Pharmacotherapy of Mood Disorders

Michael E. Thase[1] and Timothey Denko[2]

[1]University of Pennsylvania School of Medicine and Veterans Administration Medical Center, Philadelphia, Pennsylvania 19104; [2]Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania 15213;
email: thase@mail.med.upenn.edu, denkotc@upmc.edu

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Abstract

The mood disorders—primarily major depressive disorder and bipolar affective disorder—constitute one of the world's greatest public health problems and are associated with significant reductions in productivity, health, and longevity. In addition, people who suffer from these common illnesses, along with their families and loved ones, experience an incalculable toll on quality of life. Dating to the introduction of the first effective therapies for mood disorders in the late 1950s and 1960s, various types of pharmacotherapy have become a mainstay for the management of mood disorders, particularly more severe, chronic, and recurrent forms of depression and most forms of bipolar disorder. This review examines recent developments in the pharmacotherapy of both forms of mood disorder, comparing the newer antidepressants such as the selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors with their predecessors (the monoamine oxidase inhibitors and tricyclic antidepressants) and likewise comparing the older standard for management of bipolar disorder, lithium, with newer classes of medications, such as a selected group of anticonvulsants and the atypical antipsychotics. Although these newer classes of medications have generally improved upon the earlier treatments in terms of better tolerability and safety, there are no universally effective pharmacologic treatments for mood disorders, and careful medical management of these medications is still warranted.

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INTRODUCTION

The mood disorders diagnostic category subsumes the various syndromal and subsyndromal forms of depression and bipolar affective disorder (formerly known as manic depression). These conditions are considered to be among the world's greatest public health problems (Murray & Lopez 1996), in part because of their ubiquity (lifetime prevalence rates are up to 10% of men and 20% of women) (Kessler et al. 2007) and in part because they tend to be recurrent, chronic, and potentially disabling illnesses. Indeed, depression is the single greatest cause of absenteeism from the workplace in the United States (Kessler et al. 2006). Both depression and bipolar disorder reduce longevity through suicide and by worsening the prognosis of common general medical illnesses such as heart disease and diabetes (Kupfer 2005, Laursen et al. 2007, Prince et al. 2007). Across the decades, a vast majority of mood disorders research has focused on major depressive disorder (MDD)—owing to the fact that the population prevalence of depression is at least 10 times greater than that of mania as well as to the aftereffects of several decades of therapeutic complacency following the discovery of the remarkable efficacy of lithium salts. However, despite the continued importance of this inexpensive and elementally simple medication (Baldessarini et al. 2002), over the past decade the limitations of lithium have been widely recognized and there has been increasing emphasis on development of novel therapies for bipolar affective disorder, both for acute treatment of mania and subsequent prophylaxis. Research on the treatment of the bipolar depression historically has been even more overlooked, largely because of the misguided belief that findings from studies of so-called unipolar depression were directly applicable to bipolar affective disorder. This oversight is beginning to be corrected, with the recognition that standard antidepressant therapies lack robust efficacy for bipolar depression. This review updates and builds upon a decade-old review (Thase & Kupfer 1996) and highlights more recent research on the pharmacotherapy of mood disorders.

PHARMACOTHERAPY OF DEPRESSION

Illness Course and Phases of Treatment

Figure 1 illustrates the prototypic course of an episode of MDD and the corresponding phases of treatment (Kupfer 1991). One implication of this schematic

is that for every response, remission, or recovery, there is also the prospect of relapse or recurrence. Indeed, whereas it was once thought that only about 50% of people suffering from depression would experience additional episodes, careful prospective follow-up across decades indicates that more than 75% of those who experience a first episode of depression will develop a recurrent illness (Frank & Thase 1999, Keller & Boland 1998, Kessing et al. 2004). Not only do the first few depressive episodes seem to set in motion a lifetime of recurrent depressions (Kendler et al. 2001, Kessing et al. 2004), but they also increase the likelihood that the depressive episodes will be longer and more severe, with a corresponding reduction in well time (Frank & Thase 1999). Across multiple depressive episodes, there is also a progressive decrease in the strength of the well-known temporal relationship between life stress and illness onset, suggesting that over time it will take less and less stress to provoke a new episode (Kendler et al. 2001). In other words, even for people with little inherited vulnerability, recurrent depressive episodes eventually begin to happen "out of the blue." As discussed below, accurately gauging the risk of recurrent illness has important implications for treatment planning, particularly for informing decisions about the need for—and duration of—preventive treatment (Thase 2006c).

Subtypes of Depression

After weighing the risk of recurrence in depression, chronicity is arguably the next most important illness-course variable to take into account in treatment planning. Chronicity is defined in the DSM nomenclature as two years of unremitting symptoms, whether at the major, full syndromal level or at the minor, subsyndromal level (Am. Psychiatr. Assoc. 2000b). Chronic forms of depression are quite prevalent among people seeking treatment (typically prevalence rates range between 25% and 50% of depressive disorders) and are associated with greater levels of illness burden, functional impairment, and comorbidity when compared with more acute depressive episodes (Keller & Boland 1998). Moreover, because spontaneous remissions typically occur during the first 12 months of a depressive episode, in comparison with people with acute depression, individuals with chronic forms of depression have—by definition—unremitting illnesses that are unlikely to improve with the passage of time or as a result of placebo-expectancy factors. For these reasons and perhaps more, chronicity has ominous prognositic implications, which should be taken into account during treatment planning with respect to the use of psychotherapy/pharmacotherapy combinations and longer courses of therapy (Hollon et al. 2005).

Three common clinical pathways to chronicity exist: chronicity may begin in childhood or adolescence as dysthymic disorder (i.e., a persistent albeit minor or low-grade depressive episode), it can begin in adult life as a consequence of untreated, poorly treated, or treatment-resistant major depressive episodes, or it can develop when an acute depressive episode does not fully remit (Keller 2003). In the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, text revision (DSM-IV-TR; Am. Psychiatr. Assoc. 2000a), these three patterns of chronicity have different names: a major depressive episode superimposed on antecedent dysthymia (also known as double depression), chronic major depression (i.e., a major depressive episode of at least two years' duration), and recurrent major depression with incomplete interepisode recovery. Descriptive studies have found that these variations of chronic depression are much more similar than different, and Kupfer's schema works reasonably well to describe the treated course of these varieties of chronic depression (Angst & Wicki 1991; McCullough et al. 2000, 2003).

Other subtypes of MDD that are relevant to treatment planning, which are referred to as episode specifiers in DSM-IV-TR, include "with melancholic features," "with

atypical features," and "with seasonal pattern" (Am. Psychiatr. Assoc. 2000a). The criteria for melancholia describe a more severe illness characterized by the more classical or typical features of depression in later life, including anhedonia, psychomotor retardation, diurnal mood variation (mood worse in morning), and early morning awakening. The criteria for melancholia are intended to describe a form of depression that is relatively nonresponsive to nonspecific supportive models of care and psychotherapy and thus may be more likely to "require" antidepressants or electroconvulsive therapy (Am. Psychiatr. Assoc. 2000a); whether this goal is met depends on how strictly the criteria are applied, and many patients "with melancholic features" are responsive to focused forms of psychotherapy (Thase & Friedman 1999). Atypical depression, by contrast, was first described about 50 years ago, in part because the younger depressed patients—who are unlikely to experience melancholic features—often report the so-called reverse neurovegetative profile (i.e., overeating, weight gain, and oversleeping) (Thase 2007). These depressions seemed particularly atypical to the early psychopharmacologists because they tended to be less responsive to the stronger treatments of the era [tricyclic antidepressants (TCAs) and electroconvulsive therapy] and preferentially responsive to the monoamine oxidase inhibitors (MAOIs) (Thase et al. 1995). The term "with seasonal pattern" primarily refers to the tendency of a subset of patients with recurrent depression to become ill each fall or winter. This pattern of depression, also known as seasonal affective disorder, may be preferentially responsive to bright white light either alone or in combination with conventional treatments (Am. Psychiatr. Assoc. 2000b, Golden et al. 2005).

A fourth classical subtype, psychotic depression, is not considered as an episode specifier in DSM-IV-TR, but rather is classified as the highest level of severity on the ordinal severity rating. Recognition of psychotic features has important treatment implications because depressions characterized by delusions and hallucinations, which may account for up to 10% of people seeking treatment for depression in psychiatric settings, often require treatment with an antipsychotic medication in addition to an antidepressant (Am. Psychiatr. Assoc. 2000b).

The final subtype of depression with important implications for treatment selection pertains to individuals who have experienced prior episodes of mania or hypomania. It is of course the history of mania or hypomania that defines the diagnosis of bipolar affective disorder, and to prevent iatrogenic complications, individuals with bipolar depression generally should not be prescribed antidepressants unless also they are also treated with a mood stabilizer (i.e., lithium, valproate, carbamazapine, lamotrigine, or one of the atypical antipsychotic medications) (Am. Psychiatr. Assoc. 2002, Thase 2005).

Although uncovering a past history of mania (which, by definition, requires psychosis, hospitalization, or gross functional impairment) is usually not too difficult, it is more challenging to differentiate individuals with histories of only hypomanic episodes (i.e., a diagnosis of bipolar II disorder) or even shorter-lived periods of hypomanic symptoms from the remainder of individuals with recurrent MDD. People seldom seek treatment for hypomania and, more often than not, perceive the upswings in mood to be a welcome relief to the more longstanding depressive episodes. In fact, in one longitudinal study, individuals with bipolar II disorder had depressive symptoms for approximately half of their adult lives and were depressed about 20 days for every one day of hypomania. Moreover, antidepressants pose a heightened risk of adverse behavioral outcomes when prescribed concomitantly with a mood stabilizer, including treatment-emergent affective switches and rapid cycling resulting from an on-again, off-again pattern of medication

prescription (Thase 2005). Treatment of depressions within the bipolar spectrum of mood disorders is discussed in more detail in the Pharmacotherapy of Bipolar Disorder section.

Phases of Treatment

For individuals seeking treatment for a nonpsychotic, nonbipolar depressive episode, which by far is the most common presentation in ambulatory clinical settings, the initial choice of therapy largely depends on the discipline of the provider and patient preferences: Psychologists, social workers, and other nonmedical professionals are more likely to recommend psychotherapy or counseling before considering medication, primary care physicians are more likely to prescribe antidepressant medication instead of referring out for psychotherapy or counseling, and psychiatrists usually will prescribe medication either alone or in combination with psychotherapy. The delivery of pharmacotherapy—like some models of focused psychotherapy—can be thought of in terms of three strategic phases.

Acute-phase pharmacotherapy describes the period from the start of treatment until an acceptable response has been obtained. This may only take a few weeks or could extend for months. Medication management visits typically last 15 to 30 minutes and usually occur less frequently than psychotherapy (e.g., every other week or monthly until the desired response has been achieved). First-line antidepressants are usually started on the minimum therapeutic dose, and clinical judgment—informed by patient reports of side effects and past treatment history—is used to determine the speed of upward titration toward maximally tolerated therapeutic doses. Medication management visits also should include education about both the disorder and its treatment. Important points to educate patients about include adherence (although it is almost human nature to miss doses of medication, better adherence is reliably associated with a greater chance of a successful course of therapy), side effects (information about the more common side effects as well as the information that side effects will often precede therapeutic effects, can dissipate over time, and usually can be managed successfully), and realistic expectations of benefit (i.e., that the initial choice of antidepressant typically has a 50% to 60% chance of working, that it may take up to eight weeks to see full effects, and that there are many alternate medications if the first choice is ineffective or poorly tolerated).

