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Bipolar depression: Diagnostic and treatment considerations

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Abstract

Bipolar affective disorder is a recurrent, disabling, and potentially lethal illness that typically begins early in life. Although the disorder is defined by the manic and hypomanic episodes, for most people the depression episodes are the more virulent aspect of the illness. Specifically, the depressive episodes are more numerous, last longer, and are more difficult to treat than the manias, and depression is the principal cause of the illness's increased mortality due to suicide. For people with early-onset depression, predictors of subsequent bipolarity include a family history, psychotic features, and reverse neurovegetative features. Initial episodes of depression are commonly misdiagnosed, which often delays initiation of appropriate therapy and increases the likelihood of treatment with antidepressants alone. Unfortunately, the correct diagnosis is often not made until there has been a treatment–emergent affective switch. There are no treatments specifically approved for bipolar disorder in youth and, among antidepressants, only fluoxetine has received approved. When bipolarity is suspected, treatment with mood stabilizers, both conventional (i.e., lithium, valproate, and carbamazapine) and more recently classified (lamotrigine) and atypical antipsychotics should be prioritized. When antidepressants are indicated in combination with mood stabilizers, first choice options include bupropion and the selective serotonin reuptake inhibitors. Studies of adults indicate that several forms of focused psychotherapy may improve longer term outcomes.

Bipolar affective disorder, which was determined by the World Health Organisation to be the sixth most important public health problem (Murray & Lopez, 1996), is a potentially devastating mental disorder that usually begins early in life. The vast majority of people experience their first affective episode before age 30 and, for most people with such an early age of onset, the illness will run a recurrent and often chronic course, causing manifold interpersonal problems, vocational disability, considerable morbidity, and increased mortality (Angst, 2004; Perlis et al., 2004). In one large multicenter study of 1,000 patients with bipolar disorder, nearly 60% experienced their first episode before age 18, and such an early onset was associated with significantly increased risk of comorbidity and poorer outcomes (Perlis et al., 2004).

The intense, colorful, and often striking clinical presentation of mania dominates descriptions of bipolar affective disorder in youth and, of course, it is the manic and hypomanic episodes that differentiate bipolar affective disorder from the other mood disorders. Nevertheless, whereas a manic episode often results in an involuntary hospitalization and can mobilize family, employers, and health care providers to respond to the crisis, a bipolar depressive episode may smolder for months or even years without recognition of the illness or treatment. Suicide, which typically occurs in depressive or mixed episodes, ultimately may end the life of as many as 1 in 10 people with bipolar disorder (Tondo, Isacsson, & Baldessarini, 2003). Indeed, bipolar disorder is associated with a 20-fold greater risk of suicide compared to the overall population (Tondo et al., 2003). As with other markers of illness severity, early onset forms of

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bipolar disorder also are associated with a history of increased number of suicide behavior (Perlis et al., 2004)

Although once thought to be an uncommon condition (i.e., the lifetime incidence of mania, which defines the classic or type I form of the disorder, is about 1%; Kessler, Berglund, Demler, Jin, & Walters, 2005), recent evidence indicates that up to 4% of the population will experience briefer, less severe hypomanic episodes (Hirschfeld, Calabrese, et al., 2003). Moreover, when depressed individuals who report a history of hypomanic symptoms that fall below the threshold for bipolar II disorder are included within a broader bipolar "spectrum," the lifetime prevalence may exceed 6% (Hirschfeld, Calabrese, et al., 2003; Judd & Akiskal, 2003).

Despite such a high incidence within the overall spectrum of depressive disorders, bipolar affective disorder is frequently misdiagnosed. For example, a survey of 1,000 members of the National Depressive and Manic-Depressive Association (NDMDA; now known as the Depression and Bipolar Support Alliance) revealed that almost 70% had initially been diagnosed as suffering from a different mental disorder, with about one-quarter reporting four or more incorrect diagnoses (Hirschfeld, Lewis, & Vornik, 2003). As a depressive episode more often than not precedes the first mania or hypomania, major depressive disorder (MDD) is by far the most common misdiagnosis (Hirschfeld, Lewis, et al., 2003). Correctly differentiating bipolar spectrum disorders from MDD early in life thus has important treatment implications, particularly because antidepressant therapy may cause mania, mixed states, or accelerated cycling in bipolar patients unless prescribed in conjunction with mood stabilizers (Ghaemi, Boiman, & Goodwin, 2000; Joffe et al., 2002). Misdiagnosis almost ensures a delay in receiving appropriate treatment; respondents to the NDMDA survey reported that an average of nearly 9 years elapsed between the first contact with a healthcare professional and the correct diagnosis of bipolar disorder (Hirschfeld, Lewis, et al., 2003). With respect to individuals with an onset of illness during adolescence, a decade delay in appropriate therapy can have devastating effects on educational and subsequent vocational attainment, not to mention permanently altering the course of interpersonal milestones such as emancipation from one's family of origin and development of enduring intimate relationships (see, e.g., Perlis et al., 2004).

A strong case can be made that it is the depression, both syndromal and subsyndromal, that more typically dominates the course of bipolar affective disorder, not the manic and hypomanic episodes. In fact, the average person with bipolar disorder spends three to five times the number of days depressed than they spend manic or hypomanic, ultimately totaling up to one-third of one's adult life (Judd et al., 2002, 2003). Not only are bipolar depressive episodes typically longer in duration, they are also less responsive to standard therapies than mania (Hlastala et al. 1997; Kupfer et al., 2000). Moreover, whereas manic episodes are generally quite responsive to therapy, the bipolar mixed state (i.e., defined by the superimposition of a depressive syndrome on a manic episode) is one of the greatest therapeutic challenges (Thase, 2005). Better recognition and earlier intervention with appropriate therapies thus can profoundly improve the lives of young people with bipolar depressive episodes.

