimes on results from psychometric rating scales. These scales routinely are used in research to assess the efficacy of drugs or other somatic treatments; however, they are used far less commonly in clinical practice. The most commonly used rating scales are the Hamilton Rating Scale for Depression (HAM-D), the Montgomery-Asberg Depression Rating Scale (MADRS), and the Beck Depression Inventory (BDI). The Quick Inventory for Depressive Symptoms-Self-Report (QIDS-SR) is becoming an increasingly popular scale in the clinical setting. The

Clinical Global Impressions (CGI) scale measures global response to treatment and severity of illness, and can be used to assess several different psychiatric disorders.

Hamilton Rating Scale for Depression

The HAM-D is available as either a 17- or 21-item, clinician-administered tool to assess depressive symptoms. This scale includes subjective symptoms of depression, such as mood and guilt, in addition, to neurovegetative (e.g., insomnia and anxiety) and somatic (e.g., gastrointestinal) symptoms. The inclusion of somatic symptoms may provide falsely elevated ratings in the elderly or pregnant patient, as many of those symptoms may naturally occur outside of depression if baseline scoring is not taken into account. Items are scored between zero (absent) and 2 or 4 depending on the individual item. On the 21-item version, the maximum score is 72. A score between 7 and 17 typically represents mild depression and higher scores indicate more significant depression and need for treatment. Scores less than 7 indicate the absence of significant depressive symptoms and typically are used as the cut off point to define remission in research studies. In general, the patient is instructed to report signs and symptoms of depression that have occurred within the past 1–2 weeks. The scale takes about 20–30 minutes to administer. Because of the time needed to administer the HAM-D, it often is not used outside the research setting. In addition, the HAM-D relies extensively on the expertise of the interviewer and many clinicians, including psychiatrists, are not adequately trained to administer the scale.

Montgomery-Asberg Depression Rating Scale

The MADRS is a 10-item, clinician-administered depression rating scale. The MADRS assesses core depressive symptoms, but unlike the HAM-D, it does not assess neurovegetative symptoms or focus on somatic symptoms of depression. Nine items are completed based on the patient's self-report and the 10th item is completed based on the rater's observation. Each item is scored from zero to 6 (0 = no abnormality, 6 = severe) based on descriptive anchor points; the maximum possible score is 60 points. Severe depressive symptoms are represented by a score of 35 or more. Moderate depressive symptoms correlate to scores ranging from 20 to 34. Scores less than 8 are not considered to represent significant depressive symptoms. The MADRS is straightforward to administer and can be completed in about 15 minutes. However, like the HAM-D, clinicians often are not adequately trained to administer the scale and the scale is too time-consuming to use in most clinical settings.

Beck Depression Inventory

The BDI is a 21-item, self-rated psychometric scale used to assess depressive symptoms in adults and adolescents. This scale is more frequently used in clinical settings, as it takes about 5–10 minutes for patients to complete. Patients are asked to rate themselves on a 4-point scale (0 = least, 3 = most), with total scores ranging from 0 to 63. Scores greater than 30 indicate severe depression; 15–30 indicate moderate symptomatology; 14–10 indicate mild depression,

and scores less than 10 are considered normal mood variations.

Quick Inventory of Depressive Symptoms-Self-Report

An additional example of a self-rated scale that can be administered easily in a clinical setting is the QIDS-SR. The QIDS-SR is a 16-item scale that is based on the nine core symptoms of depression. Only nine of the 16 items are scored, with a maximum score of 27. The QIDS-SR is a shortened version of the Inventory of Depressive Symptoms (IDS). The IDS and the self-rated version (the QIDS-SR) have demonstrated validity and reliability and have correlated with the HAM-D and MADRS scores. In addition, the IDS and QIDS-SR have been more sensitive to change over time than either the HAM-D or MADRS. A score less than 6 on the QIDS-SR indicates remission of symptoms. The QIDS-SR takes about 5 minutes for patients to complete.

Clinical Global Impressions

The CGI is composed of three items that assess the severity of illness, global improvement, and efficacy index. The CGI frequently is used as a secondary outcome measure in clinical trials. It is unique in that it can be used to assess a variety of psychiatric illnesses. The CGI commonly is used in clinical practice. On the severity of illness item, raters are asked to assess the severity of a given patient's illness against the rater's total experience within the psychiatric population to which the patient belongs. The severity of illness is rated on a 7-point scale with 1 being normal (i.e., absence of illness) to 7 being extremely ill. On the global improvement item, the rater is asked to assess how much the patient's clinical condition has improved or worsened compared to baseline. This item is rated between 1 (very much improved) and 7 (very much worse). Finally, efficacy index is a measure of therapeutic and adverse effects on a 4-point scale ranging from "unchanged or worse" to "marked" for therapeutic effect and "none" to "outweighs therapeutic effects" for adverse effects. There are some limitations to the scale, namely it is unstructured and requires in-depth clinical knowledge. The key to successful administration of the CGI is to have the same trained rater consecutively assess the patient at baseline and throughout treatment.

Although rating scales are used routinely in the research setting, they are not always convenient to use in clinical practice. The self-rated depression scales, such as QIDS-SR or BDI, are more practical to assess a patient's depressive symptoms in the clinical setting. Minimally, a clinician should identify a list of target symptoms at the initial visit, taking into account symptom severity and impairment in functioning. Reassessing this list at each visit will help the clinician and patient more objectively assess treatment-response, as well as reassure the patient.

Pharmacotherapy of Depression

The current understanding of the pathophysiology of depression is based on two clinical observations, both of which occurred in the 1950s. Iproniazid, an antituberculin drug, was found to alleviate depressive symptoms. In a

similar serendipitous fashion, imipramine, initially used as an antipsychotic drug, revealed some evidence of antidepressant action during preclinical and clinical trials. Both drugs, through different mechanisms of action, facilitate the transmission of 5-HT and NE. Where iproniazid is an MAOI that blocks the breakdown of 5-HT, NE, and DA, imipramine blocks the reuptake of NE and 5-HT. The increase in the transmission of 5-HT and NE was related to antidepressant effects, and the blockade of other neurotransmitter receptors was related to adverse effects, such as dry mouth, sedation, or cardiac toxicities. This information, combined with the observation that a monoamine depleting drug, reserpine, potentially induced depression, led researchers to the monoamine hypothesis that a dysfunction in brain 5-HT or NE was the likely cause of depression.

Although MAOIs and TCAs were found to be efficacious for treating depression, the dietary restrictions with MAOIs and the toxic effects of both MAOIs and TCAs led researchers to develop safer antidepressant drugs that involved more selective blockade of monoamine uptake. The result of this search was the development of the selective serotonin reuptake inhibitors (SSRIs). Fluoxetine was the first SSRI to be marketed in the United States in 1987, and was followed by sertraline and paroxetine and more recently citalopram and escitalopram (S-enantiomer of citalopram); other agents, such as bupropion, venlafaxine, nefazodone, and mirtazapine, have been indicated for treating depression in the past 15 years. Fluvoxamine, another SSRI, currently has Food and Drug Administration (FDA) approval for labeling as a treatment for obsessive-compulsive disorder (OCD)

Choosing an Antidepressant Drug

Currently, all available antidepressants are considered equal in efficacy for uncomplicated unipolar depression (without melancholic features), with an overall efficacy of about 65% of patients responding to antidepressants versus 30% given placebo. Because no one agent appears superior to the others, the choice among agents is based on the indication(s) the antidepressant is being used for (i.e., a psychiatric or medical comorbidity, in addition to depression), side effect profile, potential drug interactions, safety, patient preference, and cost. Another consideration is a patient's past response to drugs or possibly a family member's response to an antidepressant drug. Failure of one drug in a drug class does not predict failure of another drug in that same class. However, if a patient's symptoms fail to respond to two drugs of the same class, a different drug class should be considered.

Although SSRIs and other newer agents have higher acquisition costs than TCAs, the total cost of treating depression is no greater. Because patients tolerate newer agents better, they are more likely to adhere to their drug regimens. This greater compliance leads to fewer clinician

visits and hospitalizations. In addition, newer antidepressant drugs require less laboratory monitoring. Of the newer drugs, it is not clear if one agent is more cost-effective than another. Drug cost, although an important consideration, should not be the sole determining factor for drug selection. Clinical judgment and patient preference should be considered when deciding which antidepressant drug to use. Generic formulations of newer antidepressant drugs are an appealing option for many formulary committees because of their lower acquisition costs than brand name drugs. Formulary committees should maintain vigilance as more and more generic formulations become available. However, some institutions are able to obtain brand name drugs at costs lower than their generic counterparts through rebates or contracts with a pharmaceutical manufacturer.

Figure 1-1 is an example of a drug algorithm for treating uncomplicated depression. This evidence-driven algorithm was developed by an expert consensus panel for the Texas Medication Algorithm Project (TMAP). The algorithm starts off with simple regimens (stages 1–3) and as the patient progresses through the stages, the regimens become more complex. The algorithm is based on safety and efficacy first. Many institutions adopting the TMAP depression algorithm have selected “preferred agents” within each stage of the algorithm. This allows the institution to practice evidence-based medicine while containing costs. Again, the preferred agents in each stage may vary from institution to institution based on the individual institutions acquisition costs for certain antidepressant drugs.

Predictors of Response

The best predictors for response are the absence of neurovegetative symptoms, past response, and familial response. Adequate patient follow-up and patient adherence with visits and drugs also are predictive of positive patient outcomes.

Some antidepressants have been efficacious in different subtypes of depression. For example, TCAs are clearly efficacious particularly in severe depression. Bupropion may theoretically work well in patients with apathy. There is some evidence that venlafaxine may be more effective in treatment-resistant depression than SSRIs, with an increase in venlafaxine dose producing a better response than switching to an SSRI. The MAOIs are particularly effective for patients with atypical depressive features. The SSRIs have also shown some promise in treating atypical features.

Treatment Response

Although most clinical trials define adequate treatment response as at least a 50% reduction in symptoms, the goal of treatment should always be remission of symptoms and restoration of functioning. Patients with MDD face the possibility of relapse (where some symptoms return) or

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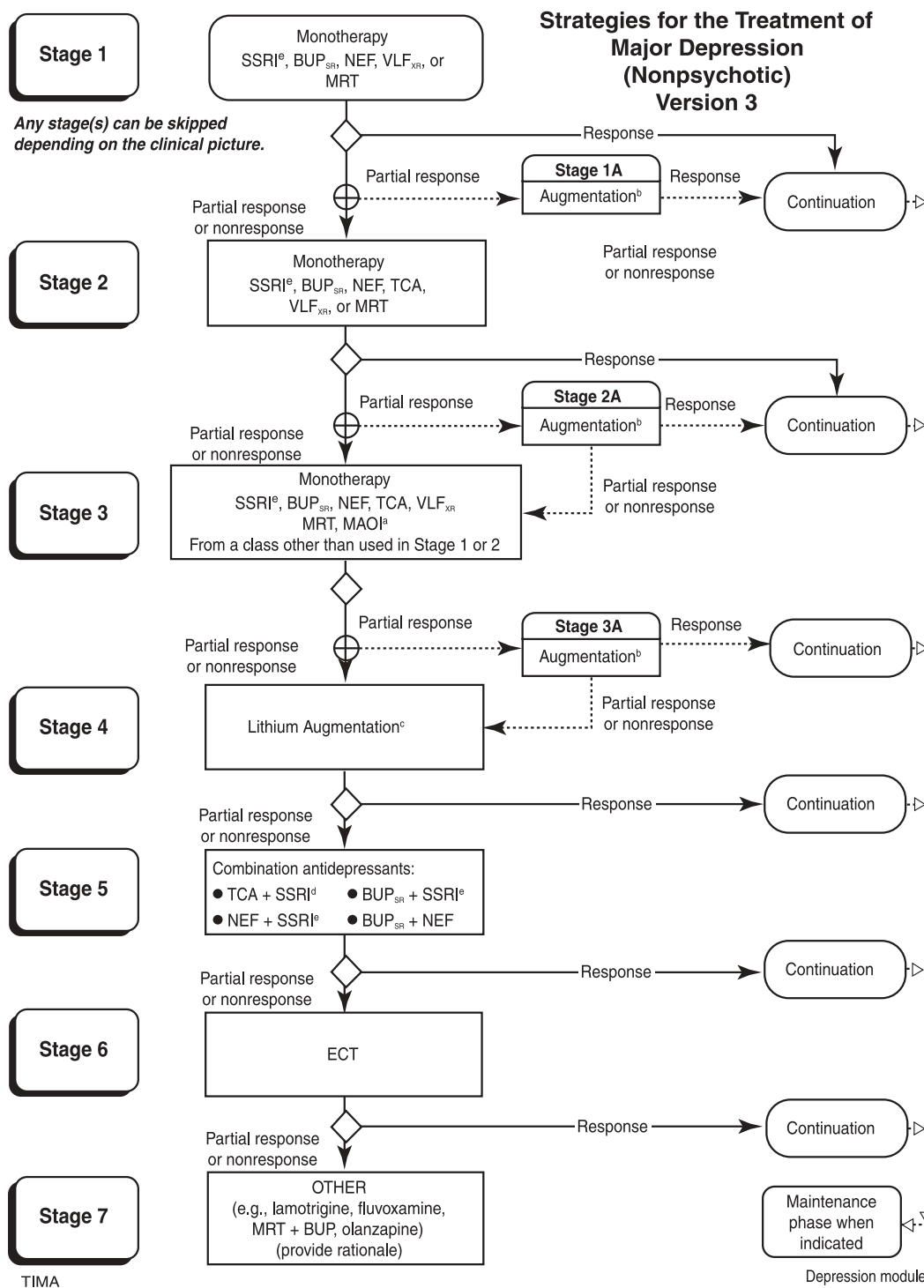


Figure 1-1. Texas Medication Algorithm Project (TMAP): Depression Algorithm.

^aConsider TCA/VLF if not tried.

^bLithium, thyroid, buspirone.

^cSkip if lithium augmentation has already failed.

^dMost studied combination.

^eSSRI = fluoxetine, sertraline, paroxetine, citalopram.

BUP_{SR} = bupropion SR; ECT = electroconvulsive therapy; MAOI = monoamine oxidase inhibitor; MRT = mirtazapine; NEF = nefazodone; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; TIMA = Texas Implementation of Medication Algorithms; VLF_{XR} = venlafaxine XR.

recurrence of significant symptoms after a period of remission. Complete symptom remission may help prevent relapse or recurrence in many patients.

All antidepressants require a minimum of a 4-week trial and preferably up to an 8-week trial at adequate doses to assess efficacy. Despite the availability of multiple pharmacological agents to treat MDD, many patients receiving drugs do not experience substantial relief from their symptoms. About 10–20% of patients cannot tolerate the side effects of antidepressant treatment. Another 25–35% of patients who complete an adequate trial of an antidepressant had symptoms that do not respond at all or do not show an acceptable response to treatment, usually defined as a 50% decline in symptom severity as measured by HAM-D. In addition, up to 50% of patients have symptoms that show an “acceptable” response continue to have residual symptoms that interfere with work, family, and social activities. Some patients will require an additional agent, such as lithium, and others will require another trial of antidepressant monotherapy or to combination therapy to achieve remission of symptoms. Treatment should be addressed on several fronts, including dosage, length of trial, and overall treatment duration. In addition, response should be evaluated objectively at specific intervals. A methodological approach is a critical tool in the effective treatment of MDD.

There are three phases of treatment: acute, continuation, and maintenance. The acute phase typically is 12 weeks. Once a patient is progressing satisfactorily, a continuation phase follows during which the therapeutic drug dose is continued for a minimum of 6–9 months. Patients who continue therapy for at least 6 months are less likely to experience relapse than patients who stop therapy earlier. It has been suggested that recurrent or chronic depressions may require maintenance treatment lasting 2 years or longer to deter relapse or recurrence of significant depressive symptoms.

Although the prevalence of treating depression has increased over the past decade, studies have not shown clear evidence of improvements in quality or continuity of care. Often, the treatment of depression is not in accordance with current evidence-based research findings. It has been estimated that as many as 40% of patients in treatment do not receive at least a moderate drug dose for an adequate time period. In addition, these patients may have inadequate follow-up, particularly during the critical initial stages of treatment. Subsequently, the desired outcomes of full symptomatic remission and return of premorbid levels of functioning often are not achieved. Undertreatment of patients with MDD, particularly in the primary care setting, is a persistent concern.

Not all patients’ depressive symptoms respond similarly to a drug at a given dose. When applicable, plasma concentrations should be measured to determine if patients are at a therapeutic level. Currently, only imipramine, desipramine, and nortriptyline have established therapeutic plasma concentrations. The clinician can titrate these drugs aggressively to reach a therapeutic concentration more

rapidly, as tolerated. Some patients may benefit from higher doses, and some symptoms may improve by increasing the drug dose. Among patients who have exhibited some improvement with antidepressant treatment but are still experiencing residual symptoms, titration to the maximum tolerated dose may enable them to achieve a full remission of symptoms, or possibly attain the desired goal of full remission. This initial strategy is only useful with agents that have a known dose-response relationship. As tolerated, patients should be brought to the minimum therapeutic drug dose, and maintained on that dose for an adequate time period to determine the effectiveness of a given treatment.

Failure to use adequate treatment (i.e., adequate dose for adequate time period) often is blamed for poor patient outcomes; however, patient nonadherence with pharmacotherapy is a substantial contributing factor. Drug trials for treating depression report a 10–30% rate of nonadherence, and nonadherence is thought to be higher in a clinical practice setting. Studies in practice settings show that patients often decide independently to discontinue treatment sooner than practice guidelines recommend. About 28% of patients stop taking antidepressant drugs in the first month of therapy, and 44% discontinue antidepressant drugs by the third month. About 60% of patients in primary care discontinue their antidepressant drugs before completion of the recommended 6 months of pharmacotherapy. These findings emphasize the importance of assessing drug adherence before deeming an antidepressant drug a treatment failure.

Pharmacists can play an active role in educating patients about the importance of drug adherence. Positive outcomes associated with pharmacist interventions have been reported in a variety of practice settings. Studies evaluating the impact of using pharmacists in educating patients on their depression, the drug(s) prescribed, and expectations with treatment, have shown improved patient outcomes. Areas of improved patient outcomes include patient satisfaction with care, increased drug adherence, decreased service use, and improvement in depressive symptoms.

In addition to inadequate treatment and patient nonadherence, unsuccessful antidepressant treatment may be a result of misdiagnosis or the presence of an unrecognized comorbid psychiatric disorder or general medical condition. Comorbid psychiatric disorders are more common in patients with MDD compared to patients without MDD. If these disorders are missed or inadequately treated, the evaluation and treatment of depression may be complicated. For example, depressed patients with comorbid anxiety disorders tend to be more severely depressed and slower to respond to treatment. They are more likely to have residual symptoms and have increased rates of relapse and recurrence. The acute and chronic effects of substance abuse may worsen symptoms of depression and increase the likelihood of nonadherence.

Selective Serotonin Reuptake Inhibitors

Since the 1990s, SSRIs have been the treatment of choice for patients suffering from uncomplicated MDD because of

Quitkin FM, Petkova E, McGrath PJ, et al. When should a trial of fluoxetine for major depression be declared failed? *Am J Psychiatry* 2003;160:734–40.

their safety profiles and once daily dosing. The SSRIs bind to the 5-HT transporter and inhibit reuptake, thereby increasing 5-HT activity within the neuronal synapse. The SSRIs have low affinity for histaminergic, cholinergic, and α -adrenergic receptors. The SSRIs approved for marketing in the United States for treating depression include citalopram, escitalopram, fluoxetine, sertraline, and paroxetine. Fluvoxamine is an SSRI available in the United States approved for marketing as an agent to treat OCD. The SSRIs are considered first-line agents for treating depression. Currently, there is no evidence to suggest that one SSRI is more efficacious than another SSRI.

Selective serotonin reuptake inhibitors, as a drug class, have been useful for treating other psychiatric comorbidities, making them ideal for patients who suffer from both depression and another psychiatric diagnosis. The SSRIs commonly are prescribed for other psychiatric conditions, such as generalized anxiety disorder, panic disorder, social phobia, OCD, bulimia nervosa, PMDD, and post-traumatic stress disorder. (See Table 1-1 for FDA-approved indications for newer antidepressants.)

Pharmacokinetics

Fluoxetine has a half-life of 1–4 days and its active metabolite, norfluoxetine, has a half life of about 7–15 days. The prolonged half-life of fluoxetine may make it a good option for patients who are nonadherent with treatment. In fact, a new dosage form of fluoxetine (Prozac Weekly 90 mg) is available for administration 1 time/week. It is clinically important to remember that elimination of fluoxetine and norfluoxetine takes about 5 weeks compared with other SSRIs which take about 1–2 weeks. The other SSRIs, paroxetine, sertraline, citalopram, and escitalopram, all have half-lives of about 24 hours. Liver cirrhosis associated with functional impairment significantly reduces the plasma clearance of SSRIs, whereas elimination is unaffected by renal impairment.

Currently, measuring serum concentrations of SSRIs does not provide clinically relevant information outside of monitoring for adherence. Unlike some TCAs, serum concentrations of SSRIs have not been related to clinical outcome.

Dosing

In general, SSRIs are administered 1 time/day. Patients should be initiated on the lowest possible dose, especially if an underlying anxiety disorder is suspected. Dosing should be started at the anxiety dose, which typically is one-half of the depression dose or lower, then titrated up as tolerated by the patient.

Fluoxetine usually is initiated at 20 mg/day. Patients with comorbid anxiety disorder may need to start at 5–10 mg/day and increase the dose every 3 days (or as tolerated) up to 20 mg/day. A patient should continue taking the 20-mg dose for 4 weeks and then symptoms should be reassessed. If a patient is tolerating the drug, but symptoms have not responded fully or only partially responded, the

dose can be increased to 40 mg. A patient should remain at this dose for an additional 2–3 weeks and then be reassessed. Doses can be increased by 20-mg increments up to 80 mg (maximum daily dose). Doses greater than 60 mg have not been clinically superior and are more likely to increase the risk of adverse effects and drug costs. About 49% of patients feel more energetic taking fluoxetine, making morning dosing a logical choice; however, some patients may feel sedated while taking fluoxetine, so nighttime dosing may be more appropriate for them.

Fluoxetine is available as a weekly 90-mg enteric-coated formulation. The enteric coating delays the release of fluoxetine by 1–2 hours. The fluoxetine (90 mg) weekly formulation provides average daily concentrations similar to 20 mg/day of the regular-release fluoxetine. Fluoxetine weekly is probably best reserved for patients in the continuation or maintenance phases of depression after immediate-release fluoxetine has been efficacious for the patient. When switching from immediate-release dosing to weekly dosing, a drug-free period should be considered because of the long half-life of fluoxetine.