The goals of acute-phase pharmacotherapy are readily accomplished if the doctor and patient have the good fortune for the first chosen treatment to be both effective and well tolerated. As discussed below, there is about a 50-50 chance that the first treatment will work. **Figure 1** illustrates the two "grades" of improvement used in both research and practice: response and remission. Response is the more inclusive outcome and is defined in research studies by a clinically significant reduction in symptom intensity [i.e., a >50% decrease in Beck Depression Inventory (BDI) scores] (Frank et al. 1991). Conceptually, a response should represent a level of improvement such that the person no longer meets syndromal criteria for a major depressive episode (i.e., the illness should not be "active"). The more exacting outcome, remission, is described using a term borrowed from oncology. Unlike malignancy, however, it is not yet possible to monitor illness activity at the pathophysiological level, so symptom levels must serve as the proxy for assessment. Thus, in this context, remission denotes a virtual absence of symptoms, and the person whose depressive episode has remitted should have no more symptoms than someone who has never been ill (Frank et al. 1991, Rush et al. 2006a). Remission should also lead to restoration of psychosocial functioning, at least to the individual's premorbid level, although the time course of

functional improvement typically lags behind symptomatic change (Mintz et al. 1992).

Remission is increasingly specified as the goal of the acute phase of therapy because, when compared with response, it is associated with a lower risk of relapse (Paykel et al. 1995, 1999; Riso et al. 1997; Thase et al. 1992), better psychosocial functioning (Miller et al. 1998), and a greater likelihood of sustained recovery (Judd et al. 1998). In fact, response without remission is a worrisome outcome, and the very benefits accrued by treatment of depression can be rapidly undone by relapse or persistent vocational or interpersonal difficulties. Although a wait-and-see approach is sometimes taken (a significant minority of incompletely remitted people will eventually remit over four to six months without changing treatment) (Kocsis et al. 2003, Koran et al. 2001), a case can be made for more vigorous targeting and focused treatment of residual symptoms (Paykel et al. 1999).

To facilitate recognition of such residual symptoms and improve monitoring of treatment response, a strategy referred to as measurement-based care has been recommended (Trivedi et al. 2006). At the heart of this strategy are relatively frequent follow-up visits and conscientious documentation of clinical outcome using a reliable, user-friendly assessment tool. Because the clinician-administered assessments such as the Hamilton Rating Scale for Depression (Hamilton 1960) and the Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery & Asberg 1979) used in research tend to be rather time consuming, self-report evaluations that have been cross validated against these measures are recommended for use in busy practices. In addition to the venerable BDI, the self-report version of Quick Inventory of Depression Symptomatology (QIDS-SR), which was used in the large Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study funded by the National Institute for Mental Health (NIMH) (Trivedi et al. 2006), is well suited for this purpose. The two major advantages of the QIDS-SR compared with the BDI are that it surveys the full range of symptoms for a DSM-IV-TR diagnosis of MDD and that it is available in the public domain, meaning that it can be used and administered free of charge.

The terms "relapse" and "recurrence," which are used almost interchangeably, describe a significant, syndromal-level worsening of depression after a response, remission, or recovery. In this review we follow the convention originally proposed by Frank and colleagues (Frank et al. 1991), namely that an exacerbation prior to recovery is called a relapse and one following recovery is called a recurrence. The implicit conceptual distinction between relapse and recurrence is that the former is the re-emergence of the index episode and the latter represents an entirely new episode of illness.

Following response or remission, the second or continuation phase of therapy begins. It is now the standard of practice for all responders to antidepressant medications to receive at least six months of continuation-phase therapy (Am. Psychiatr. Assoc. 2000b, Bauer et al. 2002). A meta-analysis of a large number of studies of continuation-phase pharmacotherapy documented that discontinuing the antidepressant during the first six to nine months following remission essentially doubled the chances of relapse (Geddes et al. 2003). The goals of continuation-phase therapy are to prevent relapse (see below) and to help the recovering depressed person achieve and/or maintain a full remission. The term "recovery" is used to describe remissions that are stable and sustained. In DSM-IV-TR, the specified duration of remission is two months (Am. Psychiatr. Assoc. 2000a); a more recent expert panel recommends longer durations of sustained remission before declaring that the person has recovered (Rush et al. 2006a). Normally, the continuation phase of treatment lasts six to nine months, during which time visits become less frequent and ideally medication dosages are constant. Thereafter, those who have recovered fully and who are judged

to be at low risk for recurrent episodes may be withdrawn from pharmacotherapy.

A third, preventive or maintenance phase of treatment is typically recommended for those judged to be at high risk for recurrent depression. The best indicator of recurrence risk is number of prior episodes, with three lifetime episodes or two episodes within the previous five years considered to identify those at greater risk (Thase 2006c). Generally, visits reduce in frequency to quarterly, biannually, or eventually annually, and the dose of medication is held constant unless there have been late-emerging side effects, such as weight gain or previously unreported sexual dysfunction. In such cases, dose reduction may be helpful, but this intervention does reduce the efficacy for preventing recurrent episodes with both the TCAs (Frank et al. 1993, Reynolds et al. 1999) and at least some newer medications (Franchini et al. 2000, Wilson et al. 2003). The maintenance phase of pharmacotherapy usually does not have a finite endpoint: There is no better proven means to reduce ongoing vulnerability to recurrent depression than an indefinite—and possibly lifelong—course of maintenance-phase pharmacotherapy, at least until treatments with more curative effects are identified. In fact, the risk of recurrence following withdrawal of antidepressant medication after one (Keller et al. 2007) or three (Kupfer et al. 1992) years of successful maintenance-phase therapy appears as great as after only six to nine months of continuation-phase therapy (Frank et al. 1990, Kocsis et al. 2007, Reynolds et al. 1999). In practice, the benefits and risks/costs of ongoing pharmacotherapy can be reviewed at periodic medication-monitoring visits, which typically take place yearly or twice a year (Thase 2006c).

CLASSES OF ANTIDEPRESSANTS

Antidepressant medications have established efficacy across the full spectrum of depressive disorders, including milder, acute major depressive episodes and dysthymic disorder as well as more prototypic episodes of melancholia (Am. Psychiatr. Assoc. 2000b; Bauer et al. 2002, 2007; Thase & Kupfer 1996). Although antidepressants were once mostly prescribed by psychiatrists, changes in health care delivery and the widespread availability of safer classes of antidepressant medications have resulted in a large increase in the number of depressed people receiving treatment from primary care providers (Bauer et al. 2007, Depression Guideline Panel 1993). In fact, primary care physicians in the United States now write about twice the total number antidepressant prescriptions as psychiatrists.

Tables 1, **2**, and **3** summarize the major classes of antidepressants, including three modern classes—the selective serotonin reuptake inhibitors (SSRIs), the serotonin and norepinephrine reuptake inhibitors (SNRIs), and the norepinephrine-dopamine reuptake inhibitor (NDRI) bupropion—as well as the standards from the first generation of psychopharmacology, the TCAs and MAOIs. With the exception of the TCAs, which were named after the three-ring chemical structure of the first member of the family to be synthesized (imipramine), the class names reflect the predominant action on monoamine neurotransmitter systems. If reclassified in terms of mechanism of action, most of the tricyclics would be called norepinephrine reuptake

Table 1 Commonly prescribed antidepressants: selective seretonin reuptake inhibitors

Generic name	Brand name	Usual dose (mg/day)	Prominent side effects
Citalopram	Celexa	20–60	Nausea, diarrhea, insomnia, tremor, sexual dysfunction, agitation/restlessness, and daytime sedation
Escitalopram	Lexapro	10–20	
Fluoxetine	Prozac	20–60	
Fluvoxamine	Luvox	100–300	
Paroxetine	Paxil	20–50	
Sertraline	Zoloft	50–100	

Table 2 Other modern antidepressants: serotonin and norepinephrine reuptake inhibitors, bupropion, and other compounds

Class	Brand name	Usual dose (mg/day)	Prominent side effects
Mixed reuptake inhibitors			
Bupropion (DA, NE)	Wellbutrin (available in immediate, sustained, and extended-release formulations)	300–450	Nausea, vomiting, insomnia, headaches, seizures
Venlafaxine (5-HT, NE)	Effexor (available in immediate and extended-release formulations)	7–225	Nausea, diarrhea, nervousness, increased sweating, dry mouth, muscle jerks, and sexual dysfunction; less commonly: vomiting, insomnia or daytime drowsiness, headaches, tremor, and increased blood pressure
Duloxetine	Celexa	60–80	Nausea, diarrhea, vomiting, nervousness, increased sweating, dry mouth, headaches, insomnia or daytime drowsiness, sexual dysfunction, tremor, and elevated liver enzymes
5-HT modulators			
Nefazodone	Serzone	30–600	Sedation, perceptual distortions, rare risk of liver failure
Trazodone	Desyrel	75–300	Orthostatic hypotension, sedation, priapism
NE and 5-HT modulator			
Mirtazapine	Remeron	15–45	Weight gain, daytime drowsiness

5-HT, serotonin; DA, dopamine; NE, norepinephrine.

inhibitors (NRIs), with clomipramine considered an SNRI.

A handful of other antidepressant medications exist that have little or no effect on monoamine reuptake and do not inhibit the enzyme MAO, including trazodone, nefazodone, mirtazapine, and agomelatine, which will soon be released in Europe. These medications affect central nervous system neurotransmission by inhibiting various pre- and postsynaptic norepinephrine and serotonin receptors (see **Table 3**).

Whereas early theories about the biology of depression posited that antidepressants corrected "deficits" in synaptic levels of monoamines (norepinephrine, serotonin, and—to a lesser extent—dopamine), contemporary models emphasize slower-emerging effects on neural circuits and gene activity (Delgado 2004, Duman et al. 1997, Thase et al. 2002). This shift reflects both clinical reality (i.e., whereas the synaptic effects of antidepressants are apparent within hours or at most a few days, therapeutic effects take weeks or even months to fully develop) and increasing knowledge about the complexity of regulation of central nervous system activity in both normal and psychopathological states. From this perspective, the monoamines merely contribute to disturbances of the processes that modulate expression of emotion and affect, psychomotor behavior, neurovegetative function, and adaption to stress (Duman & Monteggia 2006, Tardito et al. 2006).

Although they are no longer prominent in etiologic theories of depression, it is certain that the monoamines play a vital role

Table 3 Less-commonly prescribed antidepressants: monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs)

Class	Brand name	Usual dose (mg/day)	Prominent side effects[a]
MAOIs			Dry mouth, constipation, nausea, nervousness, difficulty sleeping or daytime drowsiness, tremor (shakiness), blurred vision, increased sweating, fatigue, and muscle jerks (neurologic myoclonus). Less commonly: headaches, urinary retention, appetite change with weight gain or loss, memory problems, and sexual dysfunction. Especially problematic: orthostatic hypotension (sudden drop in blood pressure upon standing that causes a person to feel dizzy or faint) and hypertensive crisis (potentially life-threatening increase in blood pressure following ingestion of certain foods or medications)
Irreversible			
Isocarboxazid	Marplan	15–30	
Phenelzine	Nardil	45–90	
Tranylcypromine	Parnate	30–60	
Reversible (Type A)			
Moclobemide	Not approved for use in the United States	300–600	
Other			
Seligiline TDS	EMSAM	6–12 (patch)	Skin irritation, insomnia. Dietary restritictions apply at doses above 6 mg
TCAs			Anticholinergic side effects (dry mouth; constipation; difficulty urinating; blurred vision; memory impairment; and confusion). Less commonly: difficulty sleeping; headaches; tremor (shakiness); appetite change with weight gain. Especially problematic: orthostatic hypotension (see MAOIs) and cardiac arrhythmias for people with heart problems (can be lethal in overdose for anyone)
Tertiary amines[b]			
Amitriptyline	Elavil	100–300	
Clomipramine	Anafranil	100–250	
Doxepin	Sinequan	100–300	
Imipramine	Tofranil	100–300	
Trimipramine	Surmontil	100–300	
Secondary amines[b]			
Desipramine	Norpramin	100–300	
Nortriptyline	Aventyl	50–200	
Protriptyline	Vivactil	15–60	
Tetracyclics[b]			
Amoxapine	Ascendin	100–400	
Maprotiline	Ludiomil	100–225	

[a]For MAOIs, TCAs, and selective seretonin reuptake inhibitors, side effects for the entire class are shown; for the other antidepressants, side effects for each agent are shown separately.