This article is about the diagnosis and treatment of bipolar depressive episodes, with particular attention to the care of depressed teenagers and young adults. As the literature on the treatment of bipolar depression in youth is sparse, evidence pertaining to pharmacologic and psychotherapeutic strategies that have been studied in adults will be emphasized. Even in adults, however, there are few data from randomized controlled trials (RCTs) on bipolar depression (see, e.g., Thase, 2005). This review thus will draw heavily on the recommendations of expert consensus practice guidelines for adults.

Recognition and Classification of Early-Onset Bipolar Disorder

Before discussing the treatment strategies for youths with bipolar depression, it is necessary

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to consider issues pertaining to recognition, assessment, and diagnosis. Although the current classification system for mood disorders is accurately described as Kraepelinian, it also owes much to the monograph of Carlo Perris (1966). Exactly 40 years ago it was Perris who recommended subdividing recurrent mood disorders into unipolar and bipolar subtypes. Within the decade of publication of Perris' monograph, Dunner and Fieve (1974) proposed that bipolar disorder be further dichotomized into Type I and Type II subforms, with the former used for patients with a history of a least one full manic episode and the latter used for patients with a history of hypomania and recurrent depressive episodes. In the American Psychiatric Association's official nomenclature, the term major depressive disorder (recurrent subtype) has been used to describe unipolar depression since 1980 (American Psychiatric Association, 1980).

With respect to diagnosis of bipolar disorder, the relevance of treatment emergent affective switches (TEAS) has been debated for almost as long as there have been antidepressants. *DSM-IV* (American Psychiatric Association, 1994) takes a conservative approach: TEAS are not counted toward the diagnosis of bipolar affective disorder. Thus, until an individual has spontaneously developed a hypomanic or manic episode, the diagnosis of bipolar affective disorder cannot be met, despite the number and intensity of TEAS.

Excluding TEAS from counting toward a diagnosis of bipolar disorder can be very problematic, however. Unlike stimulants and corticosteroids, antidepressants do not cause euthymic individuals to become euphoric. Moreover, TEAS have been shown to be one of the best predictors of subsequent bipolarity in teenagers and young adults who are treated for depression (Akiskal, 1995, 2005). Aside from the assumption of causality, TEAS look remarkably similar to spontaneous hypomanic and manic episodes (Akiskal et al., 2003; Stoll et al., 1994). The problem of how to account for TEAS in diagnosing bipolar disorder will hopefully be reexamined in the deliberations that will lead to *DSM-V*. Whether or not TEAS should be counted toward an official diagnosis of bipolar disorder, younger patients who experience a manic or hypomanic episode while being treated with an antidepressant are likely to be at extremely high risk for further switches during subsequent courses of pharmacotherapy without concomitant therapy with a mood stabilizer.

Much has been made of the observation that only a minority of individuals with early-onset forms of bipolar affective disorder are correctly diagnosed during the initial episodes of illness. However, without condoning diagnostic errors that result from failure to obtain an adequate history or not recognizing the classic phenomenologic features of the disorder, it is also important to appreciate that it can be difficult differentiate an acute episode of schizophrenia from a floridly manic episode in a teenager. Likewise, without a crystal ball, it simply may not be possible to recognize bipolarity when a depressed teenager or young adult has never experienced a manic or hypomanic episode. For these reasons, a certain amount of misdiagnosis of early-onset mood disorders is inevitable.

Ultimately, the depressed youth, as well as his or her family, typically are not seeking an accurate diagnosis but rather relief of the dysphoria and the accompanying depressive symptoms. Further, whereas mania is widely recognized as a pathologic state, many aspects of hypomania are viewed as healthy and even highly desirable, and thus may not be reported during a routine evaluation; individuals almost never seek treatment for hypomania. Akiskal (2005) has argued that, in the absence of clear-cut manic episodes, behavioral indicators of bipolarity are more valuable than subjective reports of mood swings. From this perspective, abuse of alcohol and multiple drugs, comorbidity with three or more anxiety disorders, or comorbidity with three or more Axis II disorders (especially with Cluster B personality disorders) may be more useful in recognizing a younger depressed patient at risk for bipolar disorder than a self-reported episode of spontaneous hypomania. Although problems with irritability, aggressivity, and impulsivity are endemic among youth referred for psychiatric services, when these behavioral disturbances are episodic the index of suspicion for bipolar disorder should be increased. Similarly, because

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adults with bipolar affective disorder often report that they suffered from attention-deficit/hyperactivity disorder (ADHD) in their youth (Nierenberg et al., 2005), depressed children and teenagers with a concomitant history of ADHD are also likely to be at high risk for subsequent bipolarity.

Other clinical features of the presenting depressive episode may provide additional clues about which patient with early-onset depression may be at increased risk of subsequently developing bipolar disorder. The atypical or reversed neurovegetative features (e.g., increased appetite, weight gain, and hypersomnolence) are both common in depressed youth and are associated with a greater likelihood of bipolarity, particularly bipolar II depressions (Akiskal & Benazzi, 2005). Although not many depressed youth report delusions and hallucinations, when present, psychotic features are associated with a greater risk of eventually developing bipolar affective disorder (Akiskal, 1995; Strober & Carlson, 1982). Other presenting features that are not commonly associated with the phenomenology of depression, including racing thoughts, heightened energy, decreased need for sleep, or increased libido, can be indicative of a mixed bipolar state (Akiskal, 1995, 2005; Akiskal et al., 1995). Even though a mixed subtype of bipolar II depression is not recognized in *DSM-IV*, recognition is clinically important because mixed bipolar states are less responsive to standard therapies (Hlastala et al., 1997).

Several standardized methods have been developed to improve the recognition of bipolar disorder. Among these methods, the Mood Disorder Questionnaire (MDQ; Hirschfeld et al., 2000), a self-report instrument, has been shown to be highly sensitive for identifying bipolar disorder in various adult populations. Although not yet well validated in teenagers, a parental form of the MDQ was found to improve recognition of bipolarity in one study (Youngstrom et al., 2005). The MDQ certainly does not replace a careful clinical evaluation, but may be particularly useful in nonspecialist settings such primary care and community mental health settings.