The dosing range for sertraline is 50 mg/day to 100–150 mg, and doses up to 200 mg are not uncommon. Sertraline 100 mg is scored and priced the same as the 50-mg tablet; therefore, cutting the 100-mg tablet in half to achieve a 50-mg dose can provide cost savings. Sertraline is initiated at 12.5–25 mg/day in patients with a comorbid anxiety disorder. The patient's dose should be increased in 25–50-mg increments as rapidly as tolerated to 100 mg/day. The patient should then be maintained at that dose for 4 weeks, and then the symptoms should be reassessed. Doses can be increased up to 150–200 mg/day. Like fluoxetine, sertraline should be dosed in the morning, unless the patient experiences daytime sedation.

Paroxetine can be initiated at 10–20 mg/day. If patients' symptoms do not respond within 4 weeks, the dose should be increased in 10-mg increments as tolerated to response or 50 mg/day maximum dose. Patients with comorbid anxiety disorder may need doses up to 60 mg/day, although these patients should be started on no more than 10 mg/day. Because paroxetine causes sedation in some patients, it is best to start treatment once a day at bedtime. When a controlled-release formulation of paroxetine was initially released, many clinicians falsely believed that the "CR" meant longer acting. This formulation was developed to decrease gastrointestinal adverse effects, and not to decrease the potential for discontinuation symptoms. The CR formulation may be an option when a patient has a positive effect with immediate-release paroxetine, but has unacceptable gastrointestinal side effects. Starting doses of controlled-release paroxetine are usually between 12.5 mg/day and 25 mg/day. Dose increases by 12.5–25 mg up to 62.5 mg/day can be used. Paroxetine 20 mg is equivalent to 25 mg of controlled-release paroxetine.

Citalopram typically is initiated at 20 mg/day. Like fluoxetine and sertraline, it is usually best tolerated when dosed in the morning, but it can be dosed at bedtime if

Kroenke K, West SL, Swindle R, et al. Similar effectiveness of paroxetine, fluoxetine, and sertraline in primary care: a randomized trial. *JAMA* 2001;286:2947–55.

Table 1-1. Comparison of Newer Antidepressants

Antidepressant	Place in Therapy	FDA Approved Indications	Adverse Effects	CYP
SSRIs				
	All SSRIs are considered first-line agents		Nausea, insomnia, headache, changes in weight, somnolence, sexual dysfunction, and initial increased anxiety	
Fluoxetine		MDD, OCD, BN, PMDD		Potent inhibitor of 2D6 and 3A4
Sertraline		MDD, SAD, PTSD, panic, OCD, PMDD		Moderate inhibitor of 2D6 (higher doses)
Paroxetine		MDD, PMDD, panic, GAD, OCD, SAD, PTSD		Potent inhibitor of 2D6
Citalopram		MDD		Moderate inhibitor of 2D6 (higher doses)
Escitalopram		MDD		Moderate inhibitor of 2D6 (higher doses)
Fluvoxamine		OCD		Potent inhibitor of 1A2, 2C19, and 3A4
Bupropion	First-line agent	MDD, smoking cessation	Agitation, nausea, headache, seizures, tremor, and insomnia	Moderate inhibitor of 2D6 (hydroxybupropion)
Venlafaxine	First-line agent	MDD, GAD, SAD	Agitation, headache, insomnia, nausea, sexual dysfunction, and increase in diastolic blood pressure	No significant inhibition
Mirtazapine	First-line agent	MDD	Sedation, weight gain, dry mouth, constipation, increased appetite, and orthostasis	No significant inhibition
Nefazodone	Second- or third-line agent	MDD	Sedation, orthostasis, dry mouth, nausea, and liver failure due to risk of liver failure	Potent inhibitor of 3A4

BN = bulimia nervosa; CYP = cytochrome P450; FDA = Food and Drug Administration; GAD = generalized anxiety disorder; MDD = major depressive episode; OCD = obsessive-compulsive disorder; panic = panic disorder; PMDD = premenstrual dysphoric disorder; PTSD = post-traumatic stress disorder; SAD = social anxiety disorder; SSRI = selective serotonin reuptake inhibitor.

daytime sedation occurs. If, after 4 weeks, the patient has not experienced remission of symptoms, doses may be increased in 10–20-mg increments every 2–3 weeks up to 60 mg/day.

Escitalopram is the S-enantiomer of citalopram. Escitalopram was developed because the “S” component is thought to be the clinically active enantiomer, whereas the “R” enantiomer is responsible for side effects, such as sexual dysfunction. However, clinical trial data have not shown that escitalopram is any less likely to cause sexual dysfunction than citalopram. More recent data have linked the “R” enantiomer to counteracting the clinical effects of the “S” enantiomer in studies conducted in mice. Escitalopram doses are initiated at 10 mg/day and can be increased to the maximum dose of 20 mg if there is insufficient response after 4 weeks. If a patient is particularly sensitive to the serotonergic side effects of escitalopram (i.e., increased anxiety), the clinician may choose to reduce the 10-mg dose to 5 mg/day and titrate up

as tolerated. Both the 10-mg and 20-mg tablets are scored and can easily be cut in half. Like citalopram, it is usually dosed in the morning but can be dosed at bedtime if daytime sedation occurs. (See Table 1-2 for dosage and dosage schedules for newer antidepressants.)

Drug Interactions

One of the most prominent features of SSRIs is their potential for pharmacokinetic drug interactions with other drugs. All SSRIs are substrates and inhibitors of various cytochrome P450 (CYP) enzymes. The SSRIs vary considerably in their potency and specificity to inhibit CYP isoenzymes. (See Table 1-1 for CYP inhibition potency.)

Fluoxetine, its metabolite norfluoxetine, and paroxetine are potent inhibitors of CYP2D6, with paroxetine being the most potent. Clinically relevant CYP2D6 interactions have been observed with the combined use of SSRIs and TCAs or haloperidol. In addition, fluoxetine and norfluoxetine inhibit CYP3A4 and CYP2C9, potentially increasing serum

Devane CL, Nemeroff CB. Psychotropic drug interactions 2000. TEN 2000;2:56–75.

Table 1-2. Dosing and Available Strengths of Newer Antidepressants

Generic Name	Trade Name(s)	Recommended Starting Dose	Usual Dosing Range	Recommended Dosing Schedule	Available	Generic
SSRIs						
Fluoxetine	Prozac	20 mg/day	20–80 mg/day	QAM	10, 20, 40 mg capsule	Yes
	Sarafem	20 mg/day	20–80 mg	QAM	10 mg tablet, 20 mg/5 ml liquid	Yes No
Sertraline	Prozac Weekly	90 mg/week	90 mg/week	weekly	90 mg capsule	No
	Zoloft	50–100 mg/day	100–200 mg/day	QAM	25, 50, 100 mg tablets 20 mg/ml solution	No
Paroxetine	Paxil	10–20 mg	20–50 mg/day	QD	10, 20, 30, 40 mg tablet 10 mg/ml oral suspension	Yes No
	Paxil CR	25 mg/day	25–62.5 mg/day	QAM	12.5, 25, 37.5 mg tablet	No
Citalopram	Celexa	20 mg/day	20–60 mg/day	QAM	10, 20, 40 mg tablet 5 mg/5ml solution	No
Escitalopram	Lexapro	10 mg/day	10–20 mg/day	QAM	5, 10, 20 mg tablet 2 mg/ml solution	No
Fluvoxamine	Luvox	50–100 mg/day	100–300 mg/day	QHS (doses < 150 mg) –BID	25, 50, 100 mg tablet ^a	Yes
Bupropion	Wellbutrin	75–150 mg/day	200–450 mg/day	BID–TID, (no single dose > 150 mg)	75, 100 mg tablet	Yes
	Wellbutrin SR	150 mg/day	150–400 mg/day	QD (doses < 200 mg) –BID	100, 150, 200 mg tablet	No
	Wellbutrin XL	150 mg/day	300–450 mg/day	QD	150, 300 mg tablet	No
Venlafaxine	Zyban	150 mg/day	300 mg/day	BID	150 mg	No
	Effexor	75 mg/day	150–375 mg/day	BID–TID	25, 37.5, 50, 75, 100 mg tablet	No
Mirtazapine	Effexor XR	75 mg/day	75–225 mg/day	QD–BID	37.5, 75, 150 mg caplet	No
	Remeron	15–30 mg/day	30–60 mg/day	QHS	15, 30, 45 mg tablet	Yes
Nefazodone	Remeron SolTab	15–30 mg/day	30–60 mg/day	QHS	15, 30, 45 mg dissolving tablet	No
	Serzone	200 mg/day	300–600 mg/day	BID	50, 100 ^a , 150 ^a , 200, 250 mg tablet	No

^aScored tablet.

BID = 2 times/day; CR = controlled release; QAM = each morning; QHS = at bedtime; SR = sustained release; SSRIs = selective serotonin reuptake inhibitors; TID = 3 times/day; XR = extended release.

concentrations of carbamazepine and alprazolam, or phenytoin, respectively. Because of the long half-life of fluoxetine and norfluoxetine, the potential for drug interaction needs to be considered for up to 5 weeks after fluoxetine is discontinued.

Sertraline has a lower propensity to cause CYP enzyme-mediated drug interactions that are dose-dependent. At lower doses, it is a weak inhibitor of CYP2D6, and it becomes more potent (although still weaker than fluoxetine or paroxetine) at higher doses. Although there are no known significant drug interactions, its potential is a factor to consider in clinical decision-making. Citalopram and escitalopram also may exhibit dose-dependent inhibition of CYP2D6.

As with all antidepressant drugs, SSRIs have the potential to cause serotonin syndrome when administered with an MAOI. To avoid this interaction, it is recommended that there be a 2-week drug-free interval for the short acting SSRIs (e.g., citalopram, sertraline, and paroxetine) and at least 5 weeks for fluoxetine. Elderly patients may need an

even longer drug-free interval when switching from fluoxetine to an MAOI. See the next section for a discussion on drug interactions leading to serotonin syndrome.

Adverse Effects

Adverse effects associated with SSRIs as a class can be explained by their mechanism(s) of action. Common adverse effects include nausea, headache, sleep disturbances, agitation, sexual dysfunction, and tremor. Nausea typically is transient (1–2 weeks) and can be resolved by decreasing the dose or administering it with food. Because SSRIs have low affinity for histaminergic, cholinergic, and α -adrenergic receptors, they are not associated with cardiac conduction changes, orthostatic hypotension, or urinary retention. They also are less sedating and as a whole, cause less weight gain than TCAs or MAOIs. Unlike TCAs, overdoses of SSRIs are not lethal. The SSRIs are much less likely to be discontinued because of adverse effects.

Individual SSRIs are associated with distinct side effects outside the class-specific side effects. Although paroxetine has weak muscarinic inhibition compared to TCAs, it may cause constipation, slight drowsiness, and dry mouth. Paroxetine also has a tendency to cause more somnolence than other SSRIs. Because sertraline is the most serotonergic, it may cause more gastrointestinal distress, such as diarrhea or loose stools, and neurological effects, such as insomnia or activation.

The SSRIs can cause insomnia due to disturbances in rapid eye movement (REM) sleep. For patients who have difficulty tolerating drug-induced insomnia, practitioners can prescribe sedatives for short-term use (e.g., benzodiazepines, zolpidem, zaleplon, or trazodone). For patients who have difficulty falling asleep, but without middle of the night or early morning awakenings, short-acting benzodiazepines or zaleplon can be used. For patients with difficulty sleeping throughout the night, zolpidem may be a good option. It is unclear whether tolerance to SSRI-induced insomnia develops.

The incidence of sexual dysfunction associated with SSRI use is thought to be higher than that stated in the package inserts. Delay or absence of orgasm, impaired ejaculation, decreased libido, and erectile impairment have all been reported in men and women with the use of all SSRIs. Because sexual dysfunction also can be a manifestation of depression, it is important to obtain a baseline assessment of sexual function to better evaluate the problem. Although a decrease in dose may be tried, it is unclear whether SSRI-induced sexual dysfunction is dose-related. It is unclear if patients will build up a tolerance to this adverse effect. Practitioners often will need to switch to an agent with less propensity to cause sexual dysfunction (i.e., bupropion, nefazodone, or mirtazapine) or add an agent such as cyproheptadine 4 mg, bupropion 75–150 mg, or methylphenidate 5–15 mg as needed. Cyproheptadine should be used with caution because it is a 5-HT-antagonist, and may lead to the return of depressive symptoms. Enhancing blood flow with drugs, such as sildenafil or ginkgo biloba, has improved sexual dysfunction in both men and women. Amantadine and yohimbine also have been studied for treating SSRI-induced sexual dysfunction with mixed results.

Serotonin syndrome is a combination of adverse effects that can occur when excessive 5-HT is present in the periphery. Gastrointestinal symptoms, neurologic symptoms (e.g., tremor, myoclonus, hyperreflexia, and restlessness), tachycardia, hypertension, manic-like symptoms, confusion, and hyperpyrexia may occur. Concomitant administration of SSRIs with other SSRIs; MAOIs; and other serotonergic agents, such as nefazodone, buspirone, ondansetron, and sumatriptan, make up the majority of drugs that are associated with serotonin syndrome cases. Symptoms can occur as early as a few hours after coadministration, but may occur after a few days. Current recommended treatment is the discontinuation of all serotonergic agents and providing supportive therapy. If left untreated, serotonin syndrome could be lethal. Once agents are discontinued, symptoms typically resolve within 24 hours and death is quite rare.

Because of the potential for withdrawal symptoms, abrupt discontinuation of SSRIs is not recommended for the short-acting SSRIs (paroxetine, citalopram, and sertraline). Because the half-life of fluoxetine and its active metabolite, norfluoxetine, are so long, fewer cases of withdrawal symptoms have been reported. Discontinuation syndrome has been characterized by such symptoms as vivid dreams, nightmares, tremor, dizziness, crying spells, nausea, and poor concentration. Symptoms can occur as early as 1–4 days or up to 25 days after discontinuing the SSRI. It is recommended that SSRIs, including controlled-release paroxetine, be gradually tapered down over a minimal period of 7–10 days.

Venlafaxine

In 1994, the first second-generation “dual-acting” antidepressant was indicated for use in depression. Both venlafaxine and its active metabolite, O-desmethylvenlafaxine (ODV) inhibit the presynaptic reuptake of 5-HT and NE. Antidepressants with this mechanism of action are sometimes referred to as a serotonin noradrenergic reuptake inhibitors (SNRIs). Inhibition of 5-HT reuptake is about 3–5-fold higher than inhibition of noradrenaline at doses less than 200 mg/day. In addition, venlafaxine weakly inhibits the presynaptic reuptake of DA, but the inhibition is not thought to be clinically relevant. The drug has no significant affinity for α_1 -adrenergic, muscarinic, histaminic-1, benzodiazepine, or opioid receptors and does not inhibit monoamine oxidase (MAO). Both the immediate-release and extended-release formulations have demonstrated clinical efficacy but only the extended-release formulation is considered by most clinicians and experts to be a first-line agent for treating depression.

Pharmacokinetics

Venlafaxine is well absorbed and plasma protein binding is minimal. Age and gender do not influence plasma concentrations. The half-life is about 5–11 hours for venlafaxine and ODV and steady-state is reached in about 3 days. Venlafaxine undergoes substantial first-pass oxidative metabolism through the CYP2D6 enzyme system to form ODV. In general, concentrations of ODV are 2–3 times higher than that of venlafaxine, except in patients who are poor metabolizers of CYP2D6 substrates.

Dosing

Immediate-release venlafaxine can be initiated at 25–37.5 mg/day. Doses can be increased by 25–37.5 mg every 4–7 days, as tolerated, up to 150 mg/day. That dose should be maintained for 4 weeks and then symptoms should be reassessed. Most patients’ symptoms will respond to doses between 150 and 225 mg/day, with a maximum dose of 375 mg/day. Doses of the immediate-release formulation should be given 3 times/day.

Extended-release venlafaxine is initiated at 75 mg/day and titrated up to 225 mg/day in 75-mg increments. The extended-release formulation may be preferred due to its once daily dosing, as well as fewer adverse effects (e.g., gastrointestinal effects and changes in diastolic blood

pressure [BP]). Switching from the immediate release to extended release is a dose-for-dose conversion.

Drug Interactions

Venlafaxine is a weak inhibitor of CYP2D6 and has little or no inhibition of other CYP enzymes. Because of its low potential for interactions involving CYP, venlafaxine is an option for patients who are taking other drugs that rely on the CYP system for metabolism. Some reports of increased TCA and haloperidol serum concentrations have been reported, but the clinical significance of these interactions is unknown.

There are theoretical concerns regarding combined use of venlafaxine and CYP2D inhibitors. Venlafaxine is a substrate for the CYP3A (minor pathway) and CYP2D6 (major pathway) isoenzymes and is metabolized into the active metabolite, ODV. When venlafaxine is combined with an agent that inhibits CYP2D6, venlafaxine can potentially accumulate. Although the clinical significance of this potential has not yet been determined, the combination of venlafaxine and strong CYP2D6 inhibitors should be used cautiously.

As with the SSRIs, a pharmacodynamic interaction exists between venlafaxine and MAOIs, and their concurrent use is contraindicated. Combining venlafaxine with an MAOI also should be avoided because of the risk of serotonin syndrome (due to 5-HT uptake inhibition) and hypertensive crisis (due to NE uptake inhibition). Venlafaxine treatment should not be initiated until 2 weeks after discontinuation of the MAOI, and MAOI therapy should not be initiated until 2 weeks after discontinuation of venlafaxine. In addition, the risk for developing serotonin syndrome is increased when venlafaxine is coprescribed with other serotonergic agents.

Adverse Effects

Venlafaxine, although a dual mechanism antidepressant, has a side effect profile similar to the SSRIs. At lower doses (no more than 200 mg/day), venlafaxine has mostly serotonergic activity, with little noradrenergic activity. At doses above 200 mg/day, the noradrenergic effect becomes more prominent relative to serotonergic activity. Like the SSRIs, venlafaxine is typically safe and well tolerated. Common side effects include nausea, constipation, sedation, dry mouth, insomnia, dizziness, sweating, and sexual dysfunction. Using extended-release venlafaxine will decrease the patient's risk of experiencing nausea. Most side effects should dissipate within 1–2 weeks of therapy.

Significant dose-dependent increases in supine diastolic BP have been reported in 3–13% of patients taking venlafaxine at doses as low as 75 mg/day. However, the greatest risk of elevated diastolic BP is at doses greater than 300 mg/day. The incidence of elevated diastolic BP at doses greater than 300 mg/day is 3 times that of lower doses (9% vs. 3%). For about 50% of these patients, this adverse effect is transient, but for others the elevated diastolic BP is sustained. Blood pressure should be monitored regularly at each visit and dosage reduction or discontinuation of venlafaxine may be necessary if the increase in diastolic BP does not subside. Baseline blood pressure is not a useful predictor of who will have sustained diastolic BP.

Venlafaxine is not contraindicated in manageable hypertension.

Like the SSRIs, discontinuation syndrome has been reported. If a patient has been taking venlafaxine for more than 1 week, the patient should be tapered off the drug to minimize or avoid discontinuation symptoms.

Mirtazapine

The mechanism of action of mirtazapine is unique among the currently available antidepressant drugs in the United States. Mirtazapine is a selective, presynaptic α_2 -adrenergic receptor antagonist that enhances the transmission of NE by α_2 -autoreceptor blockade. α_2 -Blockade in turn stimulates α_1 -adrenoreceptors, which leads to increased 5-HT firing. Additional increases in 5-HT concentrations are due to α_2 -adrenergic heteroreceptor blockade. Mirtazapine also is a 5-HT_{2A}-, 5-HT_{2C}-, and 5-HT₃-receptor antagonist. Because of the stimulation of 5-HT release, 5-HT_{1A} neurotransmission is enhanced. The overall effect is increased NE and 5-HT_{1A} activity. Currently, the FDA has approved the labeling of mirtazapine for use in depression.

Pharmacokinetics

Mirtazapine is well absorbed after oral administration and has a half-life of 20–40 hours; steady-state concentrations are reached in 5 days. Food does not affect the rate or extent of absorption and, therefore, does not necessitate any dosage adjustments. Mirtazapine is about 85% bound to plasma proteins. It is extensively metabolized through the CYP1A2, CYP2D6, and CYP3A3/4 liver enzyme systems and is eliminated primarily in the urine. Of interest, mirtazapine has a longer mean elimination half-life in women than men (37 hours vs. 26 hours, respectively).

Dosing

Practitioners are accustomed to starting antidepressant therapy with low doses and titrating the dose up slowly to minimize side effects. Mirtazapine has a unique, counterintuitive, pharmacological profile rendering this practice of initial titration ineffective. At doses less than 15 mg, excessive sedation will occur due to antihistaminic activity. At higher doses, NE transmission increases which in turn counteracts the antihistamine-induced sedation. Patients can be initiated on 15–30 mg at bedtime. The usual maintenance dosage range is 30–45 mg/day, with a maximum of 60 mg/day. With a decrease in sedation and an increase in activation at higher doses, administration time may be switched to the morning.

Clinicians also have the option of using the orally disintegrating tablet formulation of mirtazapine, mirtazapine dissolving tablet, that dissolves under the tongue within 30 seconds. Patients can take the drug with or without water. Patients should be instructed to handle the packaging and tablet with clean, dry hands and to take the tablet immediately after removal from the blister pack. Once the dissolving tablet is removed from the pack, it cannot be stored. The tablet cannot be split in half. Mirtazapine and mirtazapine dissolving tablet are

dose-for-dose bioequivalent. The dissolving tablet may offer advantages in patients who have difficulty swallowing pills. Otherwise, the mirtazapine dissolving tablet has no clinical advantage over the regular mirtazapine (i.e., no faster onset of action).

Drug Interactions

To date, few drug-drug interactions with mirtazapine have been identified. Although mirtazapine is extensively metabolized by the liver through CYP1A2, CYP2C9, CYP2D6, and CYP3A3/4, it apparently lacks any affinity for any specific CYP enzyme to be a meaningful inhibitor. No specific CYP-related drug interactions have been reported. Therefore, mirtazapine may be a good option in patients with complicated drug regimens. Because of the sedative effects of mirtazapine, it should be used with caution in conjunction with other sedating drugs. As with the other antidepressant drugs, concurrent use of MAOIs and mirtazapine is contraindicated and a 2-week washout period is required when switching from one agent to the other.

Adverse Effects

The frequent side effects for mirtazapine are drowsiness, dry mouth, constipation, increased appetite, and weight gain. Although weight gain and increased appetite typically are undesirable side effects, patients who have a decreased appetite or a low body mass index as a result of comorbid medical condition, such as cancer or HIV infection, may benefit from mirtazapine use. Mirtazapine also has been associated with increases in total cholesterol and triglycerides, as well as some cases of glucose dysregulation. There are no significant increases in cardiovascular or sexual side effects. Mirtazapine is associated with fewer gastrointestinal effects than the SSRIs. Less common adverse effects include elevated liver enzymes, agranulocytosis, and neutropenia.