[b]Tertiary amines, secondary amines, and tetracyclics are structurally related compounds, which collectively can be grouped together as tricyclics.

in initiating the cellular process that mediates antidepressant activity, and the therapeutic effects of antidepressants can be rapidly reversed by experimental manipulations that deplete central nervous system levels of serotonin or norepinephrine (Delgado 2004). Importantly, antidepressants that affect norepinephrine and/or serotonin appear to have both common and specific effects on neuronal processes. On the one hand, both SSRIs and NRIs dampen increased limbic blood flow and metabolic activity and suppress increased phasic rapid eye movement sleep, which are linked to dysphoric affective arousal in depression (Thase et al. 2002). Likewise, both types of antidepressants have been shown in animal models to counteract or reverse the effects of stress, including increasing neuronal synthesis of brain-derived neurotrophic factor (BDNF) and decreasing synthesis of corticotrophin-releasing factor (Duman & Monteggia 2006, Tardito et al. 2006). On the other hand, dietary depletion of tryptophan (the essential amino acid precursor of serotonin) is more likely to exacerbate depressive symptoms in recovering

patients treated with SSRIs, and pharmacologic inhibition of norepinephrine synthesis (using the "false" neurotransmitter alpha methyl-paratyrosine) is more likely to provoke depressive symptoms in recovering patients taking NRIs (Delgado 2004). Monoamine-depletion interventions, by contrast, do not have mood-lowering effects among recovering depressed people treated with placebo, cognitive therapy, or bright light (Thase et al. 2002). It is not yet clear if antidepressants that directly affect both noradrenergic and serotoninergic neurotransmission might actually have stronger or more durable effects because of the capacitiy to modify both systems directly.

No new classes of antidepressants have been introduced in the United States in the past decade, with the only new medications—escitalopram (an SSRI), duloxetine and desvenlafaxine (SNRIs), and seligiline transdermal system (an MAOI)—representing extensions of established classes. A "pause" in the commercial marketplace after the introduction of such a large number of new antidepressants during the past two decades is not such a bad thing, for it allows clinical research to be systematically reviewed and integrated and permits some reflection on the apparent strengths and limitations of both individual medications and classes of antidepressants. In this regard, the state of the field is not unlike that of the early 1980s, at which time the merits and limitations of the TCAs and MAOIs could be accurately gauged. Nevertheless, it is also a fact that the field has reached a point of diminishing returns with respect to efforts to develop "better" or more selective reuptake inhibitors. Research and development programs are under way to develop safe medications with truly novel mechanisms of action (e.g., drugs that directly antagonize corticotrophin-releasing hormone activity or modulate glutamate neurotransmission), but—as the saga of the failed neurokinan-1 antagonist aprepitant illustrates (Keller et al. 2006)—a clear theoretical rationale and strong preclinical data do not guarantee an effective antidepressant in the clinic. Whether agomelatine, the novel melatonin receptor agonist and serotonin 2 receptor antagonist that is next in line, will have a better fate is still in doubt.

The clinical pharmacology of the major classes of antidepressants now used in the United States is briefly reviewed below.

Selective Serotonin Reuptake Inhibitors

The SSRIs are now almost universally viewed as the first line of antidepressant pharmacotherapy and are widely used throughout the industrialized world (Am. Psychiatr. Assoc. 2000b; Bauer et al. 2002, 2007; Olfson et al. 2002). Although it was not uncommon in the mid-1990s for contrarians to opine that the success of the SSRIs was primarily the result of pharmaceutical marketing, as we now approach the twentieth anniversary of the introduction of fluoxetine it can be stated unequivocally that the SSRIs replaced the TCAs for four very good reasons: (*a*) They usually can be started at a therapeutic dose and require fewer titrations and, as such, are easier to prescribe, (*b*) they have fewer "nuisance" side effects, (*c*) they are profoundly safer in overdose, and (*d*) they are comparably effective, at least with respect to treatment of depressed outpatients (Am. Psychiatr. Assoc. 2000b, Bauer et al. 2007, Mulrow et al. 1999, Thase & Kupfer 1996). To place difference in lethality in overdose within context, the Fatal Toxicity Index (i.e., the number of deaths attributable to overdose per million prescriptions) of the SSRIs is between one-tenth and one-thirtieth that of the TCAs (Buckley & McManus 2002).

Beyond these considerable advantages, the SSRIs also possess a broad spectrum of therapeutic activity for a range of conditions on the conceptual and clinical boundary of depression, with one or more of the SSRIs approved by the U.S. Food and Drug Administration (FDA) for treatment of various DSM-IV-TR anxiety disorders (panic

disorder, generalized anxiety disorder, social anxiety disorder, obsessive-compulsive disorder, and posttraumatic stress disorder), premenstrual dysphoric disorder, and bulimia nervosa. For many of these conditions, the SSRIs are considered the pharmacotherapy of first choice. The only significant factor that formerly limited use of the SSRIs—cost—has essentially disappeared as all but one member of this class (escitalopram) have lost patent exclusivity and are now available in generic formulations.

Five SSRIs have received the approval of the FDA for the treatment of depression: fluoxetine, sertraline, paroxetine, citalopram, and escitalopram (see **Table 1**). The sixth SSRI, fluvoxamine, is widely used as an antidepressant in some European countries and Japan but is only approved for use in the United States for treatment of obsessive-compulsive disorder. These drugs are grouped together because they all potently inhibit neuronal uptake of serotonin and—in comparison with the TCAs—are selective to the extent that they do not have strong effects on acetylcholine, histamine, or alpha- and beta-adrenergic receptors. However, with one notable exception (the drug citalopram is actually a mixture—or racemate—of two different "mirror image" molecules—or stereoisomers—referred to as the S-citalopram and R-citalopram; all of the therapeutic activity is conveyed by the S stereoisomer, which is now marketed as the drug escitalopram), the SSRIs are distinctly different chemicals. As such, important pharmacologic differences exist across the class, including differences in elimination half-life (i.e., how long the drug stays in the system after the patient stops taking it), effects on the liver enzyme systems involved in drug metabolism (which influence the propensity for interactions with other medications), magnitude of effects on other monoamine receptors, and the antidepressant activity of one or more drug metabolites (Edwards & Anderson 1999, Gutman & Owens 2006, Thase 2006c). For this reason, these medications should not be considered interchangeable, and the practice of therapeutic substitution (i.e., filling a prescription for one SSRI with another) can be problematic, particularly when the change is made in the middle of a therapeutic trial.

Escitalopram, the last member of the SSRI class to be introduced and the only one still patent-protected in the United States, is also the most selective, has the simplest dosing characteristics, and, by virtue of a second effect on the serotonin transporter, may have stronger antidepressant activity than proportional doses of the parent drug, citalopram (Kennedy et al. 2006, Thase 2006c). Whether these potential advantages justify its use ahead of much less expensive, generically available SSRIs elicits strong opinion on both sides of the propostion and will not be resolved by this review. Most health care insurers deal with this issue by placing escitalopram on a second or third "tier" of medication options, imposing higher out-of-pocket cost if it is chosen ahead of generic members.

As noted above, one of the initial features that distinguished the SSRIs from the TCAs was a substially lower incidence of nuisance side effects such as dry mouth, blurry vision, constipation, and lightheadedness (see, for example, Preskorn 1995). The SSRIs are not innocuous compounds, however, and about 5% to 10% of people who begin therapy in double-blind randomized controlled trials (RCTs) will have to discontinue therapy because of one or more side effects. The side effects that most commonly complicate SSRI therapy reflect the gastrointestinal (i.e., nausea and diarrhea) and central nervous system (headache, tremor, nervousness, insomnia, daytime sleepiness, and sexual side effects like diminished libido or difficulty having an orgasm) effects of inhibiting serotonin uptake. More recently, an increase risk of falls and fractures has been reported in elders (Haney et al. 2007, Richards et al. 2007), which may reflect subtle, age-dependent effects on balance and bone strength.

More controversial is the relative safety of the SSRIs during pregnancy. Classified by

the FDA as "category C" for terratogenic effects, the SSRIs have been widely assumed to pose a small and nonspecific risk for the fetus, with untreated depression conveying a larger, known risk for both mother and fetus (Hendrick & Altshuler 2002). This view was reinforced by the recent findings of the naturalistic study of Cohen and colleagues (Cohen et al. 2006), which documented that pregnant women who elected to discontinue antidepressants were at dramatically higher risk of depressive relapse than were those who remained on medication throughout the pregnancy. Such benefits must again be balanced against known risks, however, and data are accumulating to suggest that several specific risks may need to be taken into account. The best documented of these risks is an SSRI discontinuation syndrome in newborns, which usually runs an entirely benign course but has been associated with seizures (Moses-Kolko et al. 2005). The SSRIs as a class may be associated with the development of pulmonary hypertension in the third trimester of pregnancy, presumably from serotoninergic effects on the muscle cells lining the walls of arteries and arterioles (Chambers et al. 2006). Evidence of even rarer cardiac terratogenic effects has specifically implicated paroxetine (Alwan et al. 2007, Bar-Oz et al. 2007, Louik et al. 2007). Obviously, the potential merits of alternate interventions with even lower risks to the fetus—such as cognitive behavior therapy or interpersonal psychotherapy—should be considered before initiating antidepressant medication during pregnancy.

Even more controversial are concerns about iatrogenic behavioral toxicities of antidepressants. As is the case with most other antidepressants, initiation of therapy with the SSRIs sometimes is associated with an uncomfortable state of behavioral activation, which is variably experienced as motor restlessness or a feeling of "crawling out of one's skin." This state—which is both similar to and in some ways different from both psychomotor agitation and akathisia (an extrapyramidal side effect associated with antipsychotic medications)—may help to explain the sporadic reports of treatment-emergent onset of worsening of suicidal ideation and behavior, particularly when uncomfortable motoric activation is coupled with a dysphoric affective state and the pessimism and hopeless associated with more severe depressions.