Whenever possible, the depressed youth's parents or guardians should be interviewed to obtain additional history suggestive of bipolarity. Although the impressions of parents do not necessarily override those of the depressed teenager or young adult, significant others may be more objective than the patient and better able to describe behavioral and temperamental characteristics. Parents and significant others also can be helpful with obtaining a comprehensive family history. Indeed, in one recent study, a family history of bipolar disorder was a powerful identifier of subsyndromal bipolar symptoms in depressed teenagers (Findling et al., 2005). Although cases of clear-cut bipolar I disorder will be relatively uncommon (i.e., perhaps no more than 10% of family members will have experienced a manic episode), the yield will be greater when the inquiry is broadened to include psychiatrically relevant events (i.e., treated depression, suicide or suicide attempts, and psychiatric hospitalizations for any reason). Again, more subtle indicators of familial bipolarity may be uncovered. Even when no one in a family has received a formal diagnosis of bipolar disorder there can be suggestive historical clues such as periods of erratic or impulsive behavior, episodic creativity or risky financial undertakings, or marked irritability (Akiskal, 2005).

Treating Early-Onset Bipolar Depression

There have been no controlled studies of pharmacotherapy for early-onset bipolar depression. In fact, there are surprisingly few controlled studies of treatment of bipolar depression in adults (Gijsman, Geddes, Rendell, Nolen, & Goodwin, 2004; Thase, 2005). Until recently, there was much less activity in development of novel treatments for all aspects of bipolar disorder (compared to schizophrenia), even though bipolar I disorder and schizophrenia are similarly prevalent. For example, whereas a large number of antipsychotic medications were introduced in the 1960s and 1970s primarily for treatment of schizophrenia, lithium was the only medication specifically approved by the US Food and Drug Administration (FDA) for treatment of bipolar disorder during this era. Nearly a quarter of a century elapsed between the FDA

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approval of lithium in 1970 and the approval of enterically coated valproate (divalproex, brand name Depakote) in 1994. The commercial success of divalproex did not go unnoticed, and across the last decade a large number of other medications have been approved by the FDA for treatment of mania, including two anticonvulsants, all of the widely used atypical antipsychotics, and the combination of the antidepressant fluoxetine (brand name Prozac) and olanzapine (brand name Zyprexa). Most of these medications were approved for treatment of mania, however, and progress in developing treatments specifically for treatment of bipolar depression. Both bipolar depression and depression in youth are difficult conditions to study via RCTs and, until most recently, the field has seemed content to let the pharmaceutical industry conduct the basic studies needed for approval of new antimanic medications and new antidepressants for adults, with the hope that the effects would generalize to younger patients with bipolar disorder.

There are also no consensus-based expert treatment guidelines for management of bipolar depression in youth, although a number of guidelines are available to aid treatment of adults. In the United States, for example, clinicians may draw upon the work of the American Psychiatric Association (2002), the Expert Consensus Guideline Series (Keck et al., 2004), and the Texas Consensus Panel on Medication Treatment of Bipolar Disorder (Suppes et al., 2002). Although each of these guidelines offer specific recommendations for treatment of bipolar depression in adults, with appropriate developmental adaptations, the principles are generally reasonable for selection of treatments for teenagers and young adults. In the following sections the major treatment options for early onset bipolar depression will be reviewed.

Monotherapy With Mood Stabilizers

A mood stabilizer is defined as a medication that treats mania and/or depression, prevents manic and/or depressive relapses, and does not induce TEAS. The three principal mood stabilizers are lithium salt, carbamazapine, and valproate. Although these medications have only been approved for treatment of mania, there is wide agreement that valproate and lithium are a reasonable first line choices for individuals suffering from milder bipolar I depressive episodes (American Psychiatric Association, 2002; Keck et al., 2004; Suppes et al., 2002). The basis for this recommendation is that there is some evidence from controlled studies that these mood stabilizers have significant antidepressant effects and, unlike antidepressants, they protect against TEAS. As mood stabilizers are the cornerstone for longer term preventive therapy, it is widely viewed as better to start them sooner than later (American Psychiatric Association, 2002; Keck et al., 2004; Suppes et al., 2002).

Despite the essentially uniform consensus supporting a "mood stabilizer first" approach to management of bipolar depression, not all psychiatrists follow this strategy. For example, in one recent survey about one-third of the bipolar patients treated by US psychiatrists were not even taking a mood stabilizer (Blanco, Laje, Olfson, Marcus, & Pincus, 2002). Assuming that these patients were correctly diagnosed, it would appear that a significant minority of patients are receiving suboptimal therapy from psychiatrists.

Lithium

When comparing lithium to the other first line mood stabilizer, valproate, there are several important pros and cons. On the plus side, lithium was the first medication to be classified as a mood stabilizer, and it has been the standard of therapy for bipolar affective disorder for more than 3 decades. Further, it is the most extensively researched treatment for bipolar depression, with positive evidence derived from a number of small placebo-controlled RCTs (see the review by Thase & Sachs, 2000). Lithium is also the only treatment of bipolar disorder that has been shown in epidemiological studies to reduce the risk of suicide and suicidal behavior (Baldessarini, Tondo, & Hennen, 2003; Tondo et al., 2003). In fact, in a recent report (Goodwin et al., 2003) based on the health service utilization data of nearly 21,000 people with bipolar affective disorder, lithium-treated patients were significantly less likely to make

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suicide attempts, require hospitalization for suicidal behaviors, or complete suicide than bipolar patients treated with valproate and carbamazapine.

On the minus side, relatively few younger bipolar patients find lithium to be an acceptable medication, and even fewer will remit and remain well on lithium monotherapy (American Psychiatric Association, 2002; Keck et al., 2004; Suppes et al., 2002). Younger bipolar depressed patients find several of the side effects of lithium to be quite obnoxious, including cognitive dulling, tremor, exacerbation of acne, and weight gain, and hearing about the need for regular blood work and the possibility of developing hypothyroidism and interstitial kidney disease after years of therapy causes further "push back." Yet another limitation of lithium for youth with bipolar disorder is that it has a relative low safety index in overdose.