Bupropion

The mechanism of action of bupropion is poorly understood. It is thought that its antidepressant effect is primarily by inhibition of NE and possibly DA reuptake, with no direct effect on 5-HT. Along with its indication for use in depression, bupropion is unique in that it has FDA approval to be labeled for use in smoking cessation under the trade name, Zyban.

Pharmacokinetics

Bupropion is well absorbed and has high protein binding (84%). The half-life is between 8 and 24 hours for the immediate-release formulations, 21 hours for the sustained-release formulation, and 20 hours for the extended-release formulation. Bupropion is broken down into three active metabolites, with hydroxybupropion being the primary active metabolite. Half-lives of the active metabolites can reach 37 hours. Steady-state concentrations are achieved in about 8 days. Concentration of hydroxybupropion is about 10 times that of bupropion. Bioavailability of the sustained-release and

extended-release formulations is equal to that of the immediate-release bupropion.

Dosing

Bupropion doses for treating depression typically start at 200 mg/day for immediate-release bupropion and 150 mg for sustained- and extended-release bupropion; doses are titrated up to a maximum of 450 mg/day, 400 mg/day, and 450 mg/day, respectively. The immediate-release formulation requires 2–3 times/day dosing, whereas the sustained-release formulation requires 1 time/day (doses less than 200 mg/day) or 2 times/day dosing (doses of 200 mg/day or greater). The extended-release formulation allows for doses of 450 mg to be administered 1 time/day. This offers a convenience for patients who are taking doses larger than 200 mg/day. The therapeutic dose for bupropion typically is considered to be between 300 mg/day and 450 mg/day for the immediate-release formulation. Doses as low as 100–150 mg/day of the sustained-release formulation can be therapeutically sufficient, and it can be dosed up to 400 mg/day. The dosing range for the extended-release formulation is 150 mg/day to 450 mg/day.

Drug Interactions

Because of bupropion's proconvulsant effects, it should be used with caution in conjunction with drugs known to lower the seizure threshold. Although bupropion is not a serotonergic agent, its use with MAOIs is contraindicated, and a 2-week window between stopping one and initiating the other is necessary.

The metabolism of bupropion through the CYP enzyme system is not clearly understood. Bupropion is metabolized by CYP2B1, CYP2D6, and CYP3A4, so inhibitors of these systems theoretically could increase the clinical effects of bupropion, but the interaction has not been observed. Because of the uncertainty of its metabolism and its seizure potential, the use of bupropion in combination with antidepressants known to be potent CYP enzyme inhibitors is best avoided. If the agents are used together, it is recommended to use bupropion doses at the lower end of the therapeutic range.

More recently, case reports of TCA toxicity after bupropion was added to the regimen allude to CYP2D6 inhibition of clinical significance by bupropion. It is thought that the active metabolite, hydroxybupropion, may be the cause of the CYP2D6 inhibition. The use of bupropion with agents metabolized through CYP2D6 should be used with caution.

Adverse Effects

Like the other newer agents, bupropion has been equal in efficacy to TCAs, but has a more favorable safety and side effect profile. One advantage that bupropion may have over the other newer agents is that it may have a lesser propensity to induce mania, although the risk still exists. In addition, it is less likely to cause sexual side effects. Bupropion has an activating effect, which can be helpful in those patients with psychomotor retardation, but can cause agitation or insomnia in others. Other common side effects include

nausea, dizziness, tremor, vomiting, constipation, and dry mouth.

Seizure induction is a rare, but serious side effect of bupropion. The occurrence of seizures appears to be strongly associated with dose. Doses above 450 mg or single doses greater than 150 mg of immediate-release bupropion or 200 mg of sustained-release bupropion increase the propensity for a seizure 10-fold. The sustained-release and extended-release formulations cause less variations in plasma concentrations, thereby decreasing the risk of a bupropion-induced seizure. The relative risk of a seizure with bupropion is no higher than that with the TCAs. Regardless, bupropion should be avoided in patients with seizure disorder, bulimia or anorexia nervosa, or alcohol withdrawal.

The extended-release formulation is less likely to induce seizures than the immediate-release formulation; however, there are no data to support any differences in seizure risk between the sustained-release and extended-release formulations of bupropion. The only advantage that extended-release bupropion may have over sustained-release bupropion is once daily dosing for doses greater than 200 mg. All efficacy data for bupropion, despite the formulation, are based on the immediate-release formulation.

Nefazodone

Nefazodone has a dual mechanism of action. It potently antagonizes the 5-HT₂-receptor and inhibits the reuptake of 5-HT. Nefazodone also inhibits the reuptake of NE, but the clinical significance of this is unknown. Nefazodone does not have any significant effect on α_2 -adrenergic, β -adrenergic, 5-HT_{1A}-, cholinergic, histaminic, dopaminergic, or benzodiazepine receptors.

Pharmacokinetics

Nefazodone is rapidly absorbed and has high first-pass liver metabolism, making its bioavailability less than 20%. Food decreases the extent of absorption and bioavailability of nefazodone. The half-life is 2–4 hours. Steady-state concentrations of nefazodone and its active metabolite, hydroxynefazodone, are achieved within 4–5 days.

Nefazodone is metabolized extensively through CYP3A4, resulting in three primary metabolites: hydroxynefazodone, meta-chlorophenylpiperazine (mCPP), and a triazoledione metabolite. Where hydroxynefazodone has similar efficacy to nefazodone, mCPP also has some 5-HT-receptor agonist activity. Little is known about the activity of the triazoledione metabolite.

Dosing

The initial starting dose of nefazodone is 200 mg/day in two divided dosages. Higher doses of 300–600 mg/day usually are needed for antidepressant efficacy. Doses can be increased by 100–200-mg increments on a weekly basis as tolerated to a maximum of 600 mg/day based on clinical response.

Drug Interactions

Nefazodone is a potent CYP3A4 inhibitor. It inhibits the metabolism of CYP3A4 substrates. When used with substrates of CYP3A4, dosage adjustments of the substrate may be necessary. Nefazodone also has increased alprazolam serum concentrations 2-fold and triazolam serum concentrations 4-fold. Nefazodone has increased digoxin serum concentrations by 30%. Nefazodone also may increase the serum concentrations of the lipid-lowering hydroxymethyl glutaryl coenzyme A reductase inhibitors, increasing the risk for rhabdomyolysis. Of the hydroxymethyl glutaryl coenzyme A reductase inhibitors, pravastatin is primarily metabolized through CYP2C19, so it is potentially a safer option for use with nefazodone.

Because nefazodone is a serotonergic agent, precautions need to be taken similar to those taken with venlafaxine or SSRIs, when stopping or starting MAOIs due to the risk of serotonin syndrome. A washout period of 14 days is necessary when switching from nefazodone to a MAOI or vice versa.

Adverse Effects

Nefazodone, like the SSRIs, has been generally well tolerated. Common side effects include dizziness, dry mouth, nausea, blurred vision, postural hypotension, somnolence, and constipation. Nefazodone is less likely than SSRIs or venlafaxine to cause sexual dysfunction, agitation, or weight changes. There is no evidence that nefazodone causes cardiotoxicity. Several cases have been reported of suspected hepatic failure secondary to nefazodone use. The risk for life-threatening hepatic failure led to the inclusion of the “black box” warning in the package insert, as well as the discontinued marketing of nefazodone in Canada. Nefazodone should not be considered a first-line agent for treating depression and many clinicians avoid its use altogether. If nefazodone is prescribed, clinicians should monitor liver enzymes at baseline and every 6–12 months during treatment. Clinicians also should educate patients on signs and symptoms of liver failure, such as jaundice, anorexia, gastrointestinal complaints, and malaise. If a patient’s liver enzymes exceed 3 times the upper normal limit, nefazodone should be discontinued and a rechallenge should not be pursued.

Tricyclic Antidepressants

From the 1960s through the 1980s, TCAs were considered first-line agents for treating depression in the United States. Newer generation antidepressants with more favorable side effect profiles are no more efficacious than TCAs in treating moderate to severe depression. The first TCA to be introduced was imipramine in the 1950s; followed by amitriptyline, nortriptyline, desipramine, doxepin, and protriptyline in the 1960s; trimipramine in the late 1970s; amoxapine in 1980; and finally, clomipramine in 1987.

Tricyclic antidepressants were once considered the gold standard pharmacotherapy for depression. Because of safety and tolerability issues, the newer agents, such as SSRIs or venlafaxine, have replaced TCAs as first-line agents. Recent meta-analyses have shown a slight

advantage of TCAs over SSRIs in patients with higher HAM-D scores. There also are positive trials with TCAs in patients with chronic depression, depression with melancholic features, and depression with psychotic features. However, newer antidepressant agents, such as SSRIs or venlafaxine, have had equal efficacy in these subtypes of depression, and without the safety and tolerability concerns.

Tricyclic antidepressants block the reuptake of NE and 5-HT, although to varying degrees. Amoxapine, a metabolite of the antipsychotic loxapine, is unique in that it also blocks the DA receptor, giving it both antidepressant and antipsychotic activity. In addition, TCAs block acetylcholine and histamine in differing degrees, providing a biochemical explanation of the side effects associated with these drugs.

Over the years, TCAs have been used for a variety of medical purposes. Examples of use include enuresis, migraines, nausea with chemotherapy, neuralgia, peptic ulcers, and urticaria. The TCAs also are used in other psychiatric disorders, such as anxiety or panic disorders, bulimia, cataplexy or narcolepsy, attention deficit or hyperactivity disorder, and OCD.

Pharmacokinetics

Tricyclic antidepressants are well absorbed from the small intestine after oral administration. Food does not delay or affect absorption. Although well absorbed, TCA bioavailability is low because of high first-pass metabolism in the liver. The half-life of all TCAs is about 24 hours, so once daily dosing can be used. Because of the sedating properties, they typically are dosed at bedtime, with the exception of protriptyline, which is known to be more activating than the other TCAs.

The TCAs are highly lipophilic and distribute widely throughout the body. The greatest areas of concentration are in the myocardial and cerebral tissues, with less than 1% in the plasma. The TCAs are highly protein bound, specifically to the α -acid glycoproteins. Because pregnancy or disease states, such as liver disease, can cause changes in α -acid glycoprotein concentrations, TCA doses may need to be increased or decreased accordingly.

The TCAs and their active and inactive metabolites are hepatically metabolized. Biotransformation takes place through demethylation, aromatic hydroxylation and glucuronide conjugation. Tertiary TCAs (amitriptyline and imipramine) undergo demethylation through CYP1A2 and CYP3A4, whereas the tertiary metabolites and secondary TCAs (nortriptyline and desipramine) undergo aromatic hydroxylation through CYP2D6. Conjugation primarily converts the lipophilic TCAs into water-soluble agents that are more readily excreted through the kidney. Glucuronidation transforms TCAs into inactive metabolites.

Dosing

Dosing TCAs can be difficult due to large interpatient pharmacokinetic variability. Patients who are considered "slow hydroxylators" can have a 30-40-fold decrease in metabolism through CYP2D6, resulting in the need for much lower doses of the TCA to achieve therapeutic concentrations. In contrast, other patients will require

abnormally high doses and still do not achieve therapeutic serum concentrations. The TCAs should be initiated at low doses and gradually titrated up, as tolerated, to a therapeutic level. A therapeutic serum concentration usually is achieved by 2–3 weeks. Most TCAs are initiated at 25–50 mg/day and increased every 2–3 days until the maximum dose is achieved (200-250 mg/day). The TCAs usually are administered once daily at bedtime but can be given in divided dosages if the patient is having difficulty tolerating the drug.

Serum Concentrations. Of the antidepressant drug classes, TCAs have the most data regarding serum drug concentrations and effect, and the data indicate large variability among patients. Therapeutic concentrations have been critically defined only for nortriptyline, imipramine, and desipramine in the adult population; however, attempts have been made to make rational estimations of therapeutic concentrations for all TCAs. The TCA serum concentrations for the child and adolescent populations have not been well established. In addition, randomized, controlled trials have failed to show TCA efficacy in youths with depression. Reasons for this are unclear.

For measuring a clinically relevant concentration, blood samples should be drawn when the patient is at steady-state, which is 4-5 times the half-life of the TCA. It is best to draw the sample 12 hours past the last dose. Desipramine serum concentrations of 108–159 ng/L or combined desipramine and imipramine concentrations greater than 244 ng/L are thought to correlate with antidepressant response. Nortriptyline is thought to exhibit curvilinear kinetics, where serum concentrations between 50 ng/L and 150 ng/L correlate with antidepressant response.

The TCAs have a narrow therapeutic index, where significant toxicity can be seen when serum blood concentrations are 2–6 times the therapeutic level. A 1-week supply of a TCA has the potential to be fatal, if ingested all at once. This is of special concern in patients who are suicidal and at risk for intentionally taking an overdose of a drug. Lack of response, suspected patient nonadherence, toxicity, attempts to use the minimally effective dose, and potential drug interactions are all reasons for obtaining TCA serum concentrations. If patients have not had a change in their drugs that could alter TCA metabolism and they currently are stable (i.e., no or minimal depressive symptoms), ongoing monitoring of TCA serum concentrations is not necessary. Serum concentrations in children and the elderly may need to be monitored more diligently when a TCA is first initiated and titrated to a therapeutic concentration. These two patient populations are particularly susceptible to the cardiac conduction problems associated with TCA use.

Adverse Effects

Based on their pharmacological profiles, tertiary amine TCAs typically produce more pronounced anticholinergic, antihistaminic, and hypotensive effects than the secondary amine TCAs. The tertiary amine TCAs should be avoided in elderly patients because of the increased risk of falls secondary to postural hypotension and other cardiovascular effects.

Anticholinergic effects are due to blockade of the muscarinic receptors. This effect is universal among the tertiary amine TCAs and may present as an irritating minor adverse effect in young, healthy patients, but can be more serious in a physically compromised or elderly patient. Common anticholinergic effects include dry mouth, blurred vision, urinary retention, and constipation. Most anticholinergic symptoms should resolve within a few weeks. Saliva substitutes, increased fluid intake, and sugarless candy are common interventions used for the symptomatic relief of dry mouth. For severe blurred vision, oral bethanechol 10–30 mg 3 times/day or one drop of 1% pilocarpine ophthalmic drops instilled 4 times/day can be used. Constipation usually responds to an increase in fluid intake, exercise, and/or bulk laxatives. The TCAs should be avoided in men who have prostatic hypertrophy. Use of TCAs in patients with closed-angle glaucoma is contraindicated. Elderly patients who are particularly sensitive to the anticholinergic effects are at an increased risk of TCA-induced cognitive toxicity. Symptoms can range from mild confusion to complete delirium.

Tachycardia is a common cardiac effect seen with the TCAs. The increase in heart rate is usually benign, 15–20 beats/minute. Orthostatic hypotension also is common and is of particular concern in the elderly population because of the increased risk of falls and injury. Some cardiac rhythm changes that can be seen with TCA administration include prolongation of the QRS, ST depression, and flattened or inverted T waves. In general, TCAs are probably best avoided in patients with underlying cardiac disease, especially those with frank bundle branch or complete heart block. Electrocardiograms (EKGs) should be performed before starting any patient on a TCA.

Additional adverse effects seen with TCAs include weight gain, sedation, and a decrease in the seizure threshold. Sexual dysfunction also is a prevalent adverse effect. Amoxapine, whose metabolite, 7-hydroxyamoxapine, has antipsychotic properties, carries the risk of acute extrapyramidal side effects, such as pseudoparkinsonism, akathisia, and dystonias. Like older antipsychotic drugs, it also has the long-term risk of tardive dyskinesia.

Toxicity

Although TCAs are not as commonly prescribed as newer antidepressant agents, they have a higher rate of overdose-related deaths. In the United States, roughly 500,000 cases of TCA toxicity are reported each year. Fatality before reaching a health care facility occurs in about 70% of patients attempting suicide with TCAs, whereas only 2–3% of TCA overdoses that reach a health care facility result in death. Doses of 10–15 mg/kg (4–7-day supply, depending on the total daily dose) are potentially lethal in adults. In infants, doses as low as 50 mg can be lethal. Onset of symptoms can be seen as soon as 2 hours after ingestion, with life-threatening effects seen within

6 hours. Symptoms tend to progress rapidly. It is not uncommon for an overdose patient to present with no or minimal symptoms and within an hour, develop life-threatening cardiac and CNS toxicities. The CNS symptoms may range from agitation to stupor to coma. Seizures also may be seen in 10–25% of patients. Cardiac complications include hypotension, dysrhythmias, and conduction blocks. Other symptoms of toxicity include mydriasis, hyperthermia, hypoventilation, decreased bowel sounds, and dry mucous membranes. Because TCAs can be fatal in overdose, suicidal patients should receive no more than a 1-week supply of TCAs at a time and sometimes less, depending on the total daily dose the patient is receiving.

Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors have been used to treat depression over the past 40 years. As previously discussed, their antidepressant effects were discovered through the observation that an antituberculin drug, iproniazid, had mood-elevating properties. The three MAOIs, phenelzine, tranylcypromine, and isocarboxazid, became available for use in the United States during the 1970s. Although MAOIs are effective drugs for treating depression, their use has greatly declined because of the potential cardiovascular effects and the dietary restrictions. Their use typically is reserved for treatment refractory patients or patients with atypical depression.

The principal action of MAOIs is in the regulation of the monoamines NE, 5-HT, DA, and epinephrine. Monoamine oxidase is the enzyme system responsible for the breakdown of these amines and MAOIs block this process, which in turn causes an increase in their concentrations in the synapse. It originally was thought that the increase in the amines explained the therapeutic effect of the MAOIs, but more recent findings suggest that secondary adaptive functions may play an important role in the antidepressant effects.

There are two types of MAO: MAO-A and MAO-B. MAO-A is selective for the degradation of epinephrine, NE, and 5-HT, whereas MAO-B is responsible for the breakdown of benzylamine and phenylethylamine. Dopamine and tyramine are broken down by both MAO-A and MAO-B. The MAOIs currently available for use in depression are “mixed” inhibitors in that they nonselectively inhibit both type A and type B. Isocarboxazid and phenelzine are irreversible inhibitors of MAO, whereas tranylcypromine is a reversible inhibitor of the enzymes.

Pharmacokinetics

All three MAOIs are rapidly absorbed and have elimination half-lives of about 1–4 hours. However, elimination half-life is of little clinical relevance because clinical effects can be seen for up to 7–14 days after discontinuing the drug. Although peak serum concentrations are seen within 3 hours, maximum inhibition of MAO is not seen for about 14 days. All MAOIs are

Thase ME, Trivedi MH, Rush AJ. MAOIs in the contemporary treatment of depression. *Neuropsychopharmacology* 1995;12:185–219.

metabolized through the liver and are inactivated by acetylation.

Dosing

The MAOIs should be initiated at low doses and titrated up as tolerated. Tolerance to side effects typically occurs within 2–3 weeks. Phenelzine typically is initiated at 15 mg 2–3 times/day and increased by 15-mg increments up to 60 mg/day. Some patients may need doses as high as 90 mg/day to obtain sufficient MAO inhibition. Isocarboxazid is initiated at 10 mg 2 times/day and increased by 10-mg increments every 2–4 days, up to 40 mg/day by the end of the first week of treatment. Isocarboxazid can be further increased by increments of 20 mg/week, as needed or tolerated, to a maximum dose of 60 mg/day. Tranylcypromine can be initiated at 10 mg 3 times/day. The dose may be increased by 10 mg every 1–3 weeks up to the maximum of 60 mg/day. As is the case with all antidepressants, full clinical effects are not seen immediately and may take up to 4–8 weeks at therapeutic doses.

Drug Interactions

Monoamine oxidase inhibitors have numerous potential drug interactions (Table 1-3). Patients should be educated about these interactions because many involve over-the-counter cough and cold products containing sympathomimetic agents. Although the food-drug interactions (see Adverse Effects section below) are well known, MAOI-drug interactions are probably more common. Ephedrine, pseudoephedrine, and phenylephrine, in the presence of an MAOI, are examples of drugs found in over-the-counter items that can precipitate a hypertensive crisis.

Table 1-3. Drugs to Avoid with MAOIs

1. Other antidepressant drugs, including herbals
2. Buspirone
3. Meperidine
4. Dextromethorphan
5. Direct sympathomimetic agents (e.g., L-dopa, epinephrine, isoproterenol, and norepinephrine)
6. Indirect sympathomimetic agents (e.g., amphetamines, methylphenidate, phenylpropanolamine, ephedrine, pseudoephedrine, and tyramine)
7. Cocaine

MAOI = monoamine oxidase inhibitor.

Another concern is the patient in need of surgery. Narcotic analgesics, particularly meperidine, in combination with MAOIs can produce a syndrome characterized by coma, hyperpyrexia, and hypertension. This syndrome has been reported with the combined use of phenelzine and meperidine, but can be seen with other MAOIs. This syndrome is thought to be because of the serotonergic properties of meperidine and is rare with other narcotic analgesics.

Concomitant use of serotonergic agents with MAOIs is contraindicated because of risk for serotonin syndrome. A washout period of 14 days is necessary when switching

from one agent to another agent. Fluoxetine requires a 5-week washout period before initiating an MAOI because of the long half-life of its active metabolite, norfluoxetine.

Because of the potential for drug-drug interactions, all patients should carry a card or wear a medical alert bracelet, indicating that they are taking an MAOI. Patients taking an MAOI also should be instructed to consult a pharmacist or physician before taking any over-the-counter drugs. In addition, they should inform other health care providers that they are receiving an MAOI to avoid potential drug-drug interactions.

Adverse Effects

The most common adverse effects seen with MAOIs include orthostatic hypotension, dizziness, mydriasis, piloerection, edema, tremor, anorgasmia, and insomnia. In addition, tranylcypromine can cause overstimulation. Weight gain and carbohydrate cravings are of greater concern during continuation and maintenance phases of treatment. Excessive daytime sleepiness has been reported and interestingly, appears after several weeks of treatment. Daytime sedation, sexual dysfunction, and weight gain often are severe enough to lead to the discontinuation of an effective course of treatment. Rare side effects include allergies, hepatic dysfunction, and blood dyscrasias. Paresthesias related to vitamin B₆ deficiency have been reported with phenelzine.