Although the issue of whether the antidepressants in general and the SSRIs in particular are associated with an increase in suicidal behavior has ebbed and flowed over the past 18 years (see, for example, Beasley et al. 1991, Kapur et al. 1992, Teicher et al. 1990), it most recently erupted as part of a broader concern about the increasing use of antidepressants in children and adolescents (Andrade et al. 2006, Bridge et al. 2007, Dubicka et al. 2006, Mann et al. 2006, Pfeffer 2007, Simon 2006). In this regard, the FDA reviewed the data from 24 double-blind, placebo-controlled RCTs and determined that the risk of suicidal behavior—broadly defined—was approximately 4 per 100 children and teenagers treated with antidepressants, an incidence that is about twice that observed on placebo (also see Posner et al. 2007). It is important to keep in mind that there were no completed suicides among the more than 4200 children and adolescent participants in the antidepressant RCTs reviewed by the FDA. A subsequent FDA review of even more extensive data sets from RCTs of adults revealed a slight increase in suicidal behavior among those 18 to 25 years old and a significant decrease among older patients, which strongly suggests that treatment-emergent suicidal ideation is an age-dependent phenomenon. Expert opinion varies as to whether this treatment-emergent behavioral activation syndrome reflects a neurodevelopmental phenomenon (i.e., delayed maturation of inhibitory serotoninergic systems in a vulnerable subset of more impulsive, higher-risk youths) or could be explained more parsimoniously by induction of mixed states in youths who have not yet been recognized to have bipolar disorder (Akiskal et al. 2005, Mann et al. 2006, Thase 2006a).

Several noteworthy consequences have resulted from the FDA warnings about the potential of antidepressants for inducing suicidal behaviors in youth. On the plus side, the rather scant evidence supporting the efficacy of antidepressants in children and teenagers has been examined more critically; risks of treatment, after all, must be balanced against an accurate appraisal of therapeutic benefit. In this regard, it is clear that well-replicated efficacy exists for one antidepressant in pediatric populations—fluoxetine—and the proportion of failed studies (i.e., the drug is not significantly more effective than placebo) is greater than observed in studies of adult populations (Mann et al. 2006). Likewise, more attention has been given to evaluating the utility of alternate nonpharmacological interventions for depressed youths, such as cognitive behavior therapy. However, results of the handful of well-controlled studies completed to date comparing CBT and pharmacotherapy, either singly or in combination, do not indicate a clear-cut winner (Goodyer et al. 2007, March et al. 2004, Melvin et al. 2006). On the negative side, regulatory warnings have led to decreased prescription of antidepressants to depressed youth (Kurian et al. 2006, Nemeroff et al. 2007b), which—given the decline in the rate of suicide in children and teenagers over the past two decades (Gibbons et al. 2006, McKeown et al. 2006)—raises countervalent concerns about the dangers of undertreatment of depressed youths.

Serotonin-Norepinephrine Reuptake Inhibitors

The SNRI class of drugs includes venlafaxine and duloxetine, which are both widely used in the United States, as well as milnacipran, which—although not available in the United States—is widely used in Japan and is available in Europe, Israel, and some South American countries. Venlafaxine is approved for treatment of generalized anxiety disorder, social anxiety disorder, and panic disorder in addition to MDD; duloxetine is approved for treatment of generalized anxiety disorder and management of neuropathic pain. The SNRI class is likely to grow to four in 2008, when desvenlafaxine (the most active metabolite of venlafaxine) is scheduled to be launched in the United States.

The SNRIs, as medications known to enhance neurotransmission of both serotonin and norepinephrine pathways in the brain, from the outset have been viewed as having the potential for stronger or broader antidepressant activity than the more selective SSRIs. The so-called dual-reuptake inhibitor hypothesis actually predates the introduction of the first selective SNRIs and initially was based on studies comparing the SSRIs with the TCA clomipramine (see Anderson 1998) or combinations of an SSRI and a TCA (Nelson et al. 1991).

Venlafaxine is the most extensively studied of the SNRIs in MDD and, consistent with the prediction of the dual-reuptake inhibitor hypothesis, results of a meta-analysis of individual patient data from the first eight comparative RCTs found a 10% advantage in remission rates for the SNRI over the SSRI studied (45% versus 35%) (Thase et al. 2001). Subsequent meta-analyses of larger sets of studies confirmed a statistically significant advantage for venlafaxine, although the magnitude of the advantage may be somewhat smaller than originally thought (Nemeroff et al. 2007a, Papakostas et al. 2007b, Smith et al. 2002) and may be heavily dependent on comparisons with fluoxetine (Cipriani et al. 2006). It is of some interest that no advantage was evident in the two studies comparing venlafaxine and escitalopram (see Kennedy et al. 2006), although a larger number of studies would be needed before any firm conclusions could be drawn.

A dual reuptake mechanism of action also conveys two pathways for causing side effects and, although better tolerated than the TCAs, venlafaxine tends to have a broader array of side effects than the SSRIs, including telltale side effects of noradrenergic activity such as dry mouth and rapid heartbeat

(Thase & Sloan 2006). Of greatest clinical importance is the risk of treatment-emergent high blood pressure, with rates ranging from about 2% above placebo at lower therapeutic doses (i.e., 75 mg to 150 mg per day) to as high as 10% at doses of 300 mg per day or higher (Thase 1998). Venlafaxine also is arguably the most difficult of the newer drugs to stop abruptly after an extended course of therapy, with a discontinuation syndrome characterized by flulike symptoms, insomnia, irritability, and paresthesias (Haddad 2001). To prevent this uncomfortable but usually not dangerous state, venlafaxine dosage is gradually tapered over a number of weeks when a course of therapy has been completed. There has been additional concern that venlafaxine may be somewhat more dangerous in overdose than the SSRIs, although less so than the TCAs (Buckley & McManus 2002). It is not clear, however, if the higher Fatal Toxicity Index score simple reflects the fact that venlafaxine is preferentially prescribed by psychiatrists to difficult-to-treat patients (and, hence, at greater risk for suicide) or if the noradrenergic effects at higher, potentially toxic doses might convey some increased risk of cardiac arrhythmias.

With these limitations in mind, it should also be noted that the extended-release formulation of venlafaxine is still patent protected and, as such, the cost of a 30-day supply of medication may be five times more than that of a generic SSRI. Thus, the relatively small (i.e., 6% to 10%) advantage in efficacy observed in RCTs generally has not been viewed as a sufficient justification to warrant first-line use. Many formulary plans place the extended-release or XR form of venlafaxine in a second or third tier and, in this regard, it is one of the better-studied switch alternatives for patients who do not benefit from SSRIs (see, for example, Thase et al. 2000). In this regard, two recent studies documented an almost identical numerical advantage for venlafaxine XR as compared with a second trial within the SSRI class: The difference was statistically significant in a large study conducted in Spain (Baldomero et al. 2005) but did not meet significance following adjustment for multiple comparison in the smaller study conducted as part of the STAR*D project (Rush et al. 2006b). Use of higher doses of venlafaxine—up to the therapeutic maximum of 375 mg per day if tolerated—may improve response in more difficult-to-treat depression (Thase et al. 2006c). A generic version of the original, immediate-release formulation of venlafaxine has recently become available, although it is not clear if the drawbacks of this form of the drug (i.e., required divided daily dosing and poorer tolerability) will also preclude first-line use.

As venlafaxine is first primarily metabolized in the liver to O-desmethylvenlafaxine, every patient treated with the parent drug has in a sense also been treated with the drug desvenlafaxine. As a drug in its own right, desvenlafaxine may offer some advantages in comparison with the parent drug (i.e., lower therapeutic dose, narrower dosing range, greater bioavailability, and greater potency for inhibiting norepinephrine reuptake) (Deecher et al. 2006). However, until the drug is available for general use, there is no clinical basis to compare its relative merits and limitations with venlafaxine or any of the SSRIs.

Duloxetine, which was introduced in the United States in 2004, differs from venlafaxine in several respects. On the plus side, it has a simpler dosing schedule (60 mg per day is both the usual starting dose and the modal therapeutic dose), stronger in vitro effects on inhibiting norepinephrine uptake, lower risk of treatment-emergent high blood pressure, and fewer discontinuation symptoms when treatment is stopped (Frampton & Plosker 2007, Gupta et al. 2007, Perahia et al. 2007, Thase 2005). On the minus side, initiating duloxetine therapy at 60 mg per day is associated with more nuisance side effects than venlafaxine XR at 75 mg per day (Perahia et al. 2007), and an efficacy advantage over SSRIs is not as well documented, with evidence of an advantage for more severely depressed

patients in one meta-analysis of six studies comparing duloxetine minimum-dose therapy with fluoxetine or paroxetine (Thase et al. 2007), but no difference in three subsequent studies comparing it with escitalopram (Khan et al. 2007, Nierenberg et al. 2007, Wade et al. 2007). In addition, because of a tendency to cause increases in liver enzymes early in therapy, the package insert for duloxetine carries a relatively stern warning about use in patients with alcoholism or liver disease (Frampton & Plosker 2007, Gupta et al. 2007).

The Norepinephrine-Dopamine Reuptake Inhibitor Bupropion

Because the commercial success of bupropion took a number of years to develop, it is sometimes forgotten that it was the first of the newer antidepressants to be approved for use in the United States and, even following a four-year voluntary delay in introduction to clarify the risk of seizure, it is second only to fluoxetine in years of use (Fava et al. 2005). Bupropion is the only medication to be classified as an NDRI, the only one of the modern antidepressants that has no direct effects on serotoninergic neurotransmission, and the only antidepressant to be approved as an aid for smoking cessation (Ascher et al. 1995, Foley et al. 2006). The unique neurochemical profile is almost certain to account for its different side effect profile from the SSRIs, which includes a virtual absence of sexual side effects (Thase et al. 2005b). Indeed, bupropion is perhaps the preferred treatment option for patients who cannot tolerate SSRIs and is commonly used in combination with SSRIs to try to enhance efficacy or reduce sexual side effects (Fava et al. 2005).

Use of bupropion was initially limited by ongoing concerns about the risk of seizure (at doses above 450 mg per day the drug does have a higher risk of seizures than all of the other newer antidepressants) and a rather cumbersome three-times-a-day dosing regimen. Moreover, whereas the beneficial effects of the SSRIs for treatment of anxiety disorders were rapidly appreciated, bupropion appeared to have less utility for the anxious patient (Thase & Kupfer 1996). Subsequent introduction of sustained release (twice daily) and extended release (once daily) made treatment more user friendly, and further clinical experience suggested that the drug was helpful for anxiety associated with depression if not for some of the primary anxiety disorders (Clayton 2007). With respect to relative efficacy, several meta-analyses have confirmed parity with the SSRIs across the broad grouping of MDD (Papakostas et al. 2007c, Thase et al. 2005b), with perhaps a small advantage going to the SSRIs for relief of anxiety and to bupropion for relief of fatigue and sleepiness symptoms (Papakostas et al. 2006). In the only two published head-to-head comparisons between venlafaxine XR and bupropion in MDD, few significant differences in efficacy were identified (Rush et al. 2006b, Thase et al. 2005a), although the NDRI did show the expected significant advantage on measures of sexual functioning in the one study that specifically measured these side effects (Thase et al. 2006a).

Other Modern Antidepressants

The seldom-used drug nefazodone has unique neurochemical and clinical effects (Taylor et al. 1995). The effects of nefazodone on inhibition of reuptake of serotonin and norepinephrine are both weak and transient, and the drug's therapeutic actions may be more closely linked to blockade of serotonin 5-HT2 receptors (Taylor et al. 1995). For these reasons, nefazodone has predictably better effects on sleep than do SSRIs such as fluoxetine (Rush et al. 1998), as well as a low risk of sexual side effects (Ferguson et al. 2001). Never a widely prescribed antidepressant, nefazodone was perceived by many clinicians to be less effective than SSRIs, although this belief has not been substantiated by the results of RCTs (Papakostas & Fava 2007). Beyond perceptions of lower efficacy,

nefazodone is more difficult to prescribe than the SSRIs, with its several subjective strengths (i.e., better sleep and little sexual dysfunction) offset by limitations like divided daily dosing and higher rates of side effects such as sedation, headaches, and visual disturbances (Preskorn 1995). More recently, nefazodone was associated with a rare but very worrisome risk of liver failure (Spigset et al. 2003), which is presumably because it—unlike the closely related psychotropic drugs trazodone and buspirone—interferes with metabolism of bile (Kostrubsky et al. 2006).