Valproate

Whereas lithium is the old standard, bipolar patients treated in the United States are now much more likely to be prescribed valproate (Goodwin et al., 2003). In fact, in children and teenagers, valproate is prescribed up to seven times more commonly than lithium (Hunkeler et al., 2005). Clinical experience suggests that the main reasons for this pattern are that valproate is both better tolerated by younger patients and a less stigmatized medication than lithium.

Although widely used, valproate monotherapy is not well studied for bipolar depression in adults, and there are no controlled studies of valproate therapy in depressed youth (Thase, 2005). To my knowledge, there have been only two relatively small placebo-controlled RCTs, and only the published study reported positive findings (Davis, Bartolucci, & Petty, 2005). Additional evidence that is suggestive of the therapeutic benefit for bipolar I depression can be gleaned from secondary analyses of RCTs examining acute phase therapy response of patients with mixed manic states(Swann, Bowden, Calabrese, Dilsaver, & Morris, 2002) and prevention of depressive relapse following successful acute phase therapy of mania (Gyulai et al., 2003).

The major tolerability drawbacks of divalproex for younger bipolar patients include weight gain, changes in hair growth (both alopecia and hirsuitism), and menstrual irregularities. These tolerability issues tend to be more problematic for young women than men. The pattern of hirsuitism, weight gain, and menstrual irregularities is suggestive of induction of polycystic ovarian changes, which is also associated with infertility (Joffe, Hall, Cohen, Taylor, & Baldessarini, 2003). However, whether divalproex actually causes ovarian change, as opposed to causing an annoying, but much less serious, virilizing effect, is not yet resolved (Joffe et al., 2006).

Lamotrigine

The therapeutic profile of lamotrigine (brand name Lamictal) challenged longstanding views of mood stabilizers, because it is the first such medication that does not have acute antimanic efficacy (Ketter & Calabrese, 2002). This novel anticonvulsant has rapidly become one of the most widely prescribed treatments for bipolar affective disorder (Marangell et al., 2004), largely because of clinical observations of benefit for acute phase and relapse prevention therapy for bipolar depression (Thase, 2005).

Enthusiasm for lamotrigine for therapy of younger patients with bipolar depression has clearly outstripped the evidence of its efficacy. There are only two unequivocally positive studies in the published literature (Calabrese et al., 1999; Frye et al., 2000). Both studies found that about 50% of bipolar depressed patients would respond to therapy, and that lamotrigine did not cause TEAS. Two other RCTs, one focusing on patients with rapid-cycling bipolar disorder (Calabrese et al., 2000) and the other (Nierenberg et al., 2006) studying refractory depression in bipolar patients, failed to confirm significant therapeutic benefit on the primary outcome measure but did observe significant effects on secondary outcome measures. At least three other of RCTs of acute-phase lamotrigine therapy of bipolar I depression have failed to detect

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significant drug–placebo differences (these results were summarized in a conference presentation by Calabrese, Sachs, et al. 2005).

The evidence base supporting the use of lamotrigine as a monotherapy for bipolar depression is thus quite mixed and clearly will not lead to FDA approval. Lamotrigine therapy has, however, been approved by the FDA for preventive therapy of bipolar I disorder on the basis of two 18-month RCTs (Bowden et al., 2003; Calabrese et al., 2003). In both of these trials, one focused on patients recovering from mania (Bowden et al., 2003) and the other enrolling patients with resolving bipolar I depressive episodes (Calabrese et al., 2003), lamotrigine significantly reduced the risk of depressive relapses. Although the effects for prevention of manic relapse were smaller, a significant protective effect against manic relapses was found when the two studies were pooled together (Goodwin et al., 2004).

When compared to the other mood stabilizers, lamotrigine clearly has the most favorable day to day tolerability profile, and it has been extensively studied in children and teenagers with epilepsy. For depressed youth, the fact that lamotrigine is unlikely to cause sedation, tremor, or weight change at therapeutic doses is a major plus. There is, however, one very serious potential problem, and that is, like carbamazapine and divalproex, lamotrigine therapy is associated with uncommon (~0.1%), but potentially fatal dermatological reactions such as Stevens Johnson syndrome (Bowden et al., 2004). Lamotrigine differs from the other anticonvulsant mood stabilizers in that it is associated with a much higher (~10%) risk of benign rash (Calabrese et al., 2002). Unfortunately for all involved, every new onset rash must be treated as if it will become Stevens Johnson syndrome, as duration of lamotrigine therapy after the onset of rash is associated with greater risk and even the most talented dermatologist may not be able to differentiate a rash that will run a benign course from one with a more ominous prognosis. Prescribers must impress upon patients and their parents that all rashes should be taken very seriously, and lamotrigine therapy must be stopped, at least temporarily, at the first sign of rash. Nevertheless, about 1 in 10 courses of lamotrigine therapy necessarily ends abruptly, with some sense of uncertainty about having averted an impending catastrophe. This does little to strengthen an ambivalent youth's interest in other forms of medication and may actually rupture a shaky treatment alliance.

The strategies used to reduce the risk of serious rash have been established in studies of epilepsy (Bowden et al., 2004). In addition to stopping therapy if any rash emerges, which is a standard of practice, lamotrigine must be initiated at a low dose (i.e., 25 mg/day) and thereafter titrated slowly upward. If the patient is already taking valproate, the dose of lamotrigine must be reduced by 50% (because valproate slows the metabolism of lamotrigine). Additional caution in titration is needed with children and smaller teenagers, who are at greater risk of developing a serious rash, although the exact magnitude of this increased risk is not. Finally, as a rapid rise in lamotrigine blood levels can trigger the onset of a rash even after years of treatment exposure, the medication must again be titrated upward when there has been any disruption in therapy that exceeds more than a few days. This is particularly important because youth with bipolar disorder frequently take surreptitious drug holidays and need to be counseled not to automatically resume the medication at the full dose.