A major safety concern with MAOIs is the risk of a hypertensive crisis. Hypertensive crisis occurs in about five per 100 patients per year taking an MAOI. Most hypertensive crises are mild, if they occur, are readily treatable with proper medical care (such as administering oral nifedipine), and may rarely result in death in vulnerable patients. The hypertensive crisis often occurs by ingesting an MAOI with food or drug products containing tyramine, which is a pressure amine (Tables 1-3 and 1-4). The risk of a hypertensive crisis from eating foods with tyramine is relatively low, with an incidence of about 6% and an incidence of 3% with the use of a special diet. Patient should be educated on the signs and symptoms of hypertensive crisis which include hypertension, occipital headache, neck stiffness, heart palpitations, nausea, and vomiting. Patients should be instructed to seek immediate medical attention if these symptoms appear.

The mechanism for the hypertensive crisis has been known for more than 30 years. At therapeutic doses, MAOIs bind to MAO in the gut and liver for periods as long as 2 weeks. This binding impedes the oxidative degradation of tyramine and related vasoactive amines. When this process is blocked, tyramine is absorbed and causes the release of NE from presynaptic sites, resulting in presser activity. The reaction usually is seen within 20–60 minutes after the ingestion of the tyramine-containing food. Patients should be educated on the dietary restrictions necessary when taking MAOIs. Currently, a selegiline (an MAOI) transdermal patch is being studied for use in depression. One advantage that the patch may provide over oral MAOIs is the decreased need for tyramine dietary restrictions. At the time this chapter was written, the selegiline transdermal patch was not available for use in the United States.

Table 1-4. Dietary Restrictions for Patients Taking MAOIs

Foods to be avoided:

- Aged, hard cheeses and strongly flavored cheeses
- Banana peel
- Fava beans
- Yeast extract
- Chianti wine and vermouth
- Beer containing high amounts of yeast
- Whiskey and liquors
- Bean curd
- Liver
- Bacon, bologna, pepperoni, or salami
- All Asian fermented fish sauces and soy sauces
- Protein extracts
- Ginseng

Foods to be consumed in moderate quantities (1/2 cup or less than 120 ml):

- Avocados (avoid overripe avocados)
- Red, white, and port wine
- Filtered beer in quantities
- Smoked, fermented, or pickled fish

Foods that may be consumed (insufficient evidence to exclude):

Anchovies	Beetroot	Chips with vinegar
Coca-Cola	Coffee	Corn, sweet
Cottage cheese	Cream cheese	Cucumbers
Egg, boiled	Figs, canned	Fish, canned
Mushrooms	Pineapple, fresh	Raisins
Salad dressings	Snails	Tea
Tomato juice	Wild game	Worcestershire sauce

MAOI = monoamine oxidase inhibitor.

Over-the-counter Dietary Supplements

One of the most popular over-the-counter dietary supplements used by patients to self-medicate depression is St. John's wort (*Hypericum perforatum*). Although not FDA-indicated for use as an antidepressant in the United States, St. John's wort is one of the most widely prescribed drugs to treat depression in Europe. In Germany, its use exceeds that of fluoxetine. Studies evaluating its use in mild to moderate depression have shown that it is superior to placebo and typically is well tolerated. However, a pharmacist should consider the risks associated with subtherapeutic treatment of depression; the most severe risk is suicide. Whether St. John's wort is equal in efficacy to currently available antidepressant drugs (e.g., imipramine and fluoxetine) requires further study. The FDA does not require the same rigorous manufacturing practices for herbal supplements as it does prescription drugs. As a result, considerable variability in potency can be seen among products.

One of the greatest concerns with St. John's wort is the risk for drug-drug interactions. St. John's wort is a weak MAOI and 5-HT-agonist. Concern has been raised about the potential risk of hyperadrenergic MAOI-reactions by mixing adrenergic preparations, such as ephedra and ephedrine-containing preparations, with St. John's wort; however, no cases of serotonin syndrome or hypertensive crisis have been linked to the use of St. John's wort. Although not a known inhibitor of any CYP isoenzymes, it has been shown to be an inducer of CYP3A4. Reports of reduced plasma concentrations and clinical efficacy of indinavir, cyclosporine, oral contraceptives, warfarin, theophylline, and digoxin have been documented with concurrent use with St. John's wort. Although most of these reports included only small samples of patients, caution with concomitant use is warranted. When St. John's wort is discontinued, plasma concentrations of the once-induced drug will increase. Pharmacists should discourage the use of St. John's wort if a patient taking other prescription drugs, unless he or she is under the supervision of a physician.

S-adenosyl-methionine is a widely available nutritional supplement sold in many nutritional/health stores. S-adenosyl-methionine is produced naturally in the CNS from L-methionine and adenosine triphosphate, and low concentrations have been correlated with depression. Its efficacy has only been evaluated in small studies, but it appears to have some benefit in mild depression, where a delay in adequate treatment would not be detrimental. It is unlikely to work in severe or treatment-resistant depression. Head-to-head trials with newer antidepressant drugs are needed to define the role of S-adenosyl-methionine for treating depression. In depression trials, the doses typically given were 200–800 mg 2 times/day.

Dehydroepiandrosterone (DHEA) is a naturally circulating adrenocorticoid in humans, but its exact physiological role currently is unknown. As well as being a precursor for testosterone and estrogen, it is thought to be involved in regulating mood and sense of well-being. Studies have shown that DHEA and its sulfated metabolite DHEA-S, decrease over a person's lifespan and also in times of chronic stress and severe illness. Two studies have reported positive results in treating depression in doses up to 90 mg/day. Although both these studies showed positive results, long-term effects of DHEA are not known. Theoretically, because it is a precursor for estrogen and testosterone, it could potentially activate hormone sensitive tumors, such as tumors of the breast, cervix, uterus, or prostate.

Because depression is a serious illness, the use of herbal supplements to self-medicate depression should be discouraged. Depression should be diagnosed and monitored by a health care professional. Although trials continue to show efficacy of these supplements, they do not entail the same rigor as prescription drug trials; therefore, the safety and efficacy of these supplements is less convincing. In addition, the production of herbal drugs is not standardized or regulated by the FDA. Until additional

Markowitz JS, DeVane CL. The emerging recognition of herb-drug interactions with a focus on St. John's wort (*Hypericum perforatum*). *Psychopharmacol Bull* 2001;35:53–64.

information about these products is available, their use should be limited.

Augmentation Agents

Switching drugs is advantageous when there is a need to keep treatment simple or patient adherence is a problem. An alternative treatment option is antidepressant augmentation. Addition of an augmenting agent may enhance the effectiveness of an antidepressant or improve response time. Augmentation strategies are an option, particularly when the antidepressant alone produces a partial response after an adequate trial. This is especially true if the patient has significant functional impairment due to depression and experienced few, if any, adverse effects from the current treatment.

There are potential advantages to augmentation, including attainment of full response without starting a new drug trial, use of lower doses of both agents to minimize side effects, treatment of comorbid disorders such as an underlying anxiety disorder, and quicker response to treatment. There may be increases in the side effect burden and drug costs, but whether those issues are of significant concern depends on the augmentation agent selected.

Lithium

Throughout the past 2 decades, case reports, open studies, and controlled studies have shown that lithium is an effective augmenting agent for treatment-refractory depression. To date, 11 double-blind, placebo-controlled trials investigating lithium as an augmenting agent have been published or presented. Although some of the earlier studies showed negative results, later studies that used more sound methodological measures resulted in more favorable outcomes.

Several mechanisms have been proposed to explain the action of lithium augmentation. In vitro studies have shown that low concentrations of lithium (0.1 mEq/L) enhance 5-HT turnover and induce a short-term effect. It also has been hypothesized that lithium's ability to increase presynaptic transmission of 5-HT would potentiate TCA-induced postsynaptic 5-HT supersensitivity, resulting in enhanced 5-HT transmission. There is a possibility that lithium potentiates or has a synergistic effect that involves other monoamines, such as NE or acetylcholine.

As a general rule, lithium is dosed at a minimum of 600–900 mg/day, with a recommended plasma concentration above 0.4 mEq/L. Reports in the literature also are mixed concerning time to treatment response. Some cases have shown a rapid response in less than 48 hours, whereas others responded after a period of more than 2 weeks. Patients should use lithium augmentation for a minimum of 2 weeks, and it typically is unnecessary for trials to extend beyond 6 weeks. However, some patients who are classified as “slow responders” by history may need a longer trial before lithium is determined to be ineffective. Once a response is achieved, the duration of lithium treatment is the subject of debate. It has been suggested that

lithium augmentation be continued for a minimum of 6 months after remission of depressive symptoms.

Although much of the literature supports the use of lithium as an effective augmentation agent in depression, its use has declined. One reason may be that its use has been best studied with MAOIs and TCAs, which are no longer considered first-line antidepressant agents by most practitioners. Literature supporting its use with SSRIs is expanding, but information on lithium augmentation of other newer antidepressant drugs is limited. Another explanation for its declining use may be the risk of toxicity associated with lithium and the need to monitor serum concentrations and thyroid and renal functioning. Lithium also is plagued with many adverse effects (e.g., weight gain, tremor, and nausea) and often is not well tolerated by patients. There also is a theoretical risk of developing serotonin syndrome when lithium is combined with other serotonergic agents. Because of these factors, lithium often is not perceived by patients or practitioners as the augmenting agent of choice despite data supporting its use.

Thyroid Hormone

Both hyper- and hypothyroidism are associated with psychiatric symptomatology. In particular, hypothyroidism is associated with depression-like symptoms that will commonly resolve after normalization of the thyroid function. Although most depressed patients are euthyroid, the use of thyroid supplementation to treat depression has been investigated.

Subclinical hypothyroidism (thyroid-stimulating hormone concentrations between 5 mU/L and 10 mU/L, in the presence of normal thyroxine [T_4] concentrations) has been associated with depression, especially in elderly women. Estimates of subclinical hypothyroidism in postmenopausal women are as high as 18%. Routine monitoring of thyroid functioning in all elderly patients is advised.

Triiodothyronine (T_3) was first tested empirically as a treatment for psychiatric illnesses in 1958. This work led to the use of low doses of T_3 to accelerate the antidepressant effects of TCAs. One of the first and most common explanations for the mechanism of action is that thyroid hormone interacts with various neurotransmitters, NE in particular. Treatment with T_3 may directly affect the thyroid axis or reduce T_4 serum concentrations. To date, the exact mechanism has yet to be explicated.

The T_3 is the preferred agent over T_4 because a controlled study found T_3 to be more effective. In addition, the study found that recurrence of depression was inversely related to T_3 but not T_4 . In patients with subclinical hypothyroidism and depression, 50–100 mcg/day of levothyroxine is an accepted intervention. The usual T_3 dose is 25–50 mcg/day. Studies have shown that increased T_4 concentrations may lead to an increased risk for osteoporosis; therefore, a patient's thyroid-stimulating hormone concentration should be monitored to ensure that the patient is not being overtreated with T_4 .

Marangell LB. Augmentation of standard depression therapy. Clin Ther 2000;22(suppl A):A25–38; discussion A39–41.

Although the duration needed to consider treatment a success or failure has not been definitely determined, a trial of 2–3 weeks usually is accepted as an adequate time period. As with lithium, it is unclear how long thyroid augmentation should be continued. Treatment commonly is continued for the duration of antidepressant therapy; however, there is no literature available that provides empirical support for this practice. Also, as with lithium, thyroid supplementation is not common in clinical practice, possibly because of limited data supporting its use with newer antidepressants, as well as thyroid monitoring requirements.

Bupirone

Bupirone is an azaspirone that currently is marketed and used as an anxiolytic agent for generalized anxiety disorder. It is believed to exert its anxiolytic effect through postsynaptic 5-HT_{1A}-receptor partial agonism. Some early evidence suggested that bupirone also exerts mild antidepressant effects through potentiation of 5-HT transmission. In these studies, bupirone monotherapy was superior to placebo for treating depression. This led to several studies looking at bupirone as an augmenting agent. Results from these studies have been mixed.

When using bupirone as an augmenting agent, doses may range from 20 mg/day to 50 mg/day, with the most common dose being 10 mg 3 times/day. If a response occurs, it usually occurs within 3 weeks. Bupirone has a distinct advantage in that it causes very mild side effects and has minimal drug interactions. It also has independent effects on anxiety and may, therefore, be the treatment of choice in patients with a comorbid anxiety disorder. Currently, bupirone augmentation has been studied only with serotonergic agents (specifically SSRIs) with inconsistent results, and it is unclear if using it as an augmenting agent with noradrenergic and/or dopaminergic antidepressants would produce similar results. Additional controlled studies should be conducted before its efficacy and potential clinical use as an augmenting agent can be fully evaluated.

Pindolol

Pindolol is a β -blocker with 5-HT_{1A}-receptor antagonistic properties. Currently, it is thought that the delay in antidepressant effects (specifically with SSRIs) is due to the inhibitory function of the presynaptic 5-HT_{1A}-receptors. As previously discussed, SSRIs cause an initial rise in extracellular 5-HT, which feeds back to the 5-HT_{1A}-receptors. This action results in an initial decrease of 5-HT firing, synthesis, and release, which may explain the 2–3-week delay in SSRI action. The rationale for using pindolol is to block the initial autoinhibitory process and theoretically cause an earlier response to antidepressant therapy and augment antidepressant effects. Studies evaluating the efficacy of pindolol as an augmenting agent have produced mixed results.

At doses of 7.5 mg/day, pindolol typically is well tolerated. However, increased irritability, insomnia, and anxiety can be seen. Pindolol should be used with caution in patients with severe allergies, asthma, cardiac conduction problems, and diabetes due to its blockade of β_1 - and

β_2 -adrenoreceptors. If there is no response after 2 weeks, it is recommended that pindolol augmentation be discontinued, as response is unlikely to occur with continued treatment. If response is seen, treatment should be continued until remission of symptoms has been achieved, although, with severely resistant cases, continuation of pindolol with the antidepressant should be considered. Because cases of rapid deterioration have been reported when pindolol was suddenly stopped due to adverse effects, pindolol can be tapered off over a period of 2–4 weeks, decreasing by 2.5 mg every 1–2 weeks.

The pindolol dose that typically has been studied has been 7.5 mg/day (2.5 mg 3 times/day). Recent positron emission tomography imaging studies have shown that pindolol at doses of 7.5 mg/day is likely a suboptimal dose to enhance 5-HT transmission. It has been hypothesized that doses of 15–25 mg/day would be necessary to block 50% of the 5-HT_{1A}-receptors. Pindolol then becomes less appealing given the cardiac effects that can occur at these doses. More controlled trials are needed before pindolol can be conclusively ruled in or out as an effective augmentation agent.

Atypical Antipsychotic Drugs

Atypical antipsychotic drugs have been studied primarily for use in psychotic depression, schizoaffective disorder and bipolar disorder, and depressive symptoms in schizophrenic patients. Affective symptom improvement in these disorders has prompted some investigators to look at atypical antipsychotic drugs as adjunctive agents in major depression. Risperidone and olanzapine augmentation of SSRIs have shown positive results in treating MDD in patients whose symptoms have not responded to SSRIs. One case report described the augmentation of venlafaxine with olanzapine 5 mg/day in a patient who experienced improvement in symptoms within 2–3 days. Suggested doses to augment antidepressants are 0.5–2 mg/day of risperidone and 5–20 mg/day of olanzapine. Results usually were seen within 1 week; therefore, 2–3 weeks should be a sufficient trial period. Risperidone and olanzapine work effectively to treat insomnia, anxiety, and agitation associated with depression. Few or no data exist for using quetiapine, ziprasidone, or aripiprazole as an adjunctive agent in major depression. Drawbacks for using atypical antipsychotic drugs include increased sedation, potential for weight gain, and higher cost. There also is the concern about acute and chronic extrapyramidal symptoms, even though this risk is thought to be less with atypical antipsychotic drugs than typical antipsychotics drugs, such as haloperidol.

Psychostimulant Drugs

Psychostimulant drugs have a long history of use in depression. Clinically, dextroamphetamine, methylphenidate, modafinil, and pemoline have all been used as augmenting agents. Although the addition of stimulants to MAOIs, TCAs, SSRIs, and even venlafaxine is becoming more popular in clinical practice, there are no controlled trials evaluating their effectiveness as augmenting agents.

The usual doses for methylphenidate and dextroamphetamine are 10 mg 3 times/day and 5 mg 3 times/day, respectively. Initial doses of the stimulant should be lower when using in conjunction with MAOIs and titrated up to therapeutic response. Common side effects are increased irritability, increased anxiety or agitation, paranoid thinking, and mania.

Psychostimulants may best be used in anergic patients. They may not be the best choice for augmentation in patients suffering from insomnia or anxiety, agitation, or substance abuse problems.

Modafinil is a stimulant used mostly for narcolepsy. Its exact mechanism of action is unclear. Unlike the amphetamines, it is highly selective for the CNS, has little effect on DA activity in the striatum, and appears to have a lower potential for abuse. Doses used usually are between 100 mg/day and 200 mg/day.

Estrogen

Although it is well established that estrogen affects mood, its role for treating MDD is unclear. One study compared the use of 100 mcg transdermal 17 β -estradiol and placebo for treating depression in perimenopausal women. Results revealed remission of symptoms in 68% of the estrogen group compared to 20% in the placebo group. Some critics argue that estrogen is simply alleviating menopausal symptoms, but there are reports showing estrogen to be effective even in patients without vasomotor symptoms. In light of recent reports of its increased risk of cardiac events, estrogen may not be as viable an option in perimenopausal woman as once thought.

Combination Pharmacotherapy

Current literature often uses the terms combination therapy and augmentation therapy interchangeably; however, a clear distinction exists between the two. Augmentation enhances the effectiveness of an ongoing antidepressant trial, whereas combined treatment involves the use of separate antidepressant agents to address different depressive symptom etiologies. Another distinction is that, although an augmenting agent is added to the current trial, two antidepressant drugs are prescribed at full therapeutic doses or to achieve therapeutic serum concentrations in combination treatments. In general, combination therapy involves using two or more drugs from different groups or classes of antidepressant drugs to produce an additive effect. Disadvantages to combined treatment include the potential for significant drug interactions, increased risk of adverse-effects, possible nonadherence, and increased cost. Most combination strategies used by practitioners have little evidence to support their use and are based on theory or case reports. Few double-blind studies of combination therapy have been completed. Most combination treatments in the literature have been reported with the use of SSRIs plus another antidepressant drug. The second antidepressant drug often is initiated to alleviate adverse effects (e.g., sexual dysfunction) as well as to improve mood. More research is needed on the use of combination therapy. Combination therapy should be reserved for patients whose symptoms are deemed treatment resistant. This particular

patient population is probably best treated by clinicians whose specialty is treatment-resistant depression.

Current data suggest that improvement with combination therapy may not be seen for 4–6 weeks. The minimum duration of combined therapy in patients whose symptoms have responded to treatment is unclear. In general, maintenance drugs should be continued for 6–9 months after symptom remission before gradually discontinuing one of the drugs.

Combinations of two SSRIs are theoretically feasible; however, no clinical evidence exists to support this combination. Although recent data suggest that paroxetine and fluoxetine are more potent NE uptake inhibitors, and sertraline is a more potent DA uptake inhibitor, than the other SSRIs, the clinical significance is likely to be of little relevance. One of the primary disadvantages in combining SSRIs is the risk of patients developing serotonin syndrome or having serotonergic side effects due to the pharmacodynamic drug interaction. Therefore, this type of combination is not recommended.

There is evidence for improvement in response after combination treatment with an SSRI and TCA. In a study of patients whose symptoms were unresponsive at the end of an 8-week trial of fluoxetine, some response was seen when patients were treated with a combination of desipramine and fluoxetine. However, TCA serum concentrations will increase because the SSRI interferes with its clearance, increasing the risk of cardiac toxicity. To manage treatment, it is suggested that clinicians use low doses of the TCA (25–75 mg/day) and monitor TCA serum concentrations. The biggest concern for a pharmacokinetic interaction between TCAs and SSRIs is the use of CYP1A2 (fluvoxamine) and CYP2D6 (paroxetine and fluoxetine) inhibitors in combination with the TCAs imipramine, clomipramine, and amitriptyline. Although sertraline, citalopram, and escitalopram are considered less potent inhibitors of the CYP2D6 enzyme system than paroxetine and fluoxetine, higher doses of these drugs increase the potential for a drug-drug interaction. The TCAs and SSRIs can be used in combination in patients with treatment-resistant depression, but should be done so with caution.

Lower doses of an antidepressant such as trazodone (50–150 mg) may be combined with the usual dose of the primary antidepressant for sleep disturbance. Trazodone doses in this range exert little, if any, antidepressant activity. Regardless, it is important to evaluate for possible drug interactions as well as a possible increase in side effects when combining drugs. Trazodone is cleaved by CYP3A, producing mCPP, which is an active metabolite with a pharmacological profile virtually the opposite of trazodone; mCPP is cleared by CYP2D6. Thus, coadministration of trazodone with fluvoxamine can slow the clearance of trazodone, leading to daytime drowsiness, whereas coadministration of fluoxetine or paroxetine with trazodone can lead to an accumulation of mCPP in the serum concentrations, leading to anxiety and agitation. Trazodone often is used as a sleep agent in conjunction with SSRIs and other antidepressants without complications.

Bupropion frequently is combined with SSRIs in clinical practice because of the different pharmacological effects of

the two agents, but there are few data to support this use. Sustained-release bupropion 100–150 mg/day often is used to help treat SSRI-induced sexual dysfunction. Clinical lore suggests bupropion may be helpful as an add-on in patients whose apathetic symptoms do not respond adequately to treatment with an SSRI. A disadvantage in using bupropion is its dose-dependent potential for inducing seizures. Currently, the metabolism of bupropion through the CYP enzymes is not clearly understood. Because of the uncertainty of its metabolism and its seizure potential, bupropion is best avoided in combination with antidepressants known to be potent CYP2D6 enzyme inhibitors or used in doses at the lower end of the therapeutic spectrum.

Mirtazapine is a dual action antidepressant that increases both serotonergic and noradrenergic activity by blocking α_2 -adrenergic autoreceptors and heteroreceptors and serotonergic 5-HT₂- and 5-HT₃-receptors. Combining mirtazapine (15–30 mg at bedtime) with a SSRI has been reported to improve depressive symptoms that have not responded. There also is evidence of a significantly higher response rate with combination therapy than monotherapy of either mirtazapine or an SSRI. In an open-label study, there was a 55% response rate at week 4 when mirtazapine (15–30 mg/day) was combined with another antidepressant after a failed trial of monotherapy. Unfortunately, at these doses in particular, mirtazapine has the potential to cause weight gain and sedation. Mirtazapine has a lower potential to cause sexual dysfunction than SSRIs, so practitioners often will switch to mirtazapine if the patient experiences this adverse effect with an SSRI. However, there is little to no evidence to support the combined use of these two agents to relieve the patient of SSRI-induced sexual dysfunction. Few data exist for the combination of mirtazapine and other antidepressant drugs at this time; therefore, this combination should be reserved for patients whose symptoms are deemed treatment-resistant.