Mirtazapine also blocks the 5-HT2 receptors, like nefazodone, and it is a potent antagonist for histamine, 5-HT3, and noradrenergic alpha2 receptors. Antidepressant effects are probably explained by the complex interplay between the 5-HT and noradrenergic effects (Thase 2006b). This neurochemical profile also explains why mirtazapine is the most sedating of the modern antidepressants, as well as the only one implicated with weight gain during acute-phase therapy. Although more severely depressed patients—particularly those at midlife or older—often benefit from a medication that can enhance sleep and appetite, the modal consumer of antidepressants in the twenty-first century is more likely to find these qualities annoying, which is why mirtazapine was not a particularly successful antidepressant in the U.S. marketplace.

Mirtazapine nevertheless has utility for selected patient subgroups, and its side effect profile is still somewhat more favorable than that of a TCA. In comparative studies, mirtazapine therapy typically results in a more rapid onset of symptom relief than do the SSRIs (Quitkin et al. 2001) and venlafaxine (Guelfi et al. 2001, Benkert et al. 2006). The neurochemical and clinical effects of mirtazapine also can complement those of a reuptake inhibitor, and today it is used as much in combination with SSRIs and SNRIs as a monotherapy. In one of the STAR*D substudies, mirtzapine alone was comparable in efficacy to the TCA nortriptyline (Fava et al. 2006); in another, the combination of mirtazapine and venlafaxine XR was better tolerated and easier to administer than the MAOI tranylcypromine, although a numeric advantage in remission rates was not statistically significant (McGrath et al. 2006). For these and other reasons, mirtazapine continues to play a role, particularly in the management of more difficult-to-treat depressions.

Selegiline Transdermal Delivery System (TDS), the only new antidepressant therapy to be introduced in 2006, actually represents a new way to deliver a relatively old member of the MAOI class. As the name reveals, TDS is a skin patch, which permits the medication to be absorbed without affecting the activity of MAO in the gut and, to a lesser extent, the liver. As discussed elsewhere in more detail (Thase & Kupfer 1996, Thase et al. 1995), for a subset of depressed patients, the MAOIs are uniquely effective medications that fell out of favor in the late 1960s because of the risk of hypertensive crisis, a rapid, large increase in blood pressure that—in a vulnerable person—can cause a stroke or heart attack. The mechanism underlying this reaction is inherent to the mechanism of the antidepressant activity of MAOIs: the same subform of MAO enzyme that is responsible for degrading serotonin and norepinephrine in the brain—type A—also degrades the vasoactive amino acid tyramine in the gut and liver. Thus, when enzymatic activity is inhibited by conventional orally administered MAOIs such as isocarboxazid, phenelzine, and tranylcypromine, unmetabolized tyramine—which is present in high concentration in certain foods (most notoriously aged cheeses) and alcoholic beverages (most notoriously chianti wine)—can trigger a massive release of norepinephrine, the proximal cause of the rise in blood pressure (Thase et al. 1995). Over the years, standard dietary restrictions have evolved which, if adhered to, can prevent the so-called cheese effect, although relatively few psychiatrists practicing today (and virtually no primary care physicians) are comfortable prescribing MAOIs.

Ongoing efforts to develop safer MAOIs led to the introduction of moclobemide, a reversible inhibitor of MAO A, which is available throughout most of the world. Moclobemide was not introduced in the United States largely for commercial reasons, as it is no longer widely prescribed anywhere and is generally viewed as more difficult to prescribe than an SSRI and less effective than the older, nonselective MAOIs (Lotufo-Neto et al. 1999, Papakostas & Fava 2006).

Selegiline, which is a nonreversible (and at low oral doses) selective inhibitor of the B subform of MAO, has been approved for use in the United States for some time for treatment of Parkinson's disease. However, the truly B-selective oral doses (5 mg to 10 mg per day), which do not require dietary restriction, are not effective for depression. Delivery of selegiline through a skin patch permits high levels of inhibition of both forms of MAO in the brain, with only modest reduction in degradation of tyramine. Although there are as of yet no comparative data—selegiline TDS has not been compared with SSRIs, moclobemide, or any of the older MAOIs—clinical experience suggests that it may have a better side effect profile than the older MAOIs, with less weight gain, orthostatic hypotension, and sexual dysfunction (Robinson & Amsterdam 2007). The FDA approved selegiline TDS for use without dietary restriction at a 6-mg-per-day patch strength, but was not satisfied with the amount of safety data on higher doses; thus, the package insert specifies that the usual dietary restrictions are necessary at the 9-mg and 12-mg-per-day doses. Moreover, patients taking selegiline TDS are not spared the risk of potentially serious drug-drug interactions at any dose, and caution must be taken to wash out SSRIs and SNRIs for at least one week (four weeks for fluoxetine) prior to initiating therapy. In short, selegiline TDS only partly resolves longstanding concerns about the safety of MAOIs, and this problem is compounded by limited formulary availability and an unusually high cost when purchased out-of-pocket. The MAOIs thus continue to be fourth- or fifth-line therapies for the most difficult-to-treat depressed patients and, as illustrated by results of the STAR*D substudy (McGrath et al. 2006), are probably of limited utility unless used by highly experienced specialists.

Atypical Antipsychotics Used to Treat Depression

In a relative vacuum of new types of antidepressant medications, the utility of the atypical antidepressants for major depressive disorder has been explored. Given the cost and side effect profiles of these medications, most of the research in this area has targeted treatment-resistant depression, for which there is emerging evidence of therapeutic benefit (Papakostas et al. 2007a). Among the almost infinite number of combinations of antidepressants and atypical antipsychotics, the pairing of olanzapine and fluoxetine has received a disproportionate amount of study, largely because the same company manufactured and marketed both of the compounds, and some early preclinical work suggested additive effects on monoamine systems in the brain (Shelton 2003). A small and carefully crafted initial study on patients who had not responded to a prospective trial of fluoxetine yielded very promising results, with the olanzapine fluoxetine combination (OFC) showing superiority to both continued therapy with fluoxetine or olanzapine monotherapy (Shelton et al. 2001). Two subsequent larger, multicenter studies yielded equivocal results in comparison with the active standards of nortriptyline (Shelton et al. 2005) and venlafaxine (Corya et al. 2006). A subsequent pair of studies, using the same basic design as that of Shelton on a larger scale, also yielded mixed results, with one study showing an unequivocal advantage for OFC in comparison with the components and the other showing no difference in comparison with olanzapine monotherapy (see Thase et al. 2007a). An application for OFC for the indication of treatment-resistant depression is currently

before the FDA, and it will probably be settled by the time this review is published. Assuming that OFC is approved, the prospects for therapeutic benefit will always need to be weighed against the cost and the propensity of OFC to cause weight gain and related metabolic adverse effects such as dyslipidemia and diabetes. Further research also will be needed to determine if the combination must be continued indefinitely or if the olanzapine component can be reduced or discontinued over time.

A simpler case can be made for the utility of a second atypical antipsychotic, aripiprazole, as an augmentation therapy for antidepressant nonresponders because fewer placebo-controlled studies have been conducted, and the results of the one published study indicated that aripiprazole produced significant reductions in depressive symptoms and significantly greater response rates (Berman et al. 2007). On the plus side, when compared with OFC, the efficacy of aripiprazole was shown in combination with a variety of SSRIs and venlafaxine, and longer-term studies of schizophrenia and bipolar disorder indicate fewer problems with weight gain and metabolic changes (Newcomer 2007). On the minus side, aripiprazole is associated with a relatively high rate of akithisia when combined with reuptake inhibitors (Berman et al. 2007), perhaps particularly if higher doses are used early in the course of therapy. Aripiprazole also lacks olanzapine's relatively nonspecific beneficial effects for sleep. The FDA recently approved aripiprazole as an augmentation agent for depressions not responsive to standard antidepressants.

Studies of acute-phase augmentation therapy with three other atypical antipsychotic medications, risperidone, quetiapine, and ziprasidone, have either been completed but not yet published or are still under way. Results of one multistage trial of risperidone augmentation of citalopram have been published, but they do not provide strong support for a sustained augmentation effect (Rapaport et al. 2006).

PHARMACOTHERAPY OF BIPOLAR DISORDER

Although depression may dominate the lives of the majority of people with bipolar disorder (Thase 2005), the general approach to treatment of bipolar disorder is distinguished by the need to treat and/or prevent episodes on the opposite pole of the mood spectrum, namely mania and its subsyndromal counterpart, hypomania. Symptoms of mania include elevated or irritable mood, grandiosity and inflated self-esteem, decreased need for sleep, rapid speech, and reckless impulsivity. By definition, mania is a severe illness and manic episodes must be characterized by at least one of the following: psychosis, hospitalization, or significant functional impairment. The diagnosis of bipolar affective disorder type I is used when an individual has experienced at least one spontaneous manic episode; according to DSM-IV-TR (Am. Psychiatr. Assoc. 2000a), episodes that appear to have been provoked by a medication, such as an antidepressant, steroid, or psychostimulant, are not counted toward fulfilling the diagnostic criterion, even though a pharmacologically induced manic episode is inarguably one of the best predictors of switching diagnoses from MDD to bipolar disorder (Thase 2005). Hypomania is a nonpsychotic state that differs from mania in terms of symptom severity, level of impairment, and/or duration; the diagnosis of bipolar affective disorder type II is used for individuals who have only experienced hypomanias and at least one major depressive episode. The seldom-used diagnosis of cyclothymia is used to classify a condition characterized by hypomania and minor depressive episodes. Although there can be problems with the reliability of diagnosing hypomania, the errors usually involve recognition (i.e., distinguishing a pathological state from a period of "top of my game" functioning); bipolar II disorder

Table 4 Agents used in bipolar disorder

"Standard" antimanic agents	Indications	Usual dosing	Comments
Lithium (Eskalith, Lithobid)	Mania, maintenance	Plasma levels 0.6 mEq/L to 1.5 mEq/L	Protective against suicide; higher levels used for mania than depression or prevention
Carbamazepine (Equetro, Tegretol)	Mania, mixed	400 to 1200 mg daily	Poorly defined target plasma concentration
Valproate (Depakote, Depakote ER)	Mania, mixed	Loading at 20 mg/kg (valproate) 25 mg/kg (ER)	Target serum levels >75
"Atypical"[b] antipsychotics			
Aripirazole (Abilify)	Mania, mixed, maintenance	15 to 30 mg once daily	Must dose vigorously for antimanic efficacy
Olanzapine (Zyprexa)	Mania, combination,[a] maintenance	5 to 20 mg at bedtime	Excellent efficacy but greatest metabolic adverse effects
Olanzapine/fluoxetine combination (Symbiax)	Bipolar depression	4 fixed doses 6(olanzapine)/25(fluoxetine), 6/50, 12/25, 12/50	1 of 2 medications approved for bipolar depression
Quetiapine (Seroquel)	Mania, depression, combination[a]	300 mg nightly for depression, 600 split dose for mania	May soon earn maintenance indication; extended release formulation just approved
Risperidone (Risperdal)	Mania, combination[a]	3 mg to 6 mg, may be in divided doses	Greatest problems with extrapyramidal symptoms and hyperprolactinemia
Ziprasidone (Geodon)	Mania, mixed	40 mg BID on day 1, increase to 60 mg BID by day 2, and 80 mg BID thereafter	Should give with lipid-rich food
Other			
Lamotrigine (Lamictal)	Maintenance	50 mg to 200 mg once daily (21-day upward titration schedule). Dose halved in combination with valproate, doubled in combination with carbamazapine	Slow titration decreases incidence of dermatologic adverse events

[a]Combination = use with lithium or divalproex in treatment of mania.
[b]Patients on "atypical" antipsychotic need glucose and lipid monitoring as well as weight tracking.

generally is not a transitional state between the classical unipolar and manic-depressive (type I) illnesses.