Combining mood stabilizers

For patients not responsive to lithium, valproate, or lamotrigine, the combination of two or more mood stabilizers represents another option to minimize exposure to antidepressants (American Psychiatric Association, 2002; Keck et al., 2004; Suppes et al., 2002). The general rationale for this strategy is that medications with modest antidepressant effects and different mechanisms of action might have additive benefit, while continuing to protect against TEAS. Use of this strategy is currently on the upswing because of clinical experiences combining lamotrigine with standard mood stabilizers such as lithium and divalproex. Despite such increasing use, however, no large-scale placebo-controlled RCTs of combined mood stabilizer therapy of bipolar depression have been completed. Results of two small studies

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suggest that the combination of two mood stabilizers may be a useful alternative to adding an antidepressant, although perhaps not as well tolerated (McIntyre et al., 2002; Young et al., 2000).

Atypical Antipsychotics: The Newest Class of Mood Stabilizers?

Initially developed for treatment of schizophrenia, the atypical antipsychotics are rapidly becoming the most important alternatives to the conventional mood stabilizers for treatment of manic episodes. In addition to the drug that defined this class, clozapine (Clozaril), there are now five atypical antipsychotics available in the United States. They are (listed in order of introduction): risperidone (Risperdal), olanzapine (Zyprexa), quetiapine (Seroquel), ziprasidone (Geodon), and aripiprazole (Abilify). All five have received FDA indication for acute phase therapy of mania, and two (olanzapine and aripiprazole) are also approved for relapse prevention following acute phase therapy.

Olanzapine was the first atypical antipsychotic to be studied for treatment of bipolar depression. The manufacturer conducted a very large ($N = 833$) RCT of bipolar I depression, finding that, although more effective than placebo, the absolute advantage of olanzapine monotherapy was relatively small (i.e., about a 10% absolute advantage in response and remission rates; Tohen et al., 2003). Further, olanzapine monotherapy was significantly less effective than the combination of olanzapine and fluoxetine (Tohen et al., 2003). It is important that neither olanzapine alone nor the olanzapine–fluoxetine combination resulted in a greater incidence of TEAS than placebo. The findings of this RCT played a pivotal role in the FDA's decision to approve of the combination of olanzapine and fluoxetine, but not olanzapine alone, for treatment of bipolar I depression.

Two large RCTs of quetiapine monotherapy of bipolar depression have now been completed, and both studies reported significant effects for two doses (300 and 600 mg/day) of the medication (Calabrese, Keck, et al., 2005; Thase et al., in press). Together, these studies, which included more than 1,000 patients, found that quetiapine was an effective treatment of patients with bipolar I and bipolar II depressions, including those with a history of rapid cycling and those with high levels of concomitant anxiety. There was no evidence of a dose–response relationship; as the lower dose was somewhat better tolerated, it should be considered the winner. It is conceivable that by the time this article is published quetiapine will have become the first monotherapy for bipolar depression to have received FDA approval.

Neither the olanzapine nor quetiapine data sets on bipolar depression have been examined with respect to effects across age groups. As pharmacoepidemiological data suggest that the atypical antipsychotic medications are increasingly used for treatment of youth with bipolar disorder and other behavioral problems, efficacy studies are urgently needed. In this respect, there is a positive RCT of add-on quetiapine therapy of youth with mania (DelBello, Schwiers, Rosenberg, & Strakowski, 2002), and studies of the antimanic effects of other atypical antipsychotics in youth are under way.

In practice, the major liabilities faced by younger bipolar patients taking atypical antipsychotic medications are weight gain and associated metabolic effects, including dyslipidemia and glucose intolerance. In adults, there is fairly good evidence from studies of schizophrenia that olanzapine is associated with the greatest risk of weight gain, followed by quetiapine and risperidone, which in turn are associated with greater weight gain than aripiprazole and ziprasidone (Melkersson & Dahl, 2004; Newcomer, 2005). To minimize the risk of weight gain, it is important to obtain weights at pretreatment and at each follow-up visit, to closely monitor changes in weight, and to encourage the patient to participate in dietary counseling and regular exercise. Laboratory monitoring of glucose, triglycerides, and other lipids also have become a standard of practice. Sedation also can be problematic, especially with olanzapine and quetiapine, although once daily dosing at bedtime tends to minimize this problem.

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Antidepressants: Understudied and Overused?

The role of antidepressant pharmacotherapy of major depressive disorder and dysthymia in youth has become a controversial topic and, to date, only one antidepressant (fluoxetine) has received FDA approval for treatment of depression in children and adolescents. The crux of the problem is that, whereas only a minority of studies of antidepressant therapy in children and adolescents has demonstrated unequivocally positive results, a composite analysis of all participants in these RCTs has identified that depressed youth receiving active antidepressants experience a small, but real, increase in the risk of treatment emergent suicidality (see Kratochvil et al., 2006, for a full discussion). Specifically, approximately 4% of the depressed children and adolescents treated in these studies have developed suicidal ideation, made a suicide attempt, or threatened suicide, compared to 2% of those randomly assigned to treatment with placebo. Of importance, none of the participants of these studies completed suicide. Although the possibility of suicidality emerging early in the course of treatment has been recognized for decades, demonstration that the risk exceeded that of placebo, in the absence of a strong signal of therapeutic benefit, has had an understandably dampening effect on the use of antidepressants in children and teenagers.