There is no strong evidence in the literature for combining nefazodone and an SSRI, but nefazodone has a lower propensity to cause sexual dysfunction. Similar to mirtazapine, there is no evidence indicating that this combination would alleviate SSRI-induced sexual dysfunction. With this combination (specifically nefazodone plus paroxetine or fluoxetine), patients may experience increased irritability and anxiety due to an accumulation of mCPP, the active metabolite of nefazodone. This situation is created because paroxetine and fluoxetine inhibit the metabolism of mCPP through the CYP2D6 enzyme. Because of the increased propensity for nefazodone to cause drug-induced hepatotoxicity, combinations with nefazodone are not recommended at this time.

There are anecdotal reports of using 75–300 mg/day of venlafaxine with patients whose symptoms have not responded to an SSRI, but no clear evidence that combination treatment with venlafaxine and an SSRI is efficacious. Combined use of venlafaxine and other antidepressant drugs also may lead to serotonin syndrome, marked elevation of BP, or severe anticholinergic side effects. Combinations with SSRIs and venlafaxine cannot be recommended at this time.

As a general rule, clinicians should avoid combining any antidepressant agent with an MAOI, because this combination may produce potentially fatal serotonin syndrome and/or a hypertensive crisis. Patients who are taking MAOI combination therapy should be under the supervision of a psychiatrist who specializes in treatment-resistant depression.

Non-pharmacological Therapies

Electroconvulsive Therapy

Electroconvulsive therapy (ECT) was introduced in the mid-1930s and used extensively through the 1950s. At that time, ECT was the primary treatment available to hospitalized patients. As effective pharmacotherapy interventions became available, the use of ECT declined. Although it continued to be used to treat depression in the 1960s, there was a social and political movement to discourage ECT treatment because of perceived misuse. By 1980, the use of ECT declined to only 0.3% in patients hospitalized for mood disorders. Today, ECT is primarily used in private facilities because of funding issues in many state facilities.

When ECT is administered, patients are first given a short-acting barbiturate to put them to sleep and then succinylcholine to paralyze the muscles to prevent muscle contractions during the procedure. An electrode is placed above the temple of the nondominant side of the brain and a second in the middle of the forehead (unilateral ECT) or one electrode is placed above each temple (bilateral ECT). A small current passes through the brain, activates it, and produces a seizure. Because patients are anesthetized and the muscles are relaxed by the succinylcholine, they feel no distress. An EEG monitors the seizure activity and an EKG monitors the heart rhythm. The current is applied for 1 second or less. The duration of the seizure is 30 seconds to sometimes longer than a minute. The patient typically wakes up 10–15 minutes after the seizure. On awakening, a patient may experience a brief period of confusion, headache, or muscle stiffness, but these symptoms typically subside in 20–60 minutes.

Effective and relatively safe, ECT should be considered when there is high suicide risk, a rapid physical decline, drug nonresponse or intolerability, or a history of response to ECT. Electroconvulsive therapy has been effective in treating severe depression, psychosis, catatonia, neuroleptic malignant syndrome, and parkinsonism. There are no restrictions in the use of ECT with regard to age or systemic conditions. The major limitations to the use of ECT include a high relapse rate and possible impairments in memory and neurocognitive functioning. Some studies suggest that bilateral ECT, compared to unilateral ECT, is associated with an increase in short-term memory difficulties. However, bilateral ECT appears to be more efficacious than unilateral ECT.

Although the presence of antidepressant drugs may not affect the duration of seizures, the response rate to ECT appears to be influenced by the quality of prior drug trials. An 86% response rate to ECT has been seen in patients who did not receive an adequate drug trial; however, if a patient received adequate prior antidepressant drug treatment, response to ECT was about 50%. This response rate was

similar to the rate that is expected when a patient switches from one drug class to another. Consequently, ECT is most effective when used as first-line treatment.

Repetitive Transcranial Magnetic Stimulation

Similar to ECT in neurophysiological, neurochemical, and behavioral effects, repetitive transcranial magnetic stimulation (rTMS) is another option for treating depression. First introduced in 1985, rTMS is a noninvasive procedure for stimulation of the cerebral cortex through the skull. A small, figure-8 shaped insulated coil is placed on the scalp, and a rapidly alternating electrical current is transmitted through the wire. The resultant magnetic pulse depolarizes neurons in a localized area of the brain, inducing ionic flow. Multiple trains of magnetic pulses at various frequencies (1–20) are applied for several seconds. The use of rTMS has several advantages compared with ECT. The patient may receive treatment as an outpatient and continue normal activities; there is no significant cognitive disruption; and because there is no need to induce seizure, anesthesia is not necessary. However, head-to-head trials between ECT and rTMS have shown ECT to be a superior intervention. Most studies have not evaluated the long-term benefits or risks of using rTMS. Recent meta-analyses have concluded that studies fail to prove that rTMS is a valid intervention for treating depression. Because a well-designed trial has not been conducted, the role of rTMS is yet not clear. After 2 weeks of rTMS, studies have failed to show sustained response once treatment was discontinued. Studies with larger sample sizes and more rigorous methodology are needed to evaluate the clinical relevance of rTMS for treating depression.

Phototherapy

Phototherapy, or light therapy, involves exposure to light (2000–10,000 lux) for 30–120 minutes in the morning. More than 20 studies have shown efficacy of phototherapy in the treatment of seasonal affective disorder. The light source can be administered through a phototherapy box, a light that the patient sits next to, or a light worn on a hat or visor. Administering the light gradually over 30–90 minutes before the patient awakens (dawn-simulating alarm clock) is an additional option. It is unclear which patients are more likely to respond to light therapy. Research has shown that patients whose symptoms are worse in the morning and those who eat a lot of sweets late in the day may respond better. On the other hand, patients who report an incomplete remission during the summer tend to have lower response rates.

Patient Counseling

One of the most important interventions by a clinician when treating a patient for depression is to educate patients about the disease state, the drug being prescribed, and expectations during treatment. Patients often are unaware that the feelings that they have been experiencing are signs and symptoms of depression. Educating patients about the symptoms of depression help them understand the disorder better, as well as help them monitor their own progress in

treatment. It also can help them identify symptoms in earlier stages of a future depressive episode.

Before initiating a drug, the clinician should discuss possible treatment options and include the patient in the decision-making process. This includes discussing possible bothersome or serious adverse effects, dosing schedules, and additional benefits the patient may experience from the drug. Patients are more likely to adhere to their treatment if they know what the positive as well as negative effects of a drug are. Clinicians should encourage patients to report side effects at every visit and should monitor for side effects at each visit. This is especially important with adverse effects such as sexual dysfunction because continued adverse effects may lead to patient nonadherence with their antidepressant drug.

Furthermore, it is important to educate patients about the onset of response and duration of antidepressant treatment. Patients should understand that antidepressant effects will not be seen immediately and the full effects can take 4–8 weeks. Patients should be aware that stopping a drug prematurely puts them at a higher risk for relapse or recurrence of a depressive episode. Patients should expect to take a drug for no less than 6–9 months after their symptoms have remitted. Patients with recurring depressive episodes may need to take maintenance drugs for several years or longer. Patients also need to understand that abruptly stopping an antidepressant drug may lead to unpleasant discontinuation symptoms. Although antidepressants are not addictive drugs, tapering off the drugs is the best way to avoid withdrawal symptoms.

Pharmacists can play an extensive role in educating patients about antidepressant drugs, explaining the need for drugs, expectations with treatment, and potential adverse effects. Pharmacists also can play an important role in conducting interim visits (i.e., between visits with the physician) to monitor patient symptom response to the drug, provide continued education to the patient, and address any concerns the patient may have at the time of the visit. Studies have shown that pharmacist involvement in the treatment of patients with depression has improved patient outcomes in terms of decreasing depressive symptoms, promoting better adherence with drugs, decreasing service use, and increasing patient satisfaction with care.

Clinicians should discuss financial issues with patients and their family. Treatment decisions are sometimes made based on economics rather than optimal care. However, for patients in need, a second-line drug that is affordable is clearly better than no drug at all. Using generic formulations of newer drugs, if available, also is a potential way to save patients money. Many antidepressant drugs (e.g., escitalopram, sertraline, and paroxetine) are available as scored tablets and can be halved. For example, for the patient requiring 50 mg/day of sertraline, the 100-mg tablet could be cut in half, and the expense to the patient would be reduced. (See Table 1-2 for generic availability and scored tablets.) Pharmacists are in a position to inform physicians and patients of such cost-saving issues.

Another cost-saving option is the pharmaceutical industry patient assistance programs that allows patients to obtain prescription drugs for free or at a reduced cost. Most manufacturers of newer antidepressant agents offer patient

assistant programs. Each program has its own qualification process and clinicians should contact individual manufacturers for detailed information concerning the application process. It also is important that clinicians be aware of resources within their own community. Many communities have clinics where services and drugs are provided for free or on a sliding scale basis; these resources are valuable for patients who are in need. It is helpful to keep an updated list of these services to distribute to patients.

Bipolar Disorder

Epidemiology

Bipolar disorder, also known as manic-depressive disorder, affects about 1% of the population. There appears to be equal distribution between men and women. However, men are more likely to experience a manic episode as their initial presentation, whereas women are more likely to initially suffer from a depressive episode. There is a strong genetic influence to this disorder, as demonstrated in twin and adoption studies. First-degree relatives of individuals with bipolar disorder have an increased risk ranging from 4% to 24% of suffering from bipolar disorder.

Economic Burden

The total costs of bipolar disorder have been estimated to exceed \$45 billion per year. This staggering figure includes both direct costs, such as hospitalization and professional service fees, and indirect costs (e.g., lost productivity of wage earners, family members, and those who commit suicide). Clearly, the impact of nonadherence with pharmacotherapy or psychotherapy significantly increases the costs associated with treatment.

Pathophysiology

Several theories have been discussed regarding the pathophysiology of bipolar disorder. These theories have included changes in neurotransmitters, neuromodulators, and second messenger systems.

The most prominent theory centers around changes in monoamine neurotransmitters within the CNS. This theory proposes that mania may be related to excessive NE and DA, and depression may be related to relative deficits in NE, 5-HT, and DA. The permissive theory proposes that in both mania and depressive episodes, there is an underlying deficiency in 5-HT, with excessive NE activity resulting in mania or decreased NE activity resulting in depression.

Neurotransmitter postsynaptic receptor binding is associated with a cascade of second messenger (e.g., cyclic adenosine monophosphate [cAMP] and phosphoinositide) intracellular events. Cyclic adenosine monophosphate is involved in neuronal excitability. Furthermore, adenylyl cyclase and phospholipase C are involved in G protein-mediated signal transduction. These proteins regulate adenylyl cyclase and phosphoinositide activity,

control cation (e.g., sodium and potassium) changes and activate phospholipase enzymes. Studies have demonstrated that untreated patients with bipolar disorder exhibit hyperactive G proteins. Lithium has normalized G proteins which are, in part, responsible for regulating appetite, wakefulness, and mood. Protein kinase C, an enzyme used in cAMP signaling within the CNS, may help regulate pre- and postsynaptic neurotransmission. Lithium and valproic acid have down-regulated protein kinase C activity.

Diagnostic Criteria

Bipolar disorder consists of recurring episodes of mania or hypomania and major depression.

In bipolar disorder, each mood episode is classified as either a manic, mixed, hypomanic, or depressive. According to the DSM-IV-TR diagnostic criteria, the key symptoms of a manic episode are the presence of an elevated, expansive, or irritable mood lasting for at least 1 week. In addition, the patient must exhibit at least three of the following symptoms (four if mood is only irritable):

- Flight of ideas or subjective racing thoughts
- Decreased need for sleep
- Inflated self-esteem or grandiosity
- More talkative than usual or pressured speech
- Distractibility
- Increase in goal-directed activity or psychomotor agitation
- Excessive involvement in pleasurable activities with a high potential for painful consequences

Furthermore, the mood disturbance is sufficient enough to cause marked impairment in occupational or social functioning or relationships with others. In the case of a depressed episode, the symptoms must be prominent enough to meet full diagnostic criteria for major depression (see discussion in Depression section) for a 2-week period. A mixed episode occurs when the patient exhibits a rapidly alternating mood and full manic and major depressive syndromes occurring together for at least a 1-week period. Hypomania is characterized by the presence of some manic symptoms lasting for at least 4 days, but the number of symptoms is not sufficient to meet criteria for a manic episode.

Bipolar Spectrum

The spectrum of bipolar disorder can be divided into the following subtypes: bipolar I, bipolar II, and cyclothymia. Bipolar I disorder is defined as the presence of one or more manic or mixed episodes plus one or more episodes of major depression. Bipolar II disorder includes a history of one or more episodes of major depression and one or more episodes of hypomania, but never presenting with a full manic or mixed episode. Cyclothymia is a disorder of reoccurring hypomanic and depressive episodes. However, the severity, duration, and number of episodes are insufficient to meet the DSM-IV-TR criteria for major depressive and manic episodes.

McGuffin P, Rijsdijk F, Andrew M, Sham P, Katz R, Cardno A. The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. *Arch Gen Psychiatry* 2003;60:497–502.

Episode Qualifiers

Each episode may be further described with many specifiers, such as describing the severity of the episode as mild to severe, noting the presence of psychotic or catatonic features or a postpartum onset. Furthermore, the following specifiers may be used to describe the pattern of episodes: with or without full interepisode recovery, rapid cycler, or with seasonal patterns. The rapid cycling subtype is defined as patients experiencing four or more episodes of major depression or mania within a 12-month period.

Course of Illness

The age of onset of bipolar disorder typically is in the late teens or early 20s. However, a few patients will experience their initial episode in childhood or after the age of 50. The duration of each episode depends on the severity of illness and whether treatment is being received. An untreated manic episode may last up to 12 months.

More than 90% of those suffering from one episode of mania will go on to experience future episodes. Often, the initial presentation will occur as one or more episodes of major depression followed by a manic phase. In those cases, the diagnosis will shift from major depression to bipolar disorder. Clarification of the diagnosis is extremely important, as the pharmacological management for a depressive episode of bipolar disorder is different from the management of an MDE. Details of these differences are presented in the Treatment section of the Major Depression and Bipolar sections. Most manic episodes occur immediately before or after an MDE. Psychotic symptoms may occur with any type of episode and may not be present until days or weeks into the episode. The number of total lifetime episodes will vary widely among individuals. Some patients may have an episode once every few years, whereas other people may have numerous episodes within a given year. The consequences of bipolar disorder are extremely debilitating, often significantly affecting a patient's social and occupational functioning. Fortunately, the time interval between episodes increases with age. Morbidity associated with bipolar disorder is linked mainly to an increased number of episodes. There is some evidence that increasing affective episodes may be associated with frank anatomical changes in the brain and the development of treatment resistance. To minimize treatment resistance and decrease morbidity, maintenance treatment is recommended for most patients after two or three episodes. Most individuals return to a normal level of functioning between intervals; however, about 25% of patients experience difficulty functioning, some depressive symptoms, and/or mood lability on a chronic basis.

Assessments

Like depression, there are no laboratory tests that are diagnostic for bipolar disorder. The clinician's observation, behavioral and diagnostic rating scale data, and psychiatric history are all used to confirm a diagnosis of bipolar

disorder. Thyroid function tests often are obtained to rule out hyperthyroidism as the cause of manic-like symptoms.

As in depression, the CGI frequently is used to assess the global functioning of a patient with bipolar disorder. See the discussion of the CGI scale in the Depression Assessment section.

Young Mania Rating Scale

The Young Mania Rating Scale (YMRS) is an 11-item scale designed to assess the severity of manic symptoms in patients with bipolar disorder. These items are assessed by the patient's self-report and clinician observation. The YMRS is the most frequently used mania scale in clinical trials but rarely used in clinical practice. In addition to core manic symptoms, psychotic symptoms, such as paranoia and auditory hallucinations, are rated on this scale. Depressive symptoms are not assessed by the YMRS. The maximal YMRS score is 60. Scores higher than 25 are indicative of severe mania; moderate manic symptoms are associated with scores between 19 and 24, whereas scores less than 11 are associated with euthymia. This scale takes about 15–20 minutes for the clinician to complete. However, in patients with significant flight of ideas and/or distractibility, the assessment may take 30–45 minutes to complete.

Goals of Treatment

The primary goals of treatment for patients with bipolar disorder are to resolve the acute symptomatology and to prevent the occurrence of future manic or depressive episodes. In addition, improving social and occupational functioning, relationships with family and friends, and patient quality of life also should be included as treatment goals. Finally, the goals of pharmacotherapy should include minimizing adverse events, maximizing response to pharmacotherapy, and promoting treatment adherence. Patients should be asked what their goals for therapy include. What may seem important to the clinician often is less important to patients or vice versa.

Although individual and group psychotherapy is beneficial for the patient with bipolar disorder, pharmacotherapy remains the cornerstone of treatment. Due to the chronic and reoccurring nature of this disorder, pharmacotherapy is used to abort an acute manic or depressive episode, as well as to maintain euthymia and prevent the recurrence of subsequent episodes. In general, discussion of pharmacotherapy is divided into the acute and maintenance phase. Table 1-5 lists treatment options according to bipolar disorder subset.

Pharmacotherapy Treatment Response

Initial pharmacotherapy of a manic episode often includes a mood stabilizer and adjunctive anxiolytics with or without a short-term antipsychotic drug. In general, mood stabilizers require 7–10 days before initial response is seen. However, in clinical practice, where concomitant

American Psychiatry Association. Practice guidelines for the treatment of patients with bipolar disorder (revision). *Am J Psychiatry* 2002;159(4 suppl):1–50.

Table 1-5. Bipolar Disorder Pharmacotherapy Options by Subset

Classic Mania
Lithium
Valproate
Carbamazepine
Oxcarbazepine
Atypical antipsychotics
Rapid Cycling
Valproate
Lamotrigine
Atypical antipsychotics
Depression
Lamotrigine
Lithium
Bipolar II
Lamotrigine
Lithium
Maintenance
Lithium
Lamotrigine
Atypical antipsychotics

benzodiazepines or antipsychotic drugs are used early in treatment for behavioral control, the onset of response may be seen within 3–5 days. Thus, benzodiazepines with or without antipsychotic drugs often are used for immediate relief of symptoms, such as decreased need for sleep and psychomotor agitation. Antipsychotic drugs are less frequently used in conjunction with mood stabilizers for behavioral control or prominent psychosis during this early treatment period. Optimal benefit from a mood stabilizer may not be reached until 2–3 weeks into treatment. In determining if optimal response has been achieved, clinicians should take into account the patient’s ability to function in daily activities and the quality of their relationships with friends and family. In clinical trials, responders typically exhibit a 50% or greater reduction in their YMRS scores. However, patients entering a trial with severe symptomatology may meet response criteria and still have considerable symptoms. Rarely do clinical trials take into account a patient’s functionality when determining a primary measure of response. Additional research issues are discussed in the Affective Research section.

Treatment of Acute Mania

Acute manic episodes are treated primarily with mood stabilizers. However, adjunctive anxiolytics or antipsychotic drugs frequently are used either on an as-needed basis or as short-term routine therapy. Recently, atypical antipsychotics, such as olanzapine risperidone, and quetiapine, received FDA approval for the labeled indication as monotherapy for acute mania. Aripiprazole and ziprasidone also have been studied as treatment options

for acute mania. However, mood stabilizers remain the primary treatment option for acute mania.

Figure 1-2 is an example of a drug algorithm for treating acute mania or hypomania. This evidence-driven algorithm was developed through an expert consensus panel for use in the TMAP. The algorithm begins treatment with monotherapy options dependent on episode type and the regimens become more complicated when response is not achieved. The algorithm is based on safety and efficacy, and is not driven by costs.

Lithium

Lithium is a one plus-cation, atomically similar to sodium. In the late 1800s, lithium was used as a treatment for gout, insomnia, and as a tonic. In the 1940s, it was used as a salt substitute for cardiac patients. As expected, this “salt substitute” led to numerous serious adverse events, including death, prompting lithium’s withdrawal from the United States market. Research investigating lithium in the treatment of bipolar illness first appeared in the scientific literature in the mid-1950s. In the 1970s, lithium was reintroduced to the United States market as a treatment for mania and was approved for maintenance therapy for bipolar disorder in the mid-1970s. Today, lithium remains a first-line treatment option for classic mania. However, due to a narrow therapeutic index or clinician reluctance, lithium remains underused in treating acute mania.

Indications. Lithium is indicated for treating acute manic episodes and for maintenance treatment. Lithium has prevented future manic and depressive episodes and reduced the risk of suicide in patients with major depression and bipolar disorder. This risk reduction appears to be greater in patients with bipolar II disorder versus bipolar I disorder. A recent study demonstrated significant reductions in suicide attempts and suicide deaths in patients with bipolar disorder treated with lithium compared to valproate. The overall response rates for lithium, during a manic episode, have ranged from 50% to 80%. However, response rates within specific types of manic episodes (e.g., classic mania vs. a mixed episode) vary. Lithium may be the best choice for patients who exhibit classic mania and do not have substance abuse issues. Lithium is less effective than valproic acid or carbamazepine in treating patients exhibiting mixed episodes and rapid cycling. Finally, symptoms in up to 30% of patients taking lithium may be classified nonresponders. Patients should receive an adequate lithium trial of 2–3 weeks at therapeutic plasma levels before categorizing their symptoms as lithium nonresponders.

Lithium therapy requires close monitoring due to its narrow therapeutic index. For acute mania, lithium usually is dosed to achieve a plasma concentration between 0.8 mEq/L and 1.2 mEq/L. Concentrations above this are associated with increased adverse effects and toxicity. Traditionally, acceptable maintenance levels of lithium have been as low as 0.4–0.6 mEq/L. More recent data suggest that maintenance levels maintained above 0.8 mEq/L are

Suppes T, Dennehy EB, Swann AC. Report of the Texas Consensus Conference Panel on Medication Treatment of Bipolar Disorder 2000. *J Clin Psychiatry* 2002;63:288–99.