The pharmacopeia of medications with demonstrated efficacy in bipolar disorder has dramatically expanded in the past decade (see **Table 4** for a summary). Whereas only lithium and valproate—a medication initially introduced for treatment of epilepsy—were approved treatments for bipolar disorder just a decade ago (Thase & Kupfer 1996), at the time this review was written, two other medications originally introduced as anticonvulsants (carbamazapine and lamotrigine) and all but one member of the atypical antipsychotic class of medications were FDA approved for the treatment of at least one phase of bipolar illness.

TREATMENT OF MANIA

FDA-approved pharmacologic treatments of acute mania are customarily broken down

into the standard mood stabilizers, which include lithium, divalproex, and carbamazapine, and five of the seven atypical antipsychotics (risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole). Additional medications that are likely to have acute antimanic efficacy but that are not FDA approved for this use include oxcarbazepine; clozapine; first-generation antipsychotics such as chlorpromazine and haloperidol; and paliperidone, a recently introduced medication that is the active metabolite of risperidone, for which data on its use in the treatment of mania are still being collected. Interestingly, although valproate, carbamazapine, and lamotrigine are classified as anticonvulsants, neither lamotrigine (which is only approved for relapse prevention) nor two other anticonvulsants that have been systematically studied—gabapentin (Pande et al. 2000) and topiramate (Kushner et al. 2006)—have meaningful antimanic activity. Thus, not all mood stabilizers are antimanic nor are all anticonvulsants mood stabilizers or antimanics. Moreover, neither gabapentin nor topiramate have established efficacy for any aspect of treatment of bipolar disorder and are generally only used adjuctively for secondary indications (e.g., gabapentin for anxiety or relief of pain, topiramate for weight loss or pain).

For decades, lithium was the only pharmacologic agent that could be considered a standard therapy for the treatment of bipolar disorder. As such, the vast majority of patients with bipolar disorder were given trials of this agent, and a significant number of patients emerged that were either not responsive or intolerant to lithium. Although lithium remains the gold standard to which all other treatments for bipolar disorder are compared, the need for alternative treatments for bipolar disorder became evident. In 1994, valproate, the enteric-coated formulation of valproic acid, earned FDA approval for the treatment of mania and quickly became the most widely prescribed agent in the United States for the treatment of mania. Not only did valproate offer a different side effect and tolerability profile, but by virtue of its different mechanism of action, it also offered an alternative spectrum of clinical activity, proving particularly well suited in the treatment of dysphoric mania (Swann et al. 2002).

The availability of valproate has greatly reduced the use of lithium but has not rendered lithium obsolete. Perhaps, most importantly, lithium appears to be protective in regard to attempted and completed suicide. For example, Goodwin and colleagues (Goodwin et al. 2003) examined pharmacy claims and emergency department records of suicide attempts and completions in more than 20,000 people in a managed care plan. After adjusting for age, comorbidities, gender, year of diagnosis, and concomitant psychotropic medications, suicide death was found to be 2.7 times more likely in people taking valproate than in people taking lithium. Also, valproate has not been granted FDA approval for long-term treatment of bipolar disorder as the only large, double-blind study of valproate as a maintenance treatment failed to separate it from placebo (Bowden et al. 2000), although significant protection against depressive relapse was observed in secondary analyses (Gyulai et al. 2003).

Although many people who had difficulty tolerating lithium found valproate to be a welcomed option, this medication can also have some tolerability issues, particularly for women. These include acne, hirsuitism, hair loss, and weight gain, as well as concerns about the possible induction of the polycystic ovarian syndrome (Cousins & Young 2007). Rarer problematic adverse effects include thrombocytopenia, hepatitis, hyperammonemia, and pacreatitis.

An extended-release formulation of divalproex sodium (Depakote ER) has been introduced that simplifies dosing regimens (once-daily dosing). This formulation is also FDA approved for the treatment of mania as the result of a large randomized-controlled trial comparing divalproex sodium ER with placebo (Bowden et al. 2006). This study randomized 377 patients with mania to

placebo or divalproex sodium ER in a 1:1 ratio. Divalproex sodium ER was initiated at 25 mg/kg in a single daily dose (rounded up to the next 500 mg increment) given in the morning. On day three, this was increased by 500 mg. Subsequent divalproex levels were drawn also in the morning, prior to medication dosing, effectively creating a 24-hour trough. Target serum levels of divalproex were 85–125 micrograms/ml. Response rates (50% reduction of Mania Rating Scale) after 21 days of therapy were 48% for the patients who were assigned divalproex and 34% for patients assigned placebo.

More significant than the results of this study was the method used to prescribe divalproex ER, which can be considered optimal. Gastrointestinal absorption of divalproex ER is up to 20% less than that of the standard formulation of valproate (Dutta et al. 2002), and this was reflected in the 25 mg/kg starting dose with subsequent increase by 500 mg on day three. Peak levels of divalproex ER occur 7–14 hours after ingestion (Thomson Healthcare Inc. 2006), which is reflected in the morning dosing used in this study. Ideally, one will have peak divalproex levels during sleep. Serum divalproex level monitoring was drawn 24 hours following ingestion of divalproex ER, which avoided spuriously high levels. Levels drawn within 12 hours of dosing divalproex ER can be 25% higher than a 24-hour trough (Reed & Dutta 2006). Like the original formulation, valproate ER will decrease the metabolism of lamotrigine, and typically the dose of the latter medication must by reduced by half (Cousins & Young 2007). Finally, a target divalproex level of greater than 80 micrograms/ml reflects a recent analysis of divalproex levels and antimanic efficacy suggesting that levels less than 54 micrograms/ml are no better than placebo, with a somewhat linear increase in response for levels between 54 and 90 micrograms/ml (Allen et al. 2006). Despite such empirical guidance, in our experience divalproex ER is almost never used properly (i.e., it is not dosed one time daily, in the morning, with trough levels drawn 24 hours after medication administration and with target levels greater than 55 micrograms/ml), which no doubt undoes some of the potential advantage of using the ER formulation.

Carbamazepine, despite having been used for many years as an alternative to lithium, has only recently been granted an FDA indication for the treatment of mania, specifically as a novel, patent-protected extended-release formulation (Cousins & Young 2007). The efficacy of extended-release carbamazepine was demonstrated in two RCTs of acutely manic or mixed patients that enrolled 443 patients. A combined analysis (Weisler et al. 2005) reported a response rate of 52% as compared with 26% for placebo, which is a fairly large effect for a contemporary three-week trial. Discontinuation owing to adverse effects was 10.8% for active medication and 5.5% for placebo. Dosing was flexible and the mean carbamazepine dose was 700 mg (+/−386 mg), with 35% of completers taking between 400 and 600 mg of carbamazepine ER and 28% taking 800 to 1000 mg. Carbamazepine levels were not associated with response, which is not unexpected, as it is exceedingly difficult to determine dose/response relationships in flexible-dose protocols.

As carbamazepine induces the metabolic enzyme cytochrome 3A4 in the liver, it will accelerate its own metabolism as well as the metabolism of a number of other psychotropic medications commonly used in the treatment of bipolar disorder (Cousins & Young 2007). These include a number of medications commonly used for treatment of bipolar disorder, including lamotrigine, risperidone, quetiapine, olanzapine, aripiprazole, and ziprasidone. Dosing of these agents will likely need to be increased to compensate for this increase in metabolism in order to maintain therapeutic effect. For example, lamotrigine doses typically need to be doubled when used in combination with carbamazapine.

With the demonstrated utility of the anticonvulsants carbamazepine and divaproex sodium in the treatment of bipolar disorder, anticonvulsants in general generate a

disproportionate level of enthusiasm among psychiatrists and are often used off-label in the treatment of acute mania. Topiramate and gabapentin are two newer anticonvulsants that soon after introduction garnered considerable attention as reasonable alternatives for the management of mania in people who were intolerant or did not respond to standard therapies. Unfortunately, under more controlled conditions, the performance of these medications did not support the degree to which they were being used; these results offer a cautionary lesson regarding the use of untested medications.

Gabapentin was widely prescribed beginning in the late 1990s as an alternative antimanic medication. Numerous open-label case reports and case series extolled the benefits of this agent. When it was studied under double-blind conditions, however, gabapentin performed surprisingly poorly. Pande and colleagues (Pande et al. 2000) compared gabapentin to placebo in patients who were not responding to standard antimanic agents (lithium, valproate, or both) as an augmentation agent. Patients randomized to placebo actually had a better outcome than did patients randomized to gabapentin, which would indicate that some of the side effects to gabapentin were actually countertherapeutic. It is highly unusual in trials of psychotropic medications for a placebo to have a statistically significant advantage over an "active" drug.

Topiramate was introduced soon after gabapentin, and again was thought to be of significant utility as an antimanic agent. It was not until 2006 that results from a number of randomized-controlled trials became available that demonstrated topiramate's ineffectiveness in the management of mania (Kushner et al. 2006). Topiramate has met the standard of being a failed drug (for mania), rather than simply not performing well in a failed trial, as in one of the randomized-controlled trials an active comparator, lithium, performed quite well, whereas topiramate did not separate from placebo.

Interest remains in topiramate because it appears to have significant anorectic qualities and it may prove to be useful in the amelioration of treatment-emergent weight gain in some patients with bipolar disorder (see, for example, McElroy et al. 2007). Data from controlled studies are needed to clarify what role topiramate may play in the management of treatment-emergent weight gain, as this agent is very costly and can have significant cognitive adverse effects.

Although the first-generation antipsychotics have long been used in the management of acute mania, tolerability issues—particularly extrapyramidal side effects—and concerns about the induction of postmanic depression and the ultimate risk of tardive dyskinesia, as well as the apparent lack of prophylactic benefit, relegated the first-generation antipsychotics to a distant third-line or adjunctive role in the treatment of mania. After early experience with the first of the atypical antipsychotics, clozapine, suggested significant benefit for the patient with bipolar disorder, the better-tolerated atypical antipsychotics that were subsequently introduced rapidly became an important option for the treatment of mania (Cousins & Young 2007).

Perlis and colleagues (Perlis et al. 2006) performed a meta-analysis comparing efficacy of the atypical antipsychotics in the treatment of acute mania. The results suggest no difference exists yet in the short-term efficacy (i.e., response rates) of olanzapine, quetiapine, risperidone, ziprasidone, or aripiprazole. Generally, these agents registered approximately a 50% response rate when using 50% reduction from baseline Young Mania Rating Scale (YMRS) as primary outcome, as compared with about a 30% response rate to placebo. Looking across studies, the atypicals as a class look to be comparable in efficacy to lithium, carbamazepine, and divalproate, although only a handful of prospective double-blind RCTs have been conducted.