Among the several explanations for this phenomenon that have been advanced, the one of greatest salience to the topic at hand proposes that the relationship is largely explained by the antidepressants inducing a mixed form of TEAS in youth with unrecognized bipolar spectrum disorders (Akiskal, Benazzi, Perugi, & Rihmer, 2005). These investigators have proposed that it is the dysphoric activation (i.e., psychomotor agitation, impulsivity, sleeplessness, and generalized arousal) that drives the increased expression of suicidal ideas and actions. The model does make sense in that individuals who develop their initial depressive episode in childhood or adolescence are at increased risk of subsequently developing bipolar disorder and prescription of antidepressants without concomitant mood stabilizers can induce mixed episodes as well as more purely euphoric manias and hypomanias. Indeed, if 20% of the study participants will eventually be rediagnosed as having bipolar disorder and the rate of TEAS is estimated to be 25% during the first 8 weeks of therapy when antidepressants are used without mood stabilizers (see, e.g., Himmelhoch, Thase, Mallinger, & Houck, 1991), the entire excess risk of treatment-emergent suicidality might be explained by this mechanism *if* approximately one-half of the episodes were mixed. Time will tell if provoking bipolar mixed episodes is the principal cause of this association or only one of the risk factors.

Assuming that the potential benefits of antidepressants in depressed youth will eventually be shown to offset the small but evidently real risk of treatment emergent suicidality, the specific questions about the utility of antidepressants in early-onset bipolar depression will not be easily resolved. In fact, there is considerable disagreement among experts on the proper role of antidepressants for the treatment of bipolar I depression in adults. As noted earlier, expert practice guidelines uniformly conclude that antidepressants alone are contraindicated for treatment of bipolar I depression because of the risk of TEAS (American Psychiatric Association, 2002; Keck et al., 2004; Suppes et al., 2002). Antidepressants thus should be reserved for bipolar I patients for three indications: (a) as an "add on" following nonresponse to mood stabilizer monotherapy, (b) as an "add on" when there is a depressive relapse during preventive therapy with a mood stabilizer, and (c) in combination with a mood stabilizer from the initiation of therapy for patients with more severe depressive episodes (American Psychiatric Association, 2002; Keck et al., 2004; Suppes et al., 2002).

Beyond a scarcity of RCTs and concerns regarding suicidality, another concern about the use of antidepressants in youth with bipolar depression pertains to the wide range of opinion regarding the likelihood of precipitating TEAS. There is close agreement in the practice guidelines that the older tricyclic antidepressants (TCAs) should not be used (American Psychiatric Association, 2002; Keck et al.,

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2004; Suppes et al., 2002) and the higher incidence of TEAS associated with TCA therapy was confirmed by a recent meta-analysis (Gijsman et al., 2004). If an additional reason to avoid TCAs for treatment of teenagers and young adults was needed, the remarkably high risk of lethality in overdose should not be discounted.

First line therapies

When antidepressant therapy is indicated, the US guidelines list the selective serotonin reuptake inhibitors (SSRIs) and bupropion (Wellbutrin) as coequal first choices (American Psychiatric Association, 2002; Keck et al., 2004; Suppes et al., 2002). The SSRI class, which has been the most widely used class of antidepressants in the United States since the early 1990s, consists of five medications (listed in order of introduction): fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), citalopram (Celexa), and escitalopram (Lexapro). All of the SSRIs but escitalopram are now available in generic formulations, which greatly reduce the cost of treatment. The SSRIs are not only generally better tolerated than the TCAs, but they are also associated with only a small risk of TEAS (Gijsman et al., 2004; Leverich et al., 2006; Nemeroff et al., 2001; Peet, 1994; Tohen et al., 2003), at least when they are used in combination with mood stabilizers in patients who are not rapid cycling. When compared to bupropion, the SSRIs have an established track record for treating many of the comorbid disorders that coaggregate with early-onset bipolar disorder, including obsessive compulsive disorder, panic disorder, social anxiety disorder, and bulimia (American Psychiatric Association, 2002; Suppes et al., 2002; Thase, 2005).

There is no compelling reason to pick one SSRI over another beyond cost. Several secondary considerations favor selection of fluoxetine, the oldest member of the class. As noted earlier, fluoxetine is the only the only antidepressant to receive FDA approval for treatment of bipolar I depression, although this statement must be qualified in that the approval is for the combination of fluoxetine and olanzapine, and it is the only antidepressant specifically approved for treatment of depressed teenagers. The efficacy and safety of fluoxetine in youth with major depressive disorder was clearly evident in the large scale study conducted under the auspices of the National Institute of Mental Health (March et al., 2004). Finally, because of the long elimination half life of norfluoxetine (i.e., the active metabolite of fluoxetine), the impact of occasional lapses in adherence also may be less troublesome.

Bupropion, which is classified as a norepinephrine–dopamine reuptake inhibitor, is structurally and functionally unrelated to all other antidepressants. Like the SSRIs, bupropion therapy has not been associated with a high risk of TEAS in RCTs of bipolar depression (Leverich et al., 2006; McIntyre et al., 2002; Sachs et al., 1994). Again, the low rate of TEAS is likely to be contingent on treating patients who are not rapid cycling and are receiving concomitant therapy with a mood stabilizer. Also like the SSRIs, bupropion is available in generic formulations, although the once daily formulation, Wellbutrin XL, is still patent protected.

Head to head RCTs of adults with major depressive disorder indicate that bupropion and the SSRIs have comparable efficacy (Thase, Haight, et al., 2005). Nevertheless, it is likely that the spectrum of efficacy of these medications is only partly overlapping. For example, whereas bupropion has not been shown to be effective for any of the anxiety disorders, it has been approved as an adjunctive therapy for use in smoking cessation. Moreover, bupropion, but not the SSRIs, has been found to have some therapeutic activity for, ADHD (Solhkhah et al., 2005), another comorbidity common in early onset bipolar disorder.

Perhaps of greater importance in selection of a first line antidepressant in everyday practice is that bupropion has a much more favorable sexual side-effect profile than any of the SSRIs. In a meta-analysis of individual patient data from five RCTs, approximately one-third of patients treated with SSRIs experienced at least one treatment-emergent sexual dysfunction, whereas the rates of diminished libido, anorgasmia, and erectile dysfunction on bupropion therapy were essentially identical

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to placebo (Thase, Haight, et al., 2005). Although parents, mental health professionals, and other concerned adults may not want to hear it, drugs that do not cause sexual difficulties are as desirable to teenagers as they are to young adults.