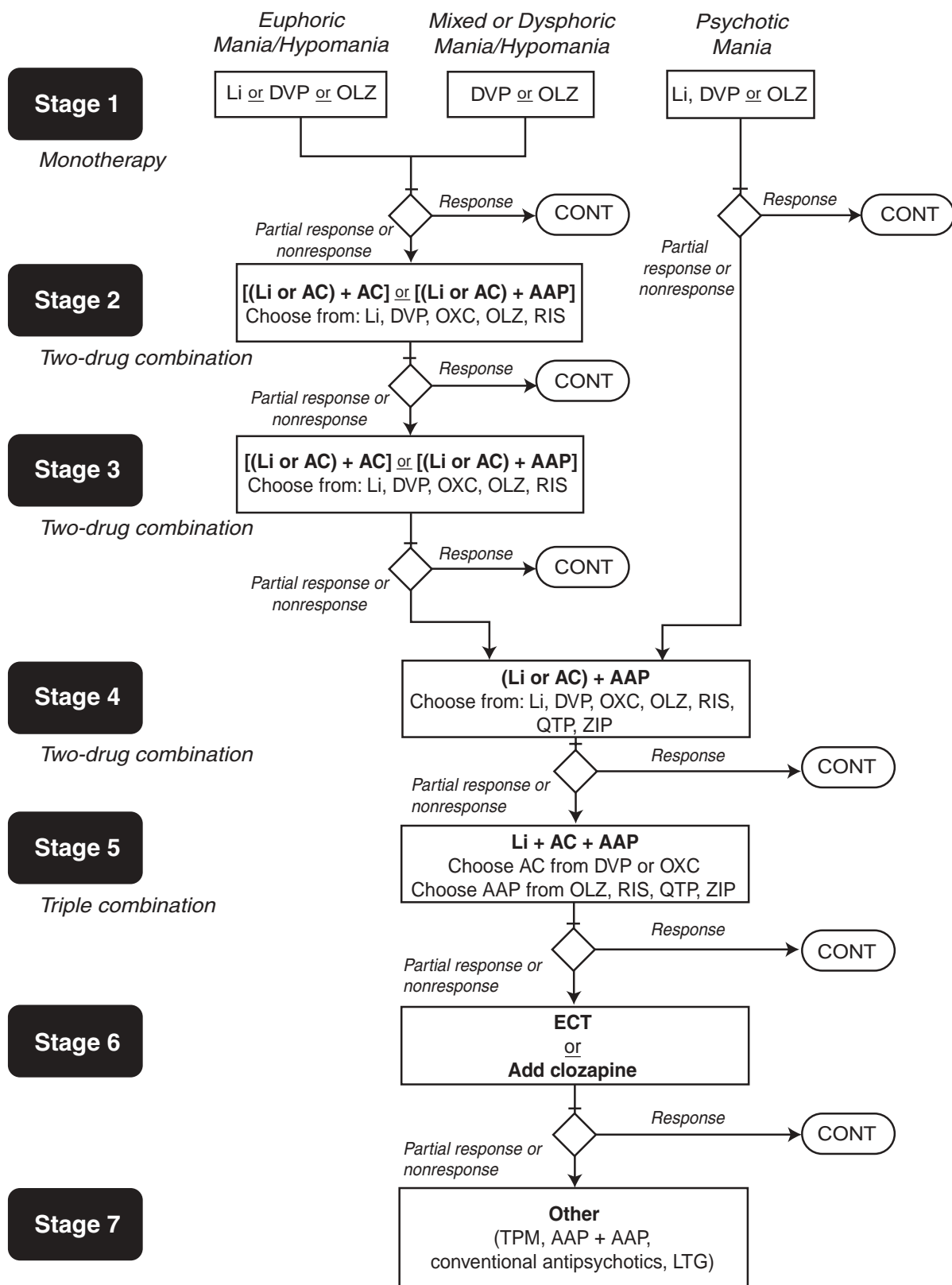


Figure 1-2. Texas Medication Algorithm Project (TMAP): Algorithm for Mania/hypomania. AAP = atypical antipsychotic; AC = anticonvulsant; CONT = continue; DVP = divalproex; ECT = electroconvulsive therapy; Li = lithium; LTG = lamotrigine; OLZ = olanzapine; OXC = oxcarbazepine; QTP = quetiapine; RIS = risperidone; TPM = topiramate; ZIP = ziprasidone.

associated with relapse rates significantly lower than at lower plasma concentrations.

Lithium Pretreatment Workup. Before initiating lithium, a pretreatment workup should include an EKG in patients older than 40 years of age, a complete blood cell (CBC) count with differential, serum electrolytes, general chemistry panel, pregnancy test (if applicable), urine analysis and toxicology, and thyroid function tests. Maintenance laboratory monitoring should be done every 6–12 months and include a CBC count with differential, serum electrolytes, thyroid function tests, and serum creatinine. More frequent monitoring of blood urea nitrogen and creatinine will be warranted in patients with impaired renal function. The lithium plasma concentration should be obtained 4–5 days after initiation or dose adjustments. When the patient's symptoms are controlled and a stable dose has been achieved, repeat lithium concentrations may be obtained every 6–12 months or when clinically indicated.

Pharmacokinetics/Dosing. Lithium does not undergo hepatic metabolism and is excreted primarily in the urine. Plasma lithium concentrations are influenced by both dose and renal clearance. Several pharmacokinetic models have been developed to predict plasma concentrations based on a given dose. However, none of these models have proven to be superior to empiric dosing in achieving a desired plasma concentration. Thus, empiric dosing is most widely used for initiating lithium. Empiric dosing assumes that for each 300 mg of lithium the patient will achieve 0.3 mEq/L of lithium in the serum; therefore, 900 mg/day of lithium would be expected to result in a serum lithium concentration of about 0.9 mEq/L. In patients with normal renal function and no apparent drug-drug interactions, lithium typically is started at doses of 300 mg 2–3 times/day. Subsequent titration in 300 mg/week increments may be used as needed based on clinical symptomatology and desired plasma levels. Steady-state plasma concentrations typically are achieved within 4–5 days of lithium initiation or dosage adjustment.

Blood for plasma lithium measurement should be drawn at a trough time, which typically is 10–12 hours after the last dose. The goal in a patient who is acutely manic is a lithium concentration of at least 0.8 mEq/L and possibly as high as 1.2 mEq/L. Lithium may be initiated in a loading dose up to 30 mg/kg/day; however, studies have not demonstrated a more rapid onset of action and many patients are unable to tolerate this loading dose. The therapeutic effects of lithium are not observed for 5–10 days, with maximal effects taking 2–3 weeks, regardless of the dosing method. During this period, clinicians typically use concomitant benzodiazepines with or without antipsychotic agents on a routine or as-needed basis to control symptomatology.

Drug Interactions. Drugs known to alter renal blood flow or sodium excretion should be used cautiously in conjunction with lithium. Angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, diuretics (especially thiazides), and nonsteroidal anti-inflammatory agents are known to alter fluid and electrolyte balances. Thus, these agents should be used cautiously in conjunction with lithium, as significant increases in lithium plasma concentrations are possible. These agents used in combination with lithium often are the cause of lithium

toxicity. Management of lithium toxicity is discussed later in this section. Loop diuretics are associated with a more modest increase in lithium concentration compared with those with thiazides. Potassium-sparing diuretics such as amiloride can be used with lithium with minimal effects on lithium levels.

Caffeine and theophylline are known to increase renal blood flow, which may lower plasma lithium concentrations. This may become a relevant interaction when patients transition from caffeine-free inpatient units to an outpatient status. In patients maintained on a stable lithium dose who consumed between four and eight cups of coffee daily, lithium levels rose 24% when caffeine was abruptly discontinued. Therefore, clinicians and patients should fully discuss the effect of caffeine on lithium concentrations and make lithium adjustments as warranted.

Lithium-associated neurotoxicity has been reported when used in combination with calcium channel blockers, antipsychotics, carbamazepine, and methyldopa. Neurotoxicity may include muscle weakness, tremor, delirium, ataxia, EEG abnormalities, extrapyramidal symptoms, and nausea. Furthermore, when used in conjunction with SSRIs, lithium has been associated with increased sedation, nausea, and tremor. Serotonin syndrome also may occur with this combination.

Adverse Effects. The most common side effects associated with lithium are gastrointestinal effects, somnolence, fatigue, tremor, and weight gain. In addition to sedation, many patients report cognitive dulling that may or may not lessen with time. Clinicians should specifically ask about cognitive dulling, as this can lead to nonadherence with treatment if not addressed. Tremor associated with lithium occurs in up to 65% of patients. It is related to the rate of lithium absorption, maximal plasma concentrations, and the extent of absorption. Lithium tremor presents as mild, action tremor, which can be managed in many ways: dosage reduction (if clinically indicated), switching to an extended-release formulation, or addition of a β -blocker (e.g., propranolol). Furthermore, lithium tremor may lessen over time. A new onset of a coarse tremor in a patient taking lithium chronically may be indicative of toxicity.

Worsening of preexisting dermatological conditions often is a treatment-limiting factor with lithium. Furthermore, lithium appears to lessen dermatological response to treatment. Lithium is associated with polyuria and polydipsia, another potentially treatment-limiting adverse effect. Up to 70% of patients may experience initial polyuria and polydipsia, although fewer will experience this chronically. These adverse events often are bothersome to patients and may lead to nonadherence with treatment.

Lithium is known to block the effect of antidiuretic hormone in the collecting ducts of the distal tubule, resulting in nephrogenic diabetes insipidus. The resulting effect is an increase in urine volume and lowering of the urine specific gravity. Frequently, consolidating the lithium dose to once daily and switching to an extended-release product are effective in minimizing urine output. In patients whose symptoms do not respond to this initial intervention, amiloride often is added. Long-term lithium treatment was once thought to cause renal morphologic changes, possibly resulting in impaired renal function. More recent data

suggest that minimal morphologic effects are associated with chronic lithium treatment, especially when the lowest possible doses are used and toxicity is avoided. Finally, it has been reported that 75–100% of patients receiving lithium will develop leukocytosis to varying degrees. Basophils are the only component of the white blood cells that are not affected by lithium. Leukocytosis secondary to lithium is not associated with a left shift, an important point when a potential infection is being assessed.

Toxicity. Lithium is a drug with a narrow therapeutic index. Significant toxicity may result from either an intentional overdose or drug-drug interactions. When drug interactions result in lithium toxicity, it is imperative that the regimen be changed and that the patient understands the lethality of such combinations to minimize future risk of toxicity. As lithium is excreted renally, factors that alter renal function, such as dehydration, decreased renal blood flow, or impaired glomerular filtration, can significantly decrease lithium clearance. The risk of toxicity is enhanced in the elderly who have decreased renal function associated with aging, are prone to dehydration, and often take concomitant drugs that alter lithium clearance. Furthermore, vomiting, diarrhea, and prolonged exposure to hot weather or sauna baths may result in significant decreases in lithium clearance.

As previously discussed, lithium has a narrow therapeutic index, which warrants extensive patient education. Knowledgeable patients can help minimize toxicity associated with lithium. In general, mild toxicity occurs when lithium serum concentrations rise between 1.5 mEq/L and 2.0 mEq/L. These symptoms may include impaired memory and concentration, fine hand tremor, nausea and/or vomiting, fatigue, or muscle weakness. Moderately severe toxicity occurs when serum concentrations are between 2.0 mEq/L and 2.5 mEq/L and includes a worsening of or coarse tremor, altered mental status, and increased deep tendon reflexes. Serum concentrations above 2.5 mEq/L are associated with seizures, coma, respiratory depression, arrhythmias, increased deep tendon reflexes, cardiovascular collapse, and death.

All patients experiencing lithium toxicity should have their lithium immediately discontinued and receive supportive care. Their fluid and electrolyte balance, and renal and neurologic function should be closely monitored. In severe toxicity, serial lithium serum concentrations should be measured every 3 hours until they are below 1.0 mEq/L. If lithium concentrations do not decrease by 10% with each subsequent measurement, or the lithium half-life is greater than 36 hours, intermittent hemodialysis should be initiated. Lithium is known to accumulate in tissues, such as the thyroid. Hemodialysis clears lithium from the peripheral circulation faster than it can redistribute from tissue stores, resulting in rebound lithium levels during hemodialysis. Due to rebound lithium serum concentrations, hemodialysis should be continued until

concentrations drawn 6–8 hours after dialysis are consistently below 1.0 mEq/L.

Teratogenicity and Fetal Toxicity. First trimester exposure to lithium is associated with an 8-fold increase in the rate of Ebstein's anomaly, a congenital cardiac malformation. Secondary to this risk, lithium is categorized as an FDA pregnancy risk category D drug. Thus, lithium should be used during the first trimester only when the benefits clearly outweigh the risks and safer drugs cannot be used.

Lithium exposure during the second and third trimester have been associated with "floppy baby syndrome". Symptomatology can include cyanosis and hypertonicity. Neonatal toxicity can be minimized by reducing the lithium dose by 50% during labor. In addition, teratogenicities associated with later exposure include: polyhydramnios, premature delivery, nephrogenic diabetes insipidus, and thyroid abnormalities.

Valproic Acid

Valproate and its divalproex sodium formulation have demonstrated efficacy in acute mania in many controlled trials. Although traditionally used as an antiepileptic agent, divalproex received an FDA-approved indication as monotherapy for acute mania in 1995. Valproate is particularly helpful for patients with rapid cycling, a mixed episode, or mania due to a medical condition. Response to valproate is lower in classic mania as compared to lithium. Currently, valproate and lithium are considered first-line treatment options for acute mania. There also is evidence that valproate maintenance treatment was superior to placebo in decreasing the risk of relapse.

Indications. Valproate and the divalproex formulation have demonstrated efficacy in more than 10 acute mania trials. In one of two pivotal trials, 48% of patients who are acutely manic and treated with divalproex responded to treatment compared to 49% treated with lithium and 25% treated with placebo. In addition to acute mania, valproate has been studied as both adjunctive and monotherapy for bipolar maintenance treatment. As a maintenance agent, valproate monotherapy has been associated with a significant increase in the number of patients maintaining a complete response over a 1-year time frame compared to placebo. When divalproex was studied in combination with olanzapine versus monotherapy with either lithium or divalproex, combination therapy was associated with a significantly longer time to relapse compared to either monotherapy. Combination therapy was associated with a significant reduction in manic recurrences; however, there were no differences in time to or rates of depression. One controlled trial found no difference in antidepressant response between divalproex and placebo.

Valproate Pretreatment Workup. Before the initiation of valproate the following laboratory tests should be obtained: general chemistry panel, CBC count with differential, liver function tests, and a pregnancy test in women of

Bowden CL, Brugger AM, Swann AC, et al. Efficacy of divalproex vs. lithium and placebo in the treatment of mania. The Depakote Mania Study Group. JAMA 1994;271:918–24.

child-bearing potential. Repeat liver function tests should be obtained monthly for the first 2 months and then every 3–6 months thereafter. Follow-up valproic acid serum concentrations should be obtained every 6–12 months in stable patients.

Pharmacokinetics/Dosing. Valproate is absorbed almost completely and exhibits linear pharmacokinetics. It is converted to the active moiety, valproic acid, in the stomach. Alternatively, divalproex sodium is converted into valproic acid in the intestines. Several different formulations of valproic acid are available: syrup, sprinkles, injection, and delayed- and extended-release divalproex sodium. Valproic acid is about 80–90% protein-bound and may display protein-binding saturation at variable doses. For most patients, protein-binding saturation will not be problematic. Clinically, protein-binding saturation occurs when dosage increases do not yield a corresponding increase in the reported valproic acid serum concentration. For example, a patient may be symptomatic at a dose of 1250 mg/day with a corresponding serum concentration of 82 mcg/ml. In the case of protein-binding saturation, further dose increases will not increase the reported valproic acid serum concentration, but will expose the patient to an increased risk of toxicity due to increased free drug.

Valproic acid is extensively metabolized through glucuronide conjugation, β -oxidation, and to a lesser extent, the CYP2C19 isoenzyme. The elimination half-life is about 8–17 hours and increases in neonates and those with hepatic impairment. The time to maximal concentration varies with each formulation: 1–4 hours for valproic acid capsules and valproate syrup; 3–5 hours for delayed-release divalproex, and 13–16 hours for extended-release divalproex. Furthermore, the maximal concentration is lower with extended- versus delayed-release divalproex, which may account for its increased tolerability. Finally, the extended-release formulation is associated with a smaller area under the curve compared to the delayed-release formulation. Thus, when switching from delayed to extended release, it is recommended that doses be increased by up to 20% to provide an equivalent exposure.

Two dosing methods are used for valproate. Some clinicians opt to empirically dose valproate beginning at doses of 250 mg 3 times/day with subsequent titration dictated by symptomatology and serum concentrations. More recently, clinicians have moved toward a loading dose strategy of 20 mg/kg/day given in divided dosages. Whichever dosing strategy is used, the ultimate goal is to achieve a minimum concentration of 60–70 mcg/ml, which has been associated with greater control of acute mania. The upper limit of the therapeutic range is approximately 125 mcg/ml; however, some patients may require concentrations as high as 150 mcg/ml. The targeted serum concentration is more rapidly achieved with the loading dose strategy. In addition, there is some evidence that patients loaded with valproate are stabilized faster.

Drug Interactions. Valproic acid is a substrate of the CYP2C19 isoenzyme and inhibits the CYP2C9 and CYP2D6 isoenzyme pathways. In addition, it appears to be a weak inhibitor of the CYP3A4 isoenzyme. Inhibitors of the CYP2C19 isoenzyme such as fluoxetine and

fluvoxamine may increase valproic concentrations; however this interaction may be secondary to inhibition of valproic acid glucuronidation. There are limited data supporting the reduction of valproic acid concentrations secondary to enzyme inducers (e.g., carbamazepine and phenytoin).

Adverse Effects. The most common adverse effects associated with valproate are CNS-, gastrointestinal-, neuromuscular-, and hematological-related effects and weight gain. The most problematic adverse effects are somnolence, dizziness, nausea, vomiting, diarrhea, and tremor. In general, tremor is an early indication of toxicity that resolves with dose reduction. The gastrointestinal-related effects typically are transient and may be minimized with the administration of the drug with food. Divalproex and extended-release divalproex formulations are associated with increasingly lower rates of gastrointestinal effects, respectively. The more favorable gastrointestinal side effect profile for the extended-release formulation is mostly accounted for by slower absorption rate and lower maximum serum concentrations. Somnolence and dizziness also are transient. Administering a larger proportion of the total daily dose at bedtime often is useful in minimizing daytime sedation. Up to 25% of patients will exhibit mild thrombocytopenia; however, it is rarely of clinical significance. It is helpful to have patients self-monitor for easy bruising and epistaxis. Weight gain may be a treatment limiting adverse event and often is cited by patients as their reason for drug nonadherence. The majority of weight gain is attributable to increased body fat and, rarely, secondary to edema. Body weight should be routinely monitored in patients receiving valproate. Furthermore, patients should be educated about possible weight gain and dietary modifications.

Valproate is known to cause mild transient elevations in liver function tests. Valproate is rarely associated with hepatotoxicity, which appears to be nondose related and idiosyncratic. The risk of hepatotoxicity is increased in children younger than 2 years of age, with concomitant hepatotoxins and with developmental disorders. Pancreatitis occurs rarely, but should be suspected in patients reporting unresolved or new-onset abdominal pain and/or vomiting, especially if patients have a history of alcohol abuse. Patients may develop a rash, which rarely progresses to Steven-Johnson syndrome. Finally, alopecia presenting as transient and mild thinning may occur in up to 12% of patients. Alopecia appears to be a dose-related phenomena. Some clinicians advocate zinc and selenium supplementation to minimize hair loss; however, the therapeutic benefit of this remains unclear.

Toxicity. In general, toxicity is associated with serum concentrations higher than 200 mcg/ml; however, toxicity may occur at doses as low as 100–150 mcg/ml. Adverse effects that lead to discontinuation typically are not related to toxic serum concentrations. Symptoms of toxicity may include visual hallucinations, deep sleep, coma, and motor restlessness. As previously discussed, new-onset tremor may be indicative of early valproate toxicity.

Teratogenicity. Valproate is characterized as an FDA pregnancy risk category D drug. First trimester exposure to valproic acid is associated with significantly higher rates of spina bifida, hypospadias, porencephaly/multiple cerebral

cysts, limb reduction, and coarctation of the aorta compared to controls. It is recommended that women of child-bearing potential receive routine supplemental folate to minimize teratogenicity should they become pregnant. If a pregnancy is planned, the patient and clinician should work together to transition from valproate to another mood stabilizer before conception.

Carbamazepine

Carbamazepine was developed and marketed for the treatment of epilepsy in the late 1950s. Serendipitously, clinicians noted increased mood stability in patients with epilepsy who had concomitant mood disorders. Carbamazepine does not have an FDA indication for acute mania; however, it is widely considered an acceptable treatment option for acute mania; however, most clinicians would opt for trials with lithium and/or valproic acid before carbamazepine.

Indications. Ten controlled trials have assessed the efficacy of carbamazepine in acute mania. Only five of the 10 trials are methodically sound and have compared carbamazepine to placebo, lithium, or chlorpromazine. Only one placebo-controlled acute mania trial has been conducted; carbamazepine was superior to placebo in reducing mania, psychosis, anxiety, and hostility. A meta-analysis of these five acute mania-controlled trials revealed response rates to be 50% for carbamazepine, 56% for lithium, and 61% for chlorpromazine. Carbamazepine may be more effective than lithium for treating rapid cycling, mixed episodes, or atypical mania presentations. There are limited controlled data assessing the efficacy of carbamazepine as a maintenance treatment of bipolar disorder. There have been several small studies that have assessed carbamazepine's efficacy in bipolar depression. In most of these trials, carbamazepine was used in combination with lithium. Collectively, these studies suggest a modest antidepressant effect for carbamazepine.

Carbamazepine Pretreatment Workup. The carbamazepine pretreatment workup should include the following laboratory tests: general chemistry panel, CBC count with differential, liver function tests, electrolytes and pregnancy test, when applicable. An EKG should be obtained before initiation of therapy in patients older than 40 years of age. For the first 2 months of therapy, repeat liver function tests should be obtained monthly and then every 3–6 months thereafter. In addition, a CBC count with differential often is repeated several times during the first few months of therapy. Follow-up carbamazepine serum concentrations should be obtained every 6–12 months or sooner when clinically appropriate.

Pharmacokinetics/Dosing. Carbamazepine is absorbed slowly and has a bioavailability of 85%. It is variably protein bound, ranging from 75% to 90%. Carbamazepine is hepatically metabolized, primarily through the CYP3A4 isoenzyme, to an active epoxide metabolite. Carbamazepine induces the CYP1A2, CYP2C, and CYP3A4 isoenzymes, resulting in the increased metabolism of itself and other

substrates for those particular pathways. This autoinduction occurs with the initiation of carbamazepine, as well as with subsequent dose increases. Consequently, the initial half-life of carbamazepine is about 18–55 hours; however, with chronic dosing, the half-life decreases to 8–14 hours. Steady-state concentrations are not achieved for about 21 days.

Carbamazepine is initiated at 200 mg 2 times/day. Subsequent dose increases in 200-mg increments should be based on symptomatology. For those who are sensitive to CNS side effects or have mild to moderate renal impairment, the drug should be started at 100 mg 2 times/day. In those experiencing excessive daytime sedation, the majority of the daily dose may be administered at bedtime. Optimal response typically is achieved when trough levels are between 8 mcg/ml and 12 mcg/ml. Ataxia, choreiform movements, seizures, and coma have been observed when serum concentrations rise above 15 mcg/ml. Dose adjustments may be necessary during the first few months of therapy secondary to autoinduction.