Although overall response rates for the various atypicals do not appear to differ

significantly across large studies, owing to differences in adverse effects and in some ways treatment effects, these agents are not interchangeable. For instance, although olanzapine has the most data supporting its utility in mania, bipolar maintenance, and, in combination with fluoxetine (Symbyax®), bipolar depression, concerns about olanzapine's long-term effects on weight, glucose, and lipid metabolism have made olanzapine less than a first-line treatment option for many clinicians.

Quetiapine is the only atypical antipsychotic with an FDA indication for the treatment of bipolar depression, and it appears to be poised to earn FDA approval as a maintenance treatment as well. When quetiapine was introduced, dosing recommendations were very cumbersome, with gradual increases (25 mg daily) to inadequate target doses. Current dosing recommendations for quetiapine in the treatment of mania include starting at 50 mg BID on day 1, increasing to 100 BID by day 2, and titrating to 600 mg by day 4 in divided doses. Sedation and orthostatic hypotension can be the limiting side effect when using this agent, and the risk of weight gain and metabolic adverse effects is intermediate—less than that of olanzapine but greater than that of aripiprazole (Newcomer 2007). The recent release of an extended-release formulation of quetiapine may make it easier to titrate to antimanic doses rapidly.

Aripiprazole and ziprasidone are the least sedating of the atypical antipsychotics and also have the least effects on weight and metabolic profiles. Aripiprazole can (and sometimes should) be started at the maximum dose of 30 mg when treating acute mania, and reduced if necessary (Sachs et al. 2006). Because aripiprazole is a partial dopamine agonist at lower doses, and ziprasidone is an NRI, they can sometimes be uncomfortably activating for the bipolar patient, and cases of switching from depression directly into hypomania, mania, or a mixed state (also referered to as treatment-emergent affective switches, or TEASs) have been reported with both drugs. As noted above, akithesia remains one of the most prominent adverse effects experienced by patients treated with aripiprazole. Aripiprazole should not be considered weight neutral, as 13% of patients in a 26-week maintenance study experienced a 7% or greater increase in body weight (Keck et al. 2006). Advantages of aripiprazole include efficacy in maintenance-phase treatment, as well as availability of an IM formulation and the Discment™, which can simplify the monitoring of ingestion in the ambivalent patient. Although not a partial agonist, ziprasidone is an NRI and can be activating at lower doses. Ziprasidone should be started at 40 mg BID on day one and increased to 80 mg BID by day two if possible. For ziprasidone to be absorbed from the gastrointestinal tract, it needs to be given with food, specifically foods rich in lipids. Failure to do so will result in approximately 50% lower absorption (Cousins & Young 2007).

Risperidone will be the first of the second-generation antipsychotics available generically. It is also the only atypical available in a depot-injectable formulation for the patient who has difficulty taking medication consistently. When introduced, risperidone was dosed very aggressively, with daily doses approaching 20 mg. At such high doses, the side effect profile of risperidone is very much like that of the older high-potency antipsychotics such as haloperidol. Current dosing recommendations would not exceed 4 to 6 mg daily, unless coadministered with carbamazepine, which will act to speed metabolism. Like the older antipsychotic medications, risperidone blocks the dopamine receptors in the posterior pituitary that inhibit secretion of the hormone and the syndrome of hyperprolactinemia, which can include breast tenderness and menstrual irregularities as well as secretion of a type of breast milk (i.e., galactorrhea), a problem even with moderate dosing of this agent. Paliperidone (Invega™), an active metabolite of risperidone, recently has been introduced for treatment of schizophrenia. One possible advantage of this agent is

that it bypasses hepatic metabolism, and although it has not yet demonstrated utility in the treatment of mania, it may in time be preferred over risperidone for treatment of patients with liver disease.

BIPOLAR DEPRESSION

In both bipolar type I and bipolar type II disorders, the depressed phase is more prevalent (Judd et al. 2002, 2003) and is associated with greater morbidity than the manias or hypomanias (Thase 2005). Despite the recent FDA approval of both OFC and quetiapine for treatment of acute bipolar depression (the only agents with this specific indication), the treatment of bipolar depression continues to raise spirited debate among psychiatrists. This is because there is ambiguity as to the efficacy of standard antidepressants in the treatment of bipolar depression, as well as concern about potential that standard antidepressants may induce TEASs and a rapid cycling course in the person with bipolar disorder (Thase 2005). Almost universal is the recommendation that if a standard antidepressant is to be used in the management of bipolar type I depression, it should always be used in addition to an antimanic agent. Unfortunately, in approximately 50% of psychiatric office visits, persons with bipolar disorder are prescribed antidepressant without concurrent antimanic agent (Blanco et al. 2002).

Two relatively large studies have recently been completed seeking to clarify the benefits and risks of standard antidepressants in the treatment of bipolar depression. The first study was performed by the Stanley Research Network (Altshuler et al. 2003, 2006; Leverich et al. 2006; Post et al. 2006) and collected data from more that 1000 patients with bipolar disorder. Seeking to clarify the role of longer-term treatment with antidepressant, Altshuler and colleagues (Altshuler et al. 2003) identified 549 patients who had been started on standard antidepressant for the treatment of breakthrough bipolar depression (i.e., all patients were maintained on mood stabilizer). Of these 549 patients, only 189 (34%) took antidepressant medication for 60 days or longer, and among this subgroup only 84 patients were considered responders, that is, reaching a clinical status of not ill or minimally ill for six consecutive weeks. This response rate (84 responders/549 starts) is 15%. Reasons for discontinuation by the 360 patients who started antidepressant but did not continue for at least 60 days were not provided, and some of these people may have been considered responders by other approaches. Nevertheless, these data are certainly more suggestive that standard antidepressant when added to mood stabilizer is not a well-accepted therapy leading to durable recovery.

Not all of the results concerning antidepressants were negative, however, and among the 84 patients who were counted as antidepressant responders, longer-term outcomes were evaluated in relation to the subsequent duration of antidepressant therapy. Time to depressive relapse was found to be much shorter (29 versus 41 weeks; $p = 0.004$) in those who received shorter courses of antidepressant therapy and, in contrast to conventional thinking about the risk factors for TEAS, the patients who remained on antidepressants were somewhat less likely to suffer manic or hypomanic relapses than were those who discontinued antidepressants (Altshuler et al. 2003). Overall, relapse rates were 36% at one year for those continuing antidepressant and 70% at one year for those who did not continue on maintenance antidepressant. This study indicates that although a very low percentage of individuals with bipolar depression who start an antidepressant will achieve a durable recovery, those who do benefit in a sustained way should continue full-dose antidepressant therapy to reduce the risk of depressive relapse/recurrence and do not appear to be at increased risk of TEAS.

A second study from this team of investigators (Altshuler et al. 2006, Leverich et al. 2006, Post et al. 2006) examined the acute-phase efficacy of three different types of antidepressants. They randomized 184 patients

with bipolar I or bipolar II depression to sertraline (SSRI), venlafaxine (SNRI), or bupropion (NDRI) in addition to ongoing therapy with at least one standard mood stabilizer. Double-blind treatment was conducted, although there was not a placebo-controlled arm in this study. With respect to efficacy, there was no clear-cut winner, and response rates at 10 weeks ranged from 49% to 53%, with remission rates ranging from 34% to 41% (Leverich et al. 2006, Post et al. 2006). With respect to tolerability, a nonsignificant trend favored bupropion (31% dropout) over sertraline (41% dropout) and venlafaxine (45% dropout) (Post et al. 2006). Across all three drugs, patients with bipolar II disorder were more likely to suffer TEAS than were those with bipolar I disorder (Altshuler et al. 2006). Rates of switching ranged from 4% to 15% using a stringent criterion and from 14% to 31% when a more liberal definition was used (Leverich et al. 2006). In either case, venlafaxine was significantly more likely to induce TEAS than bupropion or sertraline (Leverich et al. 2006, Post et al. 2006). This is the second study to report a higher switch rate for venlafaxine than for an SSRI in bipolar disorder (see Vieta et al. 2002). As the TCAs also have been found to be more likely to cause switching than the SSRIs (Gijsman et al. 2004), it has been suggested that a strong effect on norepinephrine reuptake inhibition may be the shared causal factor (Thase 2005).

The second major study published recently is from the NIMH-funded Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), which recruited 366 patients with bipolar I or bipolar II disorder who presented in a depressive episode and consented to double-blind therapy with bupropion, paroxetine, or their matching placebos (Sachs et al. 2007). As in the study conducted by the Stanley Network investigators, patients were required to take at least one medication with established antimanic efficacy (i.e., the operational definition of a mood stabilizer for this study) in addition to the study medication; most commonly, this was valproate or lithium. Neither of the active antidepressants were particularly effective, and on some outcomes there were numeric, albeit not statistically significant, advantages favoring the group receiving a mood stabilizer and placebo. For example, the primary outcome—durable recovery, that is, eight consecutive weeks of euthymia—was reached by about 24% of the antidepressant-treated patients and 27% of the placebo-treated patients. Although the antidepressants did little objective good in this study, there was little harm as well; rates of TEAS were equivalent at approximately 10%. This landmark study provides no support for routinely adding an antidepressant to a range of mood stabilizers for bipolar depression, and replication is sorely needed.

Two medications—quetiapine and OFC—have each performed well enough in monotherapy trials in the treatment of bipolar depression to earn FDA approval for treatment of bipolar depression. The discovery of the utility of the olanzapine/fluoxetine combination was somewhat fortuitous, as the original study primarily compared olanzapine to placebo, with a small third arm included to provide a pilot test of the combination of olanzapine and fluoxetine. Tohen and colleagues (Tohen et al. 2003) randomized 833 patients with bipolar I depression to placebo (N = 377), olanzapine flexibly dosed at 5 to 20 mg (N = 379), and OFC (N = 86), with three fixed doses; 6/25, 6/50, 12/50; the smaller dose of olanzapine was used in conjunction with the larger dose of fluoxetine. Both olanzapine alone and OFC outperformed placebo when change in MADRS was used as primary outcome; OFC performed better than olanzapine monotherapy as well. Response rates were 30% for placebo, 39% for olanzapine, and 56% for OFC. TEASs were low for all groups (5.7% to 6.7%). Weight gain and increased appetite were associated with olanzapine used either singly or in combination with fluoxetine.

The quetiapine studies, known by the name BOLDER (BipOLar DEpRession) I

and BOLDER II, were eight-week, placebo-controlled, and used 300 mg or 600 mg of quetiapine or placebo (Calabrese et al. 2005, Thase et al. 2006b). In BOLDER I, 539 outpatients with bipolar I disorder (two-thirds) or bipolar II disorder (one-third) were randomized. Response was defined as >50% reduction from baseline MADRS, and remission was defined as an MADRS score lower than 13. Response rates were 58% for both quetiapine groups and 36% for placebo. Remission rates were 53% for both quetiapine groups and 28% for placebo. Withdrawal due to adverse events was 16.0% for the quetiapine 300 mg group, 26.1% for the quetiapine 600 mg group, and 8.8% for the placebo group. Rates of switching to mania or hypomania were 2.2% and 3.9% for the 600 mg and 300 mg groups, respectively. The switch rate for placebo was 3.9%.

BOLDER II followed the same design and enrolled 509 patients, again in a two-thirds to one-third ratio of bipolar I to bipolar II patients. The same dosing regimen and outcome measures were used. Both doses of quetiapine were again superior to placebo, with negligible rates of manic switch induction (Thase et al. 2006b). The only tangible difference in results between the two studies was that quetiapine was effective for bipolar II patients in BOLDER II, whereas the drug versus placebo difference did not reach the threshold of statistical significance in BOLDER I.