There have been no RCTs of the efficacy and safety of bupropion in youth with major depressive disorder. Although generally well tolerated in depressed adults, one drawback of bupropion is that at doses above the therapeutic maximum (i.e., 450 mg/day) it is associated with an increased risk of seizures. This can be problematic following overdose, and prescribers need to be careful to ensure that patients do not inadvertently (or intentionally) take higher than recommended doses.

Second line therapies

Venlafaxine (Effexor XR), which is classified as a serotonin and norepinephrine reuptake inhibitor (SNRI), is generally recommended for treatment of bipolar depressed patients who do not respond to therapy with SSRIs and bupropion (American Psychiatric Association, 2002; Keck et al., 2004; Suppes et al., 2002). Venlafaxine does have a strong record of efficacy in studies of MDD (Smith, Dempster, Glanville, Freemantle, & Anderson, 2002; Thase, Entsuah, & Rudolph, 2001), particularly for patients who are not responsive to SSRIs (Thase, Friedman, & Howland, 2000). Nevertheless, there are several reasons to rank venlafaxine behind the SSRIs and bupropion. First, and most importantly, results of two RCTs of venlafaxine therapy of bipolar depression suggest no greater efficacy and higher rates of TEAS when compared to the SSRIs paroxetine (Vieta et al., 2002) and sertraline (Leverich et al., 2006). Second, generic formulations of venlafaxine are not yet available, and it is one of the most expensive antidepressants now available in the United States. Third, venlafaxine therapy also is associated with a somewhat greater side effect burden than the SSRIs, which includes a dose-dependent risk of hypertension (Thase, 1998). Fourth, results of several pharmacoepidemiologic studies suggest that venlafaxine may be more toxic in overdose than the SSRIs (although less so than a TCA; Buckley & Faunce, 2003; Cheeta, Schifano, Oyefeso, Webb, & Ghodse, 2004).

It is not yet known if duloxetine, the second SNRI to be introduced in the United States (Nemeroff et al., 2002), will share the same relative strengths or some of the same drawbacks as venlafaxine for treatment of bipolar depression. Preliminary evidence suggests that, like venlafaxine, duloxetine may have an efficacy advantage over the SSRIs in outpatients with major depressive disorder (Thase, 2004). Tolerability appears to be comparable to venlafaxine overall, although duloxetine therapy does not appear to be associated with nearly as high a risk of treatment-emergent hypertension (Thase, Tran, et al., 2005). There is as of yet little experience with duloxetine therapy of bipolar disorder, and studies of duloxetine therapy of depressed teenagers have not yet been undertaken.

Third line therapies

The older monoamine oxidase inhibitors (MAOIs), particularly tranylcypromine (Parnate), have perhaps the strongest track record of efficacy for difficult to treat episodes of bipolar depression (Himmelhoch et al., 1991; Thase, Mallinger, McKnight, & Himmelhoch, 1992; Thase, Trivedi, & Rush, 1995). However, issues of acceptability, tolerability, and safety have long undercut the potential utility of this class of medications (Thase et al., 1995); these concerns are particularly salient for selecting treatments for depressed youth.

Foremost among the issues that complicate MAOI therapy is the so-called "cheese effect," which necessitates following a special diet to avoid a hypertensive crisis (i.e., a dramatic and potentially lethal rise in blood pressure following ingestion of foods or beverages containing large amounts of the amino acid tyramine). Never known for their discretion and impulse control, some younger bipolar patients find it a challenge to adhere to the MAOI diet (which includes injunctions against aged cheese, sour cream, draft beer, and red wine). There are other problems as well. MAOIs have a much heavier side effect burden than modern antidepressants, and common side effects include orthostatic hypoten-

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sion, weight gain, peripheral edema, and anorgasmia (Thase et al., 1995). Another practical problem is that, because of the risk of serotonin syndrome, another serious (although rarely fatal) condition resulting from the drugs' irreversible enzyme inhibition, MAOIs cannot be started without at least a 1 week washout of most SSRIs and SNRIs, and at least a 4 week washout is needed following therapy with the slowly eliminated fluoxetine (Beasley, Masica, Heiligenstein, Wheadon, & Zerbe, 1993).

Despite these problems, MAOIs could be effective therapies for refractory depressions in adolescents, at least in expert hands (Ryan et al., 1989), and the therapeutic utility of the MAOIs has nevertheless sustained interest in the development of safer medications. One such medication, moclobemide, is a selective and reversible inhibitor of the A subtype of MAO and, as such, it does not require dietary restrictions at therapeutic doses (Lotufo-Neto, Trivedi, & Thase, 1999). Moclobemide appears to be effective in bipolar depression (Angst & Stabl, 1992; Silverstone, 2001), although it is not available in the United States, nor widely used in the countries in which it is available. Although internet savvy patients have no difficulty purchasing moclobemide from overseas-based pharmacies, lack of an FDA approval remains a strong disincentive against use, particularly because antidepressant therapy in youth has become a controversial topic.

A second MAOI that does not require dietary restriction, at least at the minimum therapeutic dose, has recently been approved by the FDA for treatment of major depressive disorder. This medication, selegiline (EMSAM), is delivered via a skin patch to avoid inhibition of MAO in the small intestine and, to a large extent, the liver, which greatly reduces the effect of the drug on tyramine metabolism (Amsterdam, 2003). Thus far, studies of adults with major depressive disorder have examined transdermal delivery of 6 mg/24 hr to 12 mg/24 hr, with application site reactions and, occasionally, insomnia the only side effects of note. As there have been no studies of SSRI-resistant depression, bipolar depression, nor depression in pediatric groups, and clinical experience with this treatment is limited, it remains to be seen if the selegiline patch will be a useful therapy for younger bipolar patients and, even if effective, if they will "stick to" a medication delivered by a skin patch.