Drug Interactions. Carbamazepine is hepatically metabolized as a substrate of the CYP3A4 isoenzyme. Thus, drugs which are known CYP3A4 isoenzyme inhibitors have been associated with clinically relevant increases in carbamazepine serum concentrations. These inhibitors include azole antifungal agents, macrolide antibiotics, nefazodone, fluoxetine, fluvoxamine, cimetidine, and various protease inhibitors.

Because carbamazepine induces many CYP isoenzymes, clinically relevant increases in the metabolism of a variety of substrates may occur. Enzyme induction secondary to carbamazepine has resulted in clinically significant decreases in plasma concentrations of various substrates. For example, carbamazepine has been associated with the decreased concentrations and associated decreased efficacy of antidepressants, antipsychotics, benzodiazepines, oral contraceptives agents, thyroid hormone, theophylline, phenytoin, and warfarin. Clinicians should closely monitor patients for decreasing efficacy of an existing regimen when adding carbamazepine.

Increased carbamazepine toxicity has been reported when used in combination with valproic acid. Valproic acid inhibits the degradation of the carbamazepine 10,11-epoxide metabolite, which is believed to be related to the toxic effects of carbamazepine. In addition, carbamazepine may induce the metabolism of valproic acid, resulting in lower serum concentrations. With this combination, the clinician will need higher doses of valproate to achieve the desired serum concentration. There have been reports of neurotoxicity associated with the combination of lithium and carbamazepine, especially in patients who have comorbid CNS disease. In general, this combination is safe and may be an appropriate strategy for those with little response to either agent alone.

Adverse Effects. Central nervous system effects are the most common (up to 60%) and most problematic adverse effects associated with carbamazepine. These may include

Ballenger JC, Post RM. Therapeutic effects of carbamazepine in affective illness: a preliminary report. *Commun Psychopharmacol* 1978;2:159–75.

dizziness, drowsiness, fatigue, ataxia, blurry or double vision, nystagmus, and confusion. In general, for patients older than 40 years of age, effects are transient and most common in the first few weeks of treatment. It often is helpful to administer a larger proportion of the daily dose in the evening to lessen the side effect burden. Gastrointestinal effects, such as nausea, vomiting, diarrhea, and dyspepsia, frequently occur and can be diminished by administering the drug with food.

Transient leukopenia occurs in up to 25% of patients receiving carbamazepine. Rarely does it progress to a white blood cell count below 3000/mm³ or a neutrophil count below 1000/mm³. Complete blood cell count with differential should be monitored routinely, especially within the first month of therapy. If the white blood cell count falls below 3000/mm³ or the neutrophil below 1000/mm³, the carbamazepine dose should be decreased or the drug discontinued. Other rare but clinically relevant hematologic effects include thrombocytopenia, aplasia anemia, and agranulocytosis.

Frequent increases in liver function tests occur with carbamazepine, and hepatotoxicity may occur rarely. Patients receiving other known hepatotoxins should be closely monitored. Hyponatremia and syndrome of inappropriate antidiuretic hormone may be seen and often are treatment-limiting.

Carbamazepine is associated with significant hypersensitivity and dermatological reactions. Hypersensitivity may involve multiorgan reactions and vasculitis, eosinophilia, hepatosplenomegaly, and diaphoresis. Patients should be educated about the possibility of rash and instructed to discontinue carbamazepine and contact their physician immediately. Dermatological reactions may be limited to pruritus and urticaria; however, they may progress to life-threatening Stevens-Johnson syndrome, toxic epidermal necrolysis, and exfoliative dermatitis.

Toxicity. Symptoms of carbamazepine toxicity include ataxia, dizziness, drowsiness, nausea, vomiting, nystagmus, urinary retention, seizures, coma, arrhythmias, respiratory depression, and neuromuscular disturbances. In cases of acute overdose, activated charcoal is very effective for binding carbamazepine.

Teratogenicity. Carbamazepine is associated with minor facial malformations, neural tube defects, cardiac defects, and fingernail hypoplasia. It is classified as an FDA pregnancy risk factor category C drug.

Oxcarbazepine

Oxcarbazepine is a prodrug for the monohydroxy metabolite of carbamazepine. It is structurally similar to carbamazepine. However, unlike carbamazepine, oxcarbazepine is not metabolized to the 10,11-epoxide metabolite, which is thought to be related to many of the toxicities associated with carbamazepine. Oxcarbazepine may be used as a second-line treatment option for acute mania and depression associated with bipolar disorder. However, few controlled trials have been conducted to support this practice. Several open-label trials have demonstrated improvement in its use as adjunct therapy for acute mania. Two short-term, blinded, controlled trials

comparing oxcarbazepine to lithium and to haloperidol have been completed. In each trial, oxcarbazepine demonstrated antimanic effects that were similar to the active comparator. Presently, there are no controlled studies assessing the efficacy of oxcarbazepine in depressive episodes associated with either major depression or bipolar disorder. One small open-label study suggests that oxcarbazepine may have some antidepressive activity when used as adjunctive therapy. In general, oxcarbazepine is better tolerated than carbamazepine. The most common side effects associated with it are headache, dizziness, blurred vision, gastrointestinal effects, and sedation. Like carbamazepine, oxcarbazepine has been associated with various dermatological adverse effects, including Stevens-Johnson syndrome, albeit, less frequently. For patients who are hypersensitive to carbamazepine, about 25–30% will be hypersensitive to oxcarbazepine as well. Potentially lethal hepatotoxicity and hematological effects have not been reported with oxcarbazepine. Like carbamazepine, syndrome of inappropriate antidiuretic hormone has been associated with oxcarbazepine therapy. Oxcarbazepine is associated with fewer drug-drug interactions than carbamazepine. In addition, it is not associated with autoinduction. There may be some enzyme induction at higher doses. Like carbamazepine, oxcarbazepine increases the metabolism of estrogen and progesterone; hence, patients taking oral contraceptives should be thoroughly educated about this interaction.

Lamotrigine

In addition to lithium, lamotrigine is the only other agent, which has received an FDA indication for maintenance therapy in patients with bipolar disorder. Two double-blind, randomized, controlled trials assessed lamotrigine and lithium versus placebo for preventing bipolar mood episodes. One study enrolled patients with bipolar disorder who had recently suffered a depressive episode and the other followed patients who recently had experienced manic or hypomanic episodes. Results from both studies suggest the following: lamotrigine but not lithium was superior to placebo in prolonging the time to intervention for a depressive episode, and lithium but not lamotrigine was superior to placebo in prolonging the time to intervention for a manic episode. Based on these findings, a lithium and lamotrigine combination may be a reasonable choice to prevent both future mania and depressive episodes. There are limited data supporting lamotrigine monotherapy as an appropriate treatment for acute mania. Finally, because lamotrigine prolongs the time to intervention for depressive symptoms, it is a particularly good choice for patients with bipolar II disorder who primarily experience depressive episodes.

Pharmacokinetics/Dosing. Lamotrigine is about 55% protein bound. It undergoes hepatic metabolism by glucuronosyltransferase and minimal renal elimination. Lamotrigine undergoes negligible metabolism through the CYP system. As a monotherapeutic agent, the half-life of lamotrigine ranges from 22 to 38 hours, with concomitant valproate the half-life increases to about 59 hours. Conversely, with concomitant enzyme inducers the half-life decreases to about 15 hours.

In patients receiving lamotrigine monotherapy, initial doses of 25 mg/day should be given for 2 weeks, with subsequent increases to 50 mg/day for 2 weeks, followed by 100 mg/day for 1 week. Thereafter, upward titration by increments of 100 mg/week should be made as clinically indicated. When used in combination with carbamazepine, the initial dose is 50 mg/day for 2 weeks with upward titration in increments of 50 mg/week every 1–2 weeks. When lamotrigine is added to valproic acid, initial doses of 25 mg every other day should be used for 2 weeks and then 25 mg/day for 2 weeks. Subsequent titration may occur in increments of 25 mg/week up to a target dose of 100–150 mg/day. The product labeling for lamotrigine indicates doses should be decreased in patients with significant renal impairment. However, one study found no difference in the area under the curve and maximum concentrations of lamotrigine between healthy volunteers and patients with severe renal impairment (e.g., creatinine clearance less than 25 ml/minute).

Drug Interactions. Carbamazepine, phenobarbital, and phenytoin significantly increase lamotrigine clearance secondary to induction of glucuronidation. Conversely, valproic acid, an inhibitor of glucuronidation, decreases lamotrigine clearance by about 50%.

Lamotrigine does not inhibit or induce the CYP isoenzymes. It may inhibit the metabolism of carbamazepine's 10,11-epoxide metabolite; however, published pharmacokinetic reports are conflicting. There are reports of neurotoxicity (e.g., dizziness, nausea, and diplopia) secondary to combinations of lamotrigine and carbamazepine; however, pharmacokinetic reports do not support significant interactions. Thus, the neurotoxicity associated with this combination may be related to a pharmacodynamic as opposed to a pharmacokinetic interaction.

Adverse Events. Central nervous system-related adverse events, such as headache, dizziness, ataxia, and somnolence, are common with lamotrigine. In general, these are transient in nature. In addition, visual changes including blurry vision and diplopia frequently are reported.

Lamotrigine commonly is associated with rash. Lamotrigine-associated rash rarely progresses to the life-threatening Stevens-Johnson syndrome. It appears that this risk is heightened with rapid dose titration and concomitant valproic acid therapy. There is minimal risk of rash if valproate is introduced to a patient receiving chronic lamotrigine therapy. All patients should be counseled about this potentially life-threatening adverse effect and instructed to immediately contact their physician at the first sign of a rash. Rarely, lamotrigine has been associated with serious hematological effects, such as agranulocytosis, aplastic anemia, and pancytopenia.

Other Antiepileptic Drugs

Gabapentin has failed to improve symptoms of acute mania in at least two placebo-controlled trials. It is not recommended as monotherapy for acute mania. There are several small, uncontrolled, open-label reports describing improvement in manic symptoms with adjunctive gabapentin.

Topiramate has not been studied in placebo-controlled, acute mania trials. Like gabapentin, small open-label, add-on studies and case reports suggest that topiramate may have a role as an adjunctive agent for treating acute mania and depression associated with bipolar disorder. However, the scientific rigor of these studies was not robust and many included patients with diagnoses other than bipolar disorder or who were deemed "treatment refractory". One placebo-controlled study reported topiramate at doses of 256 mg or 512 mg for 3 weeks were no different than placebo on the median change in YMRS scores. Weight loss associated with topiramate may be a possible benefit when used as adjunctive treatment although many patients do not tolerate the cognitive dulling associated with adequate doses.

Atypical Antipsychotic Drugs

In the 1990s, investigators began noticing proposed thymoleptic properties of the atypical antipsychotic drugs in patients during treatment of schizoaffective disorder and schizophrenia, and during off-label use in bipolar disorder. Based on these observations, post hoc analysis of affective factors, and prospective secondary outcome measures, researchers began to investigate the mood-stabilizing properties of the atypical antipsychotic drugs. To date, many atypical antipsychotic drugs are being studied as treatment options for bipolar disorder during acute episodes and as maintenance therapy.

Olanzapine. Olanzapine has been studied in two placebo-controlled, monotherapy trials in comparison with lithium, valproate, and haloperidol, and as adjunctive treatment. Studies suggest that olanzapine is effective as monotherapy for acute mania; it has recently received FDA approved labeling for this indication. Olanzapine has demonstrated efficacy in both psychotic and nonpsychotic mania. Post hoc analyses suggest that there is no difference in response within bipolar subgroups (e.g., mixed episodes or rapid cyclers), much like valproate. Initial doses of 15 mg/day are associated with a faster onset of action (e.g., 1 week) as opposed to doses of 10 mg/day (e.g., 3 weeks). One 47-week trial assessed the efficacy of olanzapine versus divalproex in the maintenance treatment of bipolar. Olanzapine was superior to divalproex on mean change in YMRS scores; however, the difference between treatment groups was of minimal clinical relevance (2.38 points). Olanzapine was associated with significantly shorter time to mania remission compared to divalproex. Rates for both treatment groups were similar for subsequent relapse into mania or depression.

Olanzapine and olanzapine-fluoxetine combination were compared to placebo for treating bipolar depression in an 8-week, double-blind trial. Significant improvement on the MADRS scores were observed as early as week 1 for olanzapine monotherapy and olanzapine-fluoxetine combination treatment. At the end of the study, olanzapine monotherapy and the olanzapine-fluoxetine combination therapy demonstrated significant decreases in MADRS scores compared to placebo. In fact, there was a statistically significant response favoring the combination therapy over monotherapy. There were no differences between the three treatment groups in terms of induction of mania. Based on

initial data, olanzapine-fluoxetine combination therapy appears to be more favorable compared to olanzapine monotherapy in patients with bipolar depression.

Risperidone, Quetiapine, and Aripiprazole. Several uncontrolled, open-label studies have demonstrated the efficacy of various atypical antipsychotic drugs as adjunctive therapy for acute mania. These results have been replicated in controlled adjunctive trials. There are few published trials and abstracts which have demonstrated the efficacy of risperidone, ziprasidone, aripiprazole, or quetiapine monotherapy in the treatment of acute mania. The role of atypical antipsychotic drugs in treating acute mania and bipolar depression, and as maintenance therapy, either as an adjunctive and as monotherapy, will become clearer as more clinical evidence is published.

Bipolar Depression

Depressive episodes of bipolar disorder mirror those associated with unipolar depression. The vast majority of patients with bipolar disorder will experience at least one depressive episode. For many, depression will present first followed by a subsequent manic episode. Patients with bipolar disorder often experience more overall depressive episodes than manic episodes. The lifetime risk of suicide in patients with bipolar disorder is greater than 15%. Furthermore, about 50% of all patients with bipolar disorder will attempt suicide at some point in their life. Suicidal attempts are most common during a depressive episode, but certainly are not limited to the depressive phase of the illness. The risk of suicidal acts per 100 person-years averaged 3.10 without lithium versus 0.210 during lithium treatment versus 0.0315 in the general population. Long-term lithium studies suggest that lithium is associated with significant decreases in relative risks of suicide attempts and completions. Based on these data, lithium has been associated with an 82% reduction in suicides and a 93.3% reduction in suicide attempts.

Pharmacotherapy

Lithium

Few scientific studies have been conducted regarding the treatment of bipolar depression. The mainstay of treatment for bipolar depression centers around lithium and lamotrigine. Lithium's antidepressant effect was superior to placebo in eight controlled, clinical trials in patients with bipolar depression. The overall response rate is about 79%, with about 33% of patients experiencing a pronounced response. It is recommended that lithium serum concentrations be maintained at 0.8 mEq/L or higher during a depressive episode. Patients maintained with lithium serum concentrations of less than 0.8 mEq/L may require the addition of an antidepressant or second mood stabilizer.

Lamotrigine

Lamotrigine has demonstrated superiority over placebo in two bipolar depression trials. These studies suggest that higher doses (e.g., 200 mg/day) may be associated with greater response compared to doses of 50 mg/day. In contrast, there was no difference between lamotrigine and placebo in another controlled trial. Despite these findings, lamotrigine is still recommended as a first-line treatment option for patients with bipolar depression.

Other Mood Stabilizer Options

Divalproex has not been well studied in patients with bipolar depression. In one controlled trial, investigators were unable to detect a difference between divalproex and placebo in the treatment of patients with bipolar depression. Carbamazepine has been studied in several small controlled trials, mainly in treatment-resistant depression. Results of these studies suggest a modest antidepressant effect when carbamazepine is used as an adjunctive agent. Bupropion and topiramate exhibited similar response rates when added to a mood stabilizer. Omega-3 fatty acids demonstrated reductions in global depressive symptoms when used as monotherapy or adjunctive therapy in bipolar depression. As previously discussed, olanzapine and the olanzapine-fluoxetine combination had significantly greater efficacy than placebo in a large, controlled study in patients with bipolar depression.

Antidepressants

Frequently, depressive episodes in patients with bipolar disorder are severe enough to require adjunctive antidepressant therapy. A general rule of thumb is to use monotherapy with a mood stabilizer for several weeks before adding an antidepressant. The main concern with adding an antidepressant is the risk of switching the patient into a manic state. The overall rate of switching in patients with bipolar disorder is about 25%. There are several factors that may increase the likelihood of an antidepressant-induced switch: multiple antidepressant trials, family history of bipolar disorder, and previous antidepressant-induced manias. Antidepressant-induced switches to a manic state may occur at anytime during the antidepressant therapy. Among those experiencing a switch to mania, patients not receiving a concomitant mood stabilizer had significantly higher rates of switching compared with those receiving a mood stabilizer. Thus, although mood stabilizers diminish the risk of switching, they do not fully eliminate this risk. The choice of antidepressant is an important factor in minimizing the risk of switching. Tricyclic antidepressants are associated with the highest rate of switching and may induce rapid cycling. The SSRIs, especially paroxetine and bupropion, appear to cause less switching. Fluoxetine is not recommended

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Baldessarini RJ, Tondo L, Hennen J. Lithium treatment and suicide risk in major affective disorders: update and new findings. *J Clin Psychiatry* 2003;(suppl 5):44–52.

Fawcett JA. Lithium combinations in acute and maintenance treatment of unipolar and bipolar depression. *J Clin Psychiatry* 2003;64(suppl 5):32–7.

Keck PE, McElroy SL. New approaches in managing bipolar depression. *J Clin Psychiatry* 2003;64(suppl 1):13–18.

because of its potential to cause a switch and the extremely long half-life of it and its metabolite. As previously discussed, the olanzapine-fluoxetine combination has demonstrated efficacy in bipolar depression. The presence of olanzapine in this particular combination product may provide enough mood stabilization to offset the propensity of a fluoxetine-induced switch. However, it is debatable whether to continue a patient with bipolar disorder on an antidepressant secondary to the risk of affective switching. For patients who switch to a manic state, the antidepressant should be immediately discontinued. In addition, the antidepressant-induced switch should be clearly documented in patients' medical records. In the event that future depressive episodes require an antidepressant, selecting either paroxetine or bupropion may pose the lowest risk of an antidepressant-induced switch. In these patients, starting an antidepressant at the lowest possible dose and titrating the dose slowly upward. Patients should be treated with an aggressive mood stabilizer regimen. Patients should be educated about the risk of this switch and discuss self-monitoring for early warning signs of mania, such as changes in sleeping patterns.

The treatment duration with an antidepressant continues to be an area of clinical debate. Two strategies are used by clinicians. One is to continue the antidepressant until the depression resolves and then discontinue the antidepressant. This strategy reduces the risk of an antidepressant-induced switch into mania; however, it runs the risk of a return of the original depressive symptoms. The second strategy is to treat the depressive episode in a manner similar to an MDE by continuing the antidepressant for 6–12 months after the remission of depressive symptoms. The risk of a switch is thought to be greater with this strategy, even though the risk of returning depression symptoms is lessened.

Mood Stabilizer Combinations

Several studies have looked at various mood stabilizer combinations versus monotherapy as long-term treatment options for bipolar disorder. In general, patients are tried on monotherapy with lithium, divalproex, or olanzapine before initiating combination therapy. Mood stabilizer combinations of lithium plus divalproex and olanzapine plus either lithium or divalproex have been studied in controlled trials. These data suggest that each combination significantly reduces the rate of relapse into mania or prolongs the time to recurrence compared to monotherapy. There were no significant differences between combination therapy of olanzapine plus lithium and divalproex monotherapy in the time to recurrence of depression. In general, clinicians should attempt several different combinations of lithium, anticonvulsants, and atypical antipsychotic drugs before resorting to triple therapy. Current data suggest that for some patients, long-term combination therapy may be more beneficial compared to mood stabilizer monotherapy.

Difficulties in Affective Disorder Research

There are many issues that make clinical research in the area of bipolar disorder challenging. First, the FDA continues to require placebo-controlled studies. This study design incorporates a greater degree of risk that may not be

acceptable to the patient, the investigator, or both. Continuation trials that enroll patients who responded in earlier acute trials may bias results toward a treatment response. In long-term continuation trials, it often is difficult to maintain a large enough sample to determine differences between drug and placebo because of high dropout rates and variable treatment adherence typically seen in psychiatric research. Many studies of acute mania and depression are designed to initiate patients during an inpatient hospitalization with the possibility of continued study participation after discharge. Most patients randomized to placebo will be unable to meet sufficient clinical improvement for discharge. However, patients with a sustained placebo response who are discharged into a nonsupervised setting are at an even greater risk of relapse. Often, research samples are less generalizable than many clinicians realize. For example, many patients with bipolar disorder do not see a mental health provider for years at a time. Conversely, research subjects routinely are seen by mental health providers. Furthermore, there are fewer patients seen in specialty affective disorder clinics. However, these settings are typically the sites that participate in clinical trials. In addition, many clinical trials incorporate inclusion and exclusion criteria that are strict, limiting enrollment only to those who are treatment responsive and physically healthy.

Documentation of the Pharmacotherapeutic Plan

There are many issues that should be addressed when patients are transitioning from an inpatient setting to an outpatient setting, or when care is being transferred to another clinician. Drug histories, including both positive and negative findings, dose, adverse effects and, if appropriate, serum concentration data, are critical data for a successful transition. Clinicians should provide detailed documentation on specific drug changes that may be continued in the new treatment environment. Finally, plans should be established to assist patients in purchasing their drugs or enrolling them in pharmaceutical industry-sponsored patient assistance programs.

Patient Counseling

Because patients with bipolar disorder experience both manic and depressive episodes, patient education must include both aspects of affective phases. The constellation of depressive and manic symptoms should be discussed, in addition to treatment options. Patients should be given realistic information about what to expect from treatment with respect to a delayed onset of action and when maximum results may be obtained. In addition, clinicians should ask the patients what goals they have for treatment. Often, the treatment goals of the clinicians and patients may be quite different. At times, patient goals may be unrealistic; reality-based patient education will assist patients in developing goals that are acceptable to all parties. Developing common goals, which incorporate clinician and patient desires, will improve treatment outcome and adherence. These goals should not only include attenuation or resolution of primary mood symptoms, but also increase functionality in the community and/or place of employment. Establishing a strong therapeutic alliance between patients

and clinicians helps to reinforce the need for continued psychiatric care and treatment adherence. The importance of family or friends involvement should be stressed in the development and subsequent achievement of goals.

For patients receiving lithium, carbamazepine, or divalproex, the importance of drug blood concentrations should be discussed in the context of efficacy and toxicity. Patients who understand the importance of serum concentrations, may be more adherent with their drugs. Furthermore, patients should be able to identify signs of toxicity and know when to contact their physician if toxicity develops. This is especially true for lithium, given its narrow therapeutic index.