An analysis of data combined from BOLDER I and BOLDER II examined response in bipolar I and bipolar II patients and found both groups to respond significantly when compared with placebo. Additional analyses compared patients with a history of rapid cycling (four or more episodes in the preceding year) to those with fewer recent episodes (nonrapid cyclers); results indicated that quetiapine was of significant benefit in both types of bipolar disorder and was no more likely than placebo to cause TEAS in this high-risk group. Further research is warranted to characterize the durability of response across a continuation phase as well as to determine the therapeutic merit of doses lower than 300 mg per day.

Recent research thus has failed to confirm the value of adding antidepressants to ongoing therapy with mood stabilizers in bipolar depression and instead provides further fuel to the fire of controversy surrounding whether antidepressants should be avoided or their use at least minimized. Atypical antipsychotics such as quetiapine appear to have legitimate antidepressant effects without the added risk of TEAS. Whether the side effect burden and, at least in the short run, the cost of atypical antipsychotic medications justify first-line use, either alone or in combination with standards such a lithium, remains to be seen.

Maintenance Treatments

Currently, lithium, aripiprazole, olanzapine, and lamotrigine are FDA approved as maintenance treatments for bipolar disorder. FDA labeling notwithstanding, divalproex remains the most commonly prescribed medication for this indication.

Lamotrigine

Lamotrigine earned an FDA indication for the maintenance treatment of bipolar disorder despite being unable to demonstrate acute efficacy in the treatment of manic episodes or depressive episodes. To our knowledge, this is the only example in the therapeutics of mental disorders in which a medication is proven to prevent an illness that it does not treat acutely. The FDA approval was based on the results of two studies, one enrolling individuals who were recovering from a depressive episode (Calabrese et al. 2003) and the other enrolling people who were recovering from a manic or hypomanic episode (Bowden et al. 2003). Both of these parallel-designed studies entered symptomatic bipolar I patients who were recovering from an episode of bipolar illness on

any medication regimen deemed appropriate. Lamotrigine was added first to the treatment, titrating to 200 milligrams across four weeks. Patients who continued to remit following the addition of lamotrigine next were tapered off all other psychotropic medication and, assuming that they did not abruptly relapse, entered the randomized maintenance phase. During the maintenance phase, patients received double-blind treatment with lamotrigine alone or were switched to either lithium or placebo. The primary endpoint was need for psychotropic intervention for any new mood episode (i.e., the operational definition of a failure of prophylaxis).

In the study that entered people with bipolar depression (Calabrese et al. 2003), approximately 50% of those who began open-label lamotrigine therapy were randomized to the double-blind phase. Both lithium and lamotrigine were superior to placebo in time to intervention for any mood episode, and were comparable to each other. However, lamotrigine was superior to placebo in time to depressive relapse; lithium was not superior. In time to manic relapse, lithium was superior to placebo; lamotrigine was not.

In the parallel study enrolling manic patients (Bowden et al. 2003), both active drug arms were again superior to placebo in time to intervention for any mood episode. In contrast to the depression study, lamotrigine did not separate from placebo in time to depressive episode ($p = 0.12$) or time to manic episode ($p = 0.28$). Lithium was superior to placebo in time to manic episode ($p = 0.006$) but not in time to depressive episode ($p = 0.17$).

Data from these two studies were combined (Goodwin et al. 2004), which increased the power to detect differences in treatment arms. With the added statistical power, lamotrigine emerged as superior to placebo in the prevention of both manic and depressive relapse, with the treatment effect for prevention of depressive relapse about twice as large as prevention of manic relapse. Lithium was superior to lamotrigine in the prophylaxis of manic relapse. Lithium was not superior to placebo in prevention of depressive relapse ($p = 0.12$).

Beyond establishing that lamotrigine is a useful longer-term therapy of bipolar disorder—with greater effects for prevention of depressive relapses than manic relapses—it is important to keep in mind that these studies offer a somewhat negatively biased assessment of the efficacy of lithium in relation to lamotrigine. The major aspect of the design that introduces this bias is that all of the patients enrolled in the double-blind phase were selected because they could tolerate lamotrigine and did not rapidly relapse when their other medications were withdrawn, which resulted in an "enriched" population. Had an unbiased design been chosen (i.e., all patients were first stabilized on both lithium and lamotrigine before being randomly assigned to continue on one or the other or neither) it is at least plausible that the effects in prevention of bipolar depression would have been comparable, and lithium's advantage for prevention of mania would have been even larger. If the situation were reversed, that is, by enriching the study population with known lithium responders, it seems unlikely that lamotrigine would have been superior to lithium and may actually have been weaker for prophylaxis against both mania and depression. In our practices, we assume that the primary indication for lamotrigine is prevention of depressive relapses, and for those patients for whom there is a real risk of manic relapse, we generally combine lamotrigine with either standard mood stabilizer or atypical antipsychotic.

Olanzapine

The efficacy of olanzapine for maintenance-phase therapy was established by three RCTs (Tohen et al. 2003, 2005, 2006). The first of these was an extension of an acute-phase therapy study that compared the antimanic efficacy of olanzapine and valproate (Tohen et al. 2002). A total of 251 patients entered the acute-phase study and were randomized

in a 1:1 ratio to olanzapine (5 to 20 mg) or divalproex (target serum level 50 to 125 micrograms/ml). Although olanzapine-treated patients had a larger improvement in YMRS and a significantly higher remission rate (47% versus 34%) than that of the divalproex-treated patients in the first three weeks, the two medications performed equally well in the subsequent 47-week relapse prevention phase, and there were no differences in relapse rates into either mania or depression.

The second maintenance study (Tohen et al. 2005) used a different design, in which acutely manic patients were treated openly with both lithium and olanzapine, and the patients who remitted on this combination were randomized to twelve months of double-blind monotherapy with lithium ($N = 214$) or olanzapine ($N = 217$). Olanzapine was superior to lithium with respect to rates of manic relapse (12% versus 25%; $p = 0.001$), whereas there was a numeric trend ($p = 0.11$) favoring lithium for prevention of depressive relapse (8% versus 14%).

The third olanzapine maintenance study (Tohen et al. 2006) randomized patients who had remitted from acute mania when treated with open-label olanzapine to either continuation of olanzapine or switch to placebo under double-blind conditions. Patients were eligible for randomization if they had a YMRS score of <12 and a Hamilton Rating Scale for Depression score of <8 for two consecutive weeks during the open-label lead-in phase. A total of 225 patients were randomized to continuing olanzapine, and 136 patients were switched to placebo. Time to symptomatic relapse into any mood episode (primary outcome) strongly favored olanzapine (mean 174 days versus 22 days, $p < 0.001$) over placebo. Roughly 80% of the placebo-assigned group relapsed within three months of randomization, which suggests that the abrupt withdrawal of an effective antimanic agent so early in the course of treatment of a manic episode will likely lead to relapse. We hope similarly designed studies are avoided in the future.

Aripirazole

Aripirazole earned an FDA indication for the maintenance treatment of bipolar disorder primarily on the basis of a 26-week study that enrolled recently manic individuals who had responded to aripirazole acutely (Keck et al. 2006). In contrast to the similarly designed olanzapine study mentioned above, patients needed to be less symptomatic (YMRS <10) for at least six weeks prior to entry into the randomization phase. Additionally, patients were permitted to be stabilized openly for up to 18 weeks prior to randomization. These differences prior to randomization are reflected in the survival curve from the double-blind phase, which shows placebo-treated patients and aripiprazole-treated patients faring comparably well until approximately 100 days, when the placebo-treated patients began to relapse significantly more rapidly than did the aripirazole-treated patients. This benefit was exclusively due to prevention of manic relapse, as the rates of depressive relapse were similar in treatment and placebo groups.

Lithium

Far more data are available to support the utility of lithium in the maintenance treatment of bipolar disorder than for all the other commonly prescribed agents combined, and for this reason lithium is the prophylactic therapy against which all other novel therapies still are judged. Baldessarini and colleagues (Baldessarini et al. 2002) performed a meta-analysis of lithium in the prevention of recurrence in mood disorders. Twenty-eight studies, involving 2351 patients taking lithium for an average of almost 10 years, were analyzed and compared with a control group of 2308 patients not on lithium for an average of roughly four years. Of these patients, 78.4% were diagnosed with bipolar disorder; the others were diagnosed with MDD. Studies were subanalyzed to compare outcomes in placebo-controlled studies with those that were not

placebo controlled, blinded assessments were compared with nonblinded, and studies with a higher proportion of bipolar individuals were compared with studies with a higher proportion of unipolar individuals. The results were highly similar. Those patients taking lithium were more than threefold more likely not to have a recurrence of a mood episode than were patients not on lithium.

CONCLUSIONS

During the past decade, there have been a number of developments in the pharmacotherapy of mood disorders, and for the first time, more medications have been introduced for the treatment of bipolar disorder than for the treatment of MDD. With respect to pharmacotherapy of bipolar disorder, the challenge for the next decade will be to integrate these new developments into standards of practice, such that the greater costs of the newer therapies to patients and society are realistically weighed against benefits, and the potential side effects of these therapies—particularly the atypical antipsychotics—are minimized. With respect to the antidepressants, a period of quiet is useful for gaining perspective after a period of remarkable growth in the number of new medications, the number of related disorders for which these medications are also indicated, and the overall number of patients treated with antidepressants. Along with perspective has come greater caution, and the past decade has witnessed renewed concerns about the relatively small specific effect of antidepressants, their potential for induction of suicidal behavior—particularly for youths—and new evidence about small but potentially real risks for the developing fetus and neonates as well as the frail elderly. These concerns underscore older teachings that psychotropic medications—even the newer, safer ones—are not truly innocuous medications and that medications should be prescribed instead of nonpharmacologic alternatives only when the likelihood of benefit outweighs the known risks.

DISCLOSURE STATEMENT

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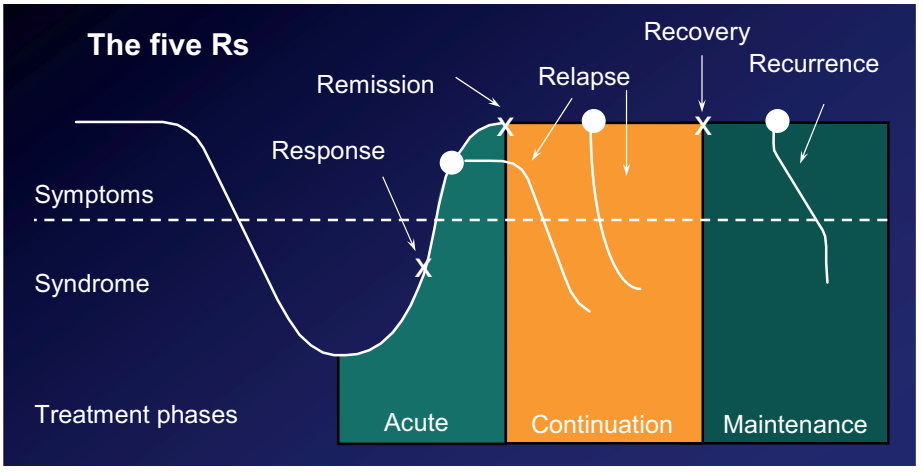

Figure 1

Phases of treatment and the five "Rs" of depression: response, remission, relapse, recovery, and recurrence. The solid line represents the course of a prototypical episode of depression, the dotted line represents normalization that occurs if the oncoming episode is prevented, and the dashed lines represent the return of symptoms associated with relapse and recurrence.

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