Patients receiving lithium should be informed of the importance of avoiding dehydration and wide fluctuations in caffeine and sodium intake. Women receiving lithium, carbamazepine, and divalproex should be informed about potential teratogenicity. Furthermore, women of childbearing age receiving carbamazepine and divalproex should receive supplemental folate. Finally, women receiving carbamazepine should be fully informed about the potential drug interaction with oral contraceptive agents and be counseled on alternative birth control methods.

As discussed in the Depressive Disorder section, there are a variety of ways to reduce patient drug costs. However, the use of generic formulations of some mood stabilizers is not always warranted. For instance, because of bioavailability issues, using generic carbamazepine of various manufacturers or switching back and forth between generic and brand name Tegretol should be avoided. Although available valproic acid is readily available, some patients may tolerate it poorly compared to enteric-coated divalproex.

Unfortunately, when patients with bipolar disorder are at their sickest, they often lack insight and judgment about their illness and the need for treatment. Patients in the throes of a manic episode may refuse treatment because they enjoy the highs of mania. In addition, many patients complain that treatment interferes with their creativity or artistic abilities. During these times, it is especially important to include patients' families and friends in the educational process. Patients and their support network should be educated about the chronicity and recurring nature of bipolar disorder, treatment options, importance of treatment adherence, community resources, and the increased need for hospitalization due to relapse if maintenance therapy is discontinued. Lifestyle modifications also are important aspects of treatment. Maintaining a routine sleep habit, minimizing caffeine intake, exercising, and decreasing stress are all beneficial in maintaining an euthymic state.

Finally, clinicians should inform patients about available community resources (see Table 1-6). Many patients and families will benefit greatly from such groups. There are many local groups such as the National Alliance for the Mentally Ill, Internet-based support groups, or online chat rooms. Many groups are designed to facilitate discussion among patients about their thoughts and concerns about having an affective disorder, coping with familial stressors, and proceeding with their lives after diagnosis. For families, these groups provide important education about

psychiatric illnesses, suggestions on how to adjust to a family member's diagnosis, and tips to new members for working the health care system.

Conclusion

Both major depression and bipolar disorder treatment includes acute and maintenance treatment options. Although depressive and bipolar disorders often share similar types of symptoms, each requires highly individualized treatment. For example, patients with major depression are treated with antidepressants, whereas patients with bipolar disorder almost always require an antidepressant and a mood stabilizer. Adjunctive treatment with benzodiazepines and/or antipsychotic agents often is warranted. Because of fundamental differences in the pharmacological treatment of these two disorders, an accurate diagnosis is absolutely critical. Furthermore, within each disorder, diagnostic subtypes or symptom clusters may respond to one treatment more readily than another. For instance, in a depressed patient who is experiencing hypersomnia, an activating antidepressant as opposed to a sedating one would be more favorable.

Table 1-6. Patient and Clinician Resources

Patient	National Institute of Mental Health <i>http://www.nimh.nih.gov/publicat/index.cfm</i>
	National Alliance for the Mentally Ill <i>http://www.nami.org</i>
	Depression and Bipolar Support Alliance <i>http://www.dbsalliance.org/</i>
	American Psychiatric Association <i>http://www.psych.org</i>
Clinician	National Institute of Mental Health <i>http://www.nimh.nih.gov/HealthInformation/index.cfm</i> <i>http://www.nimh.nih.gov/researchfinding/index.cfm</i>
	American Psychiatric Association <i>http://www.psych.org</i>
	National Alliance for Research on Schizophrenia and Depression <i>http://www.narsad.org</i>
	The Stanley Medical Research Institute <i>http://www.stanleyresearch.org/</i>

Annotated Bibliography

1. Stahl SM. Basic psychopharmacology of antidepressants, Part 1: antidepressants have seven distinct mechanisms of action. *J Clin Psychiatry* 1998;59(suppl 4):5–14.

The author reviews the different mechanisms of action of the currently available antidepressant drugs. He discusses the monoamine hypothesis of depression and its relationship to the proposed mechanism of action of antidepressants. In addition, a brief explanation of the clinical applications of norepinephrine, serotonin, and dopamine and the pre- and postsynaptic receptor antagonists is provided. Therapeutic effects of these drugs, as well as adverse effects associated with each agent, are discussed. This article provides a general overview of antidepressant drug mechanisms of action in terms that are easy for the reader to understand. This article is a good introduction to antidepressant drugs.

2. Vaswani M, Linda FK, Ramesh S. Role of selective serotonin reuptake inhibitors in psychiatric disorders: a comprehensive review. *Prog Neuropsychopharmacol Biol Psychiatry* 2003;27:85–102.

This article is a general review of selective serotonin reuptake inhibitors (SSRIs) and their use in psychiatry. The authors describe why SSRIs were developed and how SSRIs are thought to exert their pharmacological effects. The pharmacokinetics of each SSRI is discussed in detail, including cytochrome P450 (CYP) drug interactions. The authors provide a brief evaluation of studies comparing SSRIs with tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and other newer antidepressants for treating depression. The authors also review the role of SSRIs in anxiety and eating disorders. Data concerning SSRI use in special populations are presented. Finally, the authors discuss adverse effects associated with SSRIs and provide information on interventions used to manage some of the adverse effects. This article has an extensive reference list, so it may be a good starting point when trying to find more in-depth information concerning the use of SSRIs.

3. Hirschfeld RM, Montgomery SA, Aguglia E, et al. Partial response and nonresponse to antidepressant therapy: current approaches and treatment options. *J Clin Psychiatry* 2002;63:826–37.

Many times patients' symptoms fail to respond to their initial antidepressant therapy. Clinicians are then left to decide what the next best option will be. Currently, few data exist to help clinicians make this decision. The authors of this article were involved in a roundtable discussion where they evaluated the current published literature and clinical experience to provide clinicians with evidence-based principles on managing patients whose symptoms fail their first-line agent. The authors describe rationale for switching therapy or using an augmentation or combination agent. They also present current literature supporting or disproving each of these interventions. The authors provide an algorithm with a step-wise approach to managing patients who have an inadequate response to an antidepressant drug. This article provides a great explanation of the current issues involving partial or nonresponse of symptoms to antidepressants. It also has an extensive list of references, so the reader is able to obtain additional information if desired.

4. American Psychiatric Association. Practice guidelines for the treatment of patients with bipolar disorder (revision). *Am J Psychiatry* 2002;159(4 suppl):1–50.

These are revised practice guidelines, which summarize data on the specific somatic and psychosocial interventions for bipolar disorder, published by the American Psychiatric Association. The guideline, developed under the auspices of the American Psychiatric Association Steering Committee on Practice Guidelines, was developed in the following manner: a comprehensive literature review and compilation of evidence tables, initial drafting by a working group of psychiatrists with clinical and research expertise, extensive draft review by various organizations and individuals, and approval at the American Psychiatric Association Assembly and Board of Trustees. The guidelines are divided into three parts: part A, treatment recommendations; part B, background information and review of available evidence; and part C, future research needs. Each part is subdivided into sections to aid the reader in retrieving desired information more readily. Treatment recommendations are based on the best available data and clinical consensus. Each treatment recommendation is coded with a level of endorsement representing the level of clinical confidence. For example, level I is a recommendation with substantial clinical confidence. Individual sections discuss the recommendations for an acute manic or mixed episode, rapid cycling, depressed episodes, and maintenance treatment.

5. Freeman MP, Stoll AL. Mood stabilizer combinations; a review of safety and efficacy. *Am J Psychiatry* 1998;155(1):12–21.

Combination mood stabilizer therapy often is used, especially in treating patients with refractory bipolar disorder. Unfortunately, there is a paucity of data regarding the efficacy and safety of these combinations. Mood stabilizer combination therapy places the patient at increased risk of developing side effects and toxicity. However, in certain cases, pharmacokinetic interactions between two agents can be beneficial. This article, published in 1998, reviews the existing literature on the efficacy and safety of mood stabilizers (i.e., lithium, valproate, and carbamazepine) and antipsychotic drugs, in combination with various anticonvulsants, calcium channel blockers, and benzodiazepines. The data are ranked in accordance with the number of published studies and study design. Despite more recent efficacy publications, the safety data presented are thorough and remain clinically relevant. The authors concluded that mood stabilizers used in conjunction with lithium represented the safety combinations.

SELF-ASSESSMENT QUESTIONS

Questions 1 and 2 pertain to the following case.

R.T. is 27-year-old woman who comes to the medical clinic for her initial visit. During the interview, she states that she has been feeling sad and cries “for no good reason.” Per her report, she has lost 12 pounds in the past 6 weeks but has not been purposefully dieting. She says that food is tasteless. Her symptoms typically are worse in the morning and improve slightly as the day goes on, but never really go away. R.T. states that she often feels like she is moving in slow motion. She has completely isolated herself from friends and rarely socializes any more. She has even stopped answering calls from friends or family. R.T. says that the symptoms have been present for about the past 7 months, and that they have gotten significantly worse in the past 2 months. This is the first time that R.T. has ever sought treatment for her symptoms.

1. Which one of the following is R.T.’s diagnosis?
 - A. Major depressive disorder (MDD) not otherwise specified.
 - B. Major depressive disorder with atypical features.
 - C. Major depressive disorder with melancholic features.
 - D. Major depression in partial remission.
2. Which one of the following is the best antidepressant drug choice for R.T.?
 - A. Sertraline.
 - B. Phenelzine.
 - C. Nefazodone.
 - D. Imipramine.
3. J.M. comes to the clinic for a follow-up appointment 1 week after initiating fluoxetine 20 mg and demands that her antidepressant be changed. She is upset that the pharmacy gave her a generic drug and is convinced that fluoxetine does not work. She denies any adverse

effects from fluoxetine. You reassure J.M. that her symptoms will respond in time and recommend which one of the following treatment options for her?

- A. Switch to bupropion.
 - B. Add on bupropion to “boost” the effects of the fluoxetine 20 mg.
 - C. Add a small dose of olanzapine to augment the fluoxetine 20 mg.
 - D. Continue the current drug regimen of fluoxetine 20 mg.
4. W.T. is a 45-year-old man who comes to your drug clinic for a follow-up appointment. Four months ago, W.T. was diagnosed with his first episode of MDD (moderate without psychotic features) and received a prescription for mirtazapine. His current dose of mirtazapine is 45 mg at bedtime. W.T. has been free of depressive symptoms for the past 3 weeks. Which one of the following represents how much longer W.T. should continue mirtazapine?
 - A. It can be discontinued today because he is symptom-free.
 - B. For 6–9 months, at which time an attempt can be made to taper W.T. off from drug.
 - C. Schedule an appointment in 8 weeks and if W.T. is still symptom-free, he can be tapered off the mirtazapine.
 - D. For W.T.’s lifetime.
 5. A 32-year-old woman presents to the emergency department with a fever of 102°F. She is tremulous, is having great difficulty sitting still, has a pulse rate of 110 beats/minute, and has hyperreflexia. When obtaining a history on the patient, you learn that she suffers from migraine headaches. Her last migraine headache had occurred earlier in the day and she had given herself a shot of sumatriptan (she cannot

- remember the dose) about 6 hours ago. You also discover that 2 days ago, the patient stopped taking fluoxetine 40 mg/day and was started on sustained-release bupropion 150 mg/day. Which one of the following is the patient most likely suffering from?
- Discontinuation syndrome from fluoxetine.
 - Allergic reaction to sustained-release bupropion.
 - Serotonin syndrome.
 - Hypertensive crisis.
- G.F. has been taking desipramine for about 6 months for depression and has had a positive response, but is now complaining of recurring symptoms of depression. Two months ago, his desipramine serum concentration at the current dose was 139 ng/L. Which one of the following actions is indicated for G.F. at this time?
 - Add paroxetine to increase the serum concentration of desipramine.
 - Add lithium to boost the effects of desipramine.
 - Switch to a new antidepressant.
 - Obtain a current desipramine serum concentration.
 - B.D. is a 63-year-old woman who came to your clinic complaining of feelings of sadness, low energy, inability to concentrate, difficulty falling asleep, and feelings of worthlessness for the past month. The psychiatrist determines that she is having a major depressive episode (MDE) of moderate severity. After discussing antidepressant treatment options with B.D., the decision is made to begin extended-release venlafaxine. Which one of the following should you monitor regularly?
 - Fasting blood glucose.
 - Serum concentrations of venlafaxine and O-desmethylvenlafaxine.
 - Blood pressure (BP).
 - Liver enzymes.
 - S.W. is a 37-year-old woman who has been treated with desipramine 150 mg/day for the past 4 months. Her depressive symptoms have been in remission for 4 weeks. A physician at another clinic recently initiated fluoxetine 20 mg/day as migraine prophylactic therapy for S.W. Which one of the following is the best way to manage S.W.'s depression?
 - Desipramine should be discontinued and fluoxetine used to treat her depression.
 - Her desipramine dose should be decreased by 50%.
 - There is minimal risk of serotonin syndrome.
 - Her desipramine dose should be increased by 25%.
 - Which one of the following drugs is most commonly associated with liver toxicity?
 - Mirtazapine.
 - Venlafaxine.
 - Paroxetine.
 - Nefazodone.
 - F.P., a 19-year-old woman, is at your general medical clinic for her annual check-up. You notice that she has been crying. When you ask her if she is okay, she proceeds to tell you that her childhood pet passed away 3 days ago and she has been quite upset about it. She has not been sleeping well and has not felt like eating. She also is having a difficult time studying for school because she is unable to stay focused. All of these symptoms were brought on by the death of her pet. She denies any suicidal thoughts at this time. She has never had a depressive episode before. She currently is only taking the birth control pill, Ortho Novum 1/35. Which one of the following is the best treatment option for F.P.?
 - Start mirtazapine 15 mg. This will help F.P.'s mood, as well as help her sleep and stimulate her appetite.
 - Suggest that F.P. take an over-the-counter antidepressant, such as St. John's wort to help with her mild depressive symptoms.
 - No pharmacological intervention is necessary. Follow-up with F.P. in 2 weeks to see if symptoms have remitted.
 - Start F.P. on a stimulant, such as methylphenidate, to help her stay focused on her studies.
 - L.N. is an 83-year-old man who is seen by his primary care physician and subsequently diagnosed with major depression. His past medical history includes hypertension, which is treated with clonidine, and chronic constipation. His blood pressure today is 147/91 mm Hg. Which one of the following is the best antidepressant choice for L.N.?
 - Venlafaxine.
 - Sertraline.
 - Paroxetine.
 - Desipramine.
 - R.J. is a 34-year-old man who comes to your clinic today for a follow-up appointment. Two months ago, R.J. was diagnosed with his second episode of depression and was started on escitalopram 10 mg/day. His initial Hamilton Rating Scale for Depression (HAM-D) score was 26. At week 4 of treatment, his HAM-D score was 18 (indicating moderate symptoms). The decision was made to increase escitalopram to 20 mg/day. Today (week 8 of treatment), R.J.'s HAM-D score is 12, and he comments that he still feels slightly depressed. Which one of the following is the best treatment option for R.J.?
 - Add lithium to the current dose of escitalopram.
 - Increase escitalopram to 30 mg to gain further benefit from the drug.
 - Make no changes in his pharmacotherapy because R.J. he has had a 50% reduction in symptoms.
 - Add nefazodone for more serotonergic activity.
 - H.B. is a 24-year-old woman who is experiencing a depressive episode. Ten weeks ago, H.B. was started on paroxetine 20 mg/day and was titrated up to her current dose of 50 mg/day. She has been taking

50 mg/day of paroxetine for 2 weeks with some response, but continues to have residual symptoms that are impairing her ability to function “normally.” She says that she still does not feel like her normal self. She continues to complain about her low energy level, trouble sleeping, and a decreased interest in the activities she used to enjoy. She has thoughts that life is not worth living, but has no active suicidal plan. The only adverse effect of paroxetine that she continues to complain about is anorgasmia. The only other drug that H.B. is taking is gabapentin for her seizure disorder. Which one of the following is the next best treatment step for H.B.?

- Taper off paroxetine and initiate sustained-release bupropion 150 mg.
- Add sustained-release bupropion 150 mg/day to paroxetine 50 mg.
- Taper off paroxetine and start mirtazapine 30 mg.
- Increase paroxetine to 60 mg.

Questions 14 and 15 pertain to the following case.

R.K. is a 27-year-old who presents to your medical clinic for an initial appointment. She recently has been transferred from another state. She reports a history of two MDEs. She began experiencing moderate depressive symptoms about 4 weeks ago. She is still depressed and currently is being treated with sertraline 100 mg/day. During the interview, she reports a 2-week period last year when her husband and friends commented on her talkativeness and increased energy, feeling “fantastic”, and getting by on 4–5 hours of sleep per night. In addition, she reports that these mood symptoms occurred when she was not taking her antidepressant. Currently, no manic symptoms are noted.

- Which one of the following is the best diagnosis for R.K.?
 - Bipolar I disorder.
 - Bipolar II disorder.
 - Cyclothymia.
 - Substance-induced manic disorder.
- Which one of the following is the best treatment for R.K.?
 - Continue sertraline monotherapy.
 - Continue sertraline and add gabapentin.
 - Discontinue sertraline and initiate carbamazepine.
 - Add lithium to the ongoing sertraline therapy.
- Which one of the following items should be discussed with a patient before lithium initiation?
 - Lithium’s effect on liver function tests.
 - Potential neural tube defects associated with lithium.
 - Importance of avoiding dehydration, which may lead to lithium toxicity.
 - Potential thrombocytopenia associated with lithium.

17. K.G. is a 26-year-old woman who presents to your drug management clinic for a routine appointment. She was diagnosed with bipolar disorder 1 year ago. Her current drug regimen is divalproex 1500 mg/day, which provides a serum concentration of 75 mcg/ml. K.G. currently is euthymic. Which one of the following concerns regarding K.G.’s drug regimen and routine follow-up might you have?

- K.G. needs to have a 1-year follow-up for an electrocardiogram.
- K.G. should be taking supplemental folate.
- K.G.’s divalproex serum concentration is too low; her dose should be increased to achieve a serum concentration of 100 mcg/ml.
- K.G. should be routinely monitored for hypothyroidism secondary to divalproex.

Questions 18 and 19 pertain to the following case.

A.L. is a 33-year-old man who presents to the emergency department with racing thoughts, pressured speech, and grandiosity. Suspecting drug nonadherence, you draw a serum valproic acid concentration that is reported to be 83 mcg/ml. The psychiatry resident decides to increase A.L.’s divalproex dose by 500 mg and sends him home with a follow-up clinic and laboratory appointment in 5 days. At his follow-up appointment, A.L. exhibits the same symptoms plus a noticeable tremor. His reported valproic acid serum concentration is now 89 mcg/ml.

- Which one of the following is the best interpretation of A.L.’s laboratory work?
 - Valproic acid exhibits linear pharmacokinetics and the dose must be further increased to achieve a higher plasma concentration.
 - The laboratory specimen must have been drawn at a time not consistent with a 8-hour trough.
 - A.L. has developed a divalproex allergy, resulting in his new-onset tremor.
 - A.L. is exhibiting valproic acid protein-binding saturation.
- It is decided that a second mood stabilizer will be added to A.L.’s regimen. Which one of the following mood stabilizer combinations is the most effective and least likely to result in a pharmacokinetic interaction?
 - Divalproex plus lamotrigine.
 - Divalproex plus gabapentin.
 - Divalproex plus lithium.
 - Divalproex plus carbamazepine.
- Which one of the following adverse events is most commonly associated with valproic acid?
 - Extrapyramidal symptoms.
 - Diplopia.
 - Thrombocytopenia.
 - Nephrogenic diabetes insipidus.

21. Which one of the following mood stabilizer combinations is most likely to increase a patient's risk of Stevens-Johnson syndrome?
- Carbamazepine plus lithium.
 - Lamotrigine plus lithium.
 - Carbamazepine plus gabapentin.
 - Divalproex plus lamotrigine.

Questions 22 and 23 pertain to the following case.

R.W. is a 45-year-old man who has a 20-year history of bipolar disorder with at least six psychiatric admissions. He has been maintained for 8 months on lithium 900 mg/day; the most recent serum lithium concentration was 0.7 mEq/L. During this 8-month period, he has remained symptom-free. He calls the drug management clinic complaining of new-onset gastrointestinal symptoms, shaky hands, and weakness. His symptoms started about 7 days ago. You ask him to go to the laboratory for a lithium serum concentration and then proceed to the clinic. The lithium serum concentration, which was drawn 10 hours after his last dose, is reported to be 1.3 mEq/L.

22. In the clinic, R.W. says that he recently started a new drug to treat his high BP. Which one of the following antihypertensive drugs, is the most likely cause of R.W.'s sudden increase in lithium serum concentration?
- Bumetanide.
 - Nifedipine.
 - Propranolol.
 - Hydrochlorothiazide.
23. Given that R.W.'s hypertension is well controlled, he will remain on his current antihypertensive drug. Which one of the following is the best intervention for R.W. at this time?
- Decrease the lithium to 600 mg/day.
 - Hold the lithium dose until symptoms resolve and then resume lithium at 900 mg/day.
 - Hold the lithium dose until symptoms resolve and then resume lithium at 600 mg/day.
 - Discontinue the lithium and wait to see if a mood stabilizer is still required.
24. B.J. is a 27-year-old man who is treated with carbamazepine for bipolar I disorder. He is seen by his primary care physician and complains of some upper respiratory symptoms, including yellow-green discharge, fever (102.4°F), and a productive cough for the past 7 days. His tuberculin skin test is negative and his white blood cell count is 11,200/mm³ with 82% neutrophils. Which one of the following antibiotics is the best choice for B.J.?
- Doxycycline.
 - Clarithromycin.
 - Amoxicillin-clavulanate.
 - Erythromycin.
25. C.Y. is a 23-year-old woman who was admitted to the psychiatric unit 6 days ago for an acute manic episode.

She presented with euphoria, extremely pressured speech, grandiose and paranoid delusions, hypersexuality, and increased energy. She was started on lithium 900 mg/day and discharged 5 days after admission. At the time of discharge, her lithium serum concentration was 0.6 mEq/L. Two weeks after her admission, her mood is slightly elevated, speech is verbose at times but conversation is not difficult, and she denies an increase in energy. She continues to be grandiose. She and her family state that she is adherent with her drugs. Which one of the following is the best treatment option for C.Y. at this time?

- Add an antipsychotic agent because she remains delusional.
 - Add valproic acid as a second mood stabilizer.
 - Increase lithium to 1200 mg/day.
 - Augment lithium with lamotrigine 50 mg/day.
26. For a patient who presents to the emergency department with manic symptoms, which one of the following laboratory tests should be ordered as part of the routine diagnostic assessment to rule out general medical condition causes?
- Electrocardiogram.
 - Urine toxicology.
 - Complete blood cell count.
 - Thyroid function tests.