The Special Case of Bipolar II Depression

There is no consensus about the best way to treat bipolar II depression (American Psychiatric Association, 2002; Keck et al., 2004; Suppes et al., 2002). Elsewhere I have recommended that treatment selection for a patient with bipolar II depression should be primarily guided by the patient's longitudinal clinical course and past treatment history (Thase, 2005). At the heart of this suggested approach is the assumption that each patient should be assessed in relation to prototypes of (nonbipolar) major depressive disorder or bipolar I affective disorder. For those with infrequent, mild, or highly functional hypomanias, antidepressants alone may be considered as long as there is no past history of rapid cycling or severe TEAS. Indeed, several studies have illustrated that, at least in the short run, many depressed patients with this more benign course of bipolar II disorder can be treated effectively without mood stabilizers (Amsterdam & Brunswick, 2003; Amsterdam & Garcia-Espana, 2000; Amsterdam, Shults, Brunswick, & Hundert, 2004; Kupfer, Carpenter, & Frank, 1988).

Of course, this recommendation is void if a patient should develop a TEAS or rapid cycling on antidepressant monotherapy. For bipolar II patients who have experienced more numerous or severe hypomanias or who have suffered clear-cut episodes of TEAS, mood stabilizers should be considered the preferred first line intervention (perhaps lamotrigine or valproate before lithium), followed by atypical antipsychotics or "add on" antidepressant therapy (Thase, Bhargava, & Sachs, 2003).

Longer Term Approaches to Pharmacotherapy: Relapse Prevention

When bipolar disorder begins in adolescence, the issue of indefinite or even lifelong treat-

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ment must be dealt with: the likelihood of both manic and depressive episodes is so great that ongoing preventive therapy is now recommended for all patients with bipolar disorder. Longer term therapy with mood stabilizers not only lessens the risk of relapse, but, at least for lithium, reduces the likelihood of suicide attempts and completed suicide. A treatment plan focusing on relapse prevention should emphasize mood stabilizers first (singly and, if necessary, in combination). Atypical antipsychotics and antidepressants should be considered second if mood stabilizers have not been effective in preventing relapse.

Lithium certainly has the longest track record as a preventive therapy for bipolar affective disorder, although its efficacy is well known to be stronger for protecting against manic rather than depressive relapse (Geddes, Burgess, Hawton, Jamison, & Goodwin, 2004; Sachs & Thase, 2000). Studies suggest that divalproex and carbamazepine may protect against both poles of bipolar relapse, although neither medication has yet received a formal FDA indication for this purpose. Of interest, whereas one large study of divalproex maintenance phase therapy failed to document a statistically significant relapse prevention effect for manic relapses (Bowden et al., 2003), a secondary analysis revealed significant protection against depressive relapses (Gyulai et al., 2003). The data on lamotrigine are more clearcut: both of the 18-month placebo-controlled RCTs of lamotrigine demonstrated significant protective effects against depressive relapse (i.e., about a 20% reduction in absolute risk and a doubling of time spent well), as well as about a 10% reduction in the risk of manic relapse (Goodwin et al., 2004). The relatively weaker effect against manic relapses probably explains why significant prophylaxis was observed only among the subset of patients with bipolar II disorder in the rapid cycling study only among the subset of patients with bipolar II disorder (Calabrese et al., 2000).

Data on the longer term relapse prevention effects of atypical antipsychotics are still weak and, drawing from studies of schizophrenia, the data on longer term problems with tolerability are quite strong. As noted earlier, only olanzapine and aripiprazole have FDA indications for longer term therapy in bipolar disorder, and in both cases the studies were based primarily on prophylaxis against manic, not depressive, relapse. Problems with weight gain and other metabolic complications commonly complicate longer term therapy with olanzapine and, to a lesser extent, quetiapine and risperidone. Ziprasidone and aripiprazole tend to be more difficult to initiate therapy, although they appear to have more favorable long term metabolic profiles, and have a particularly lower risk of weight gain. Although the risk of tardive dyskinesia is no doubt lower with these compounds (compared to the older antipsychotics), the specter of this potentially irreversible and disfiguring neurologic side effect cannot be dismissed: ongoing monitoring for signs of emerging dyskinesias is a necessity during maintenance therapy with any of the atypical antipsychotics.

Just as the evidence for acute phase antidepressant therapy of bipolar depression is weak, the evidence underpinning the use of antidepressants for relapse prevention is inadequate to inform practice guidelines for adults, let alone youth (Thase, 2005). In fact, not a single RCT of longer term therapy of bipolar depression has been conducted with any of the modern antidepressants. When antidepressants are necessary during acute phase therapy, some experts favor short trials (i.e., <6 months), whereas others approach prevention with a strategy that mirrors the current standard of practice for recurrent major depressive disorder (see, e.g., Keck et al., 2004).

Given the lack of evidence from longer term RCTs and the lack of consensus, the naturalistic study of Altshuler and colleagues (2003) is probably the best source of data to guide practitioners. In this prospectively monitored but nonrandomized study, antidepressant responders could either be withdrawn or remain on antidepressant therapy, based on the judgment of the treating psychiatrist and the patient's wishes. Although less interpretable than a randomized study, the naturalistic design of this study does reflect what is done every day in clinical practice. They found that briefer courses of antidepressant therapy were associated with a significantly greater risk of

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depressive relapse, but only a negligibly higher risk of manic relapse (Altshuler et al., 2003). Until better data are available, these data have changed my practice: I now keep bipolar depressed patients of all ages on antidepressants, assuming, of course, their response to medication has been stable and the drug is well tolerated.

Reevaluating the Role of Psychotherapy

Recognition of the real limitations of available medications, both the risk of relapse despite appropriate therapy and problems with adherence and tolerability, fostered renewed interest in the potential role of psychotherapies tailored to the needs of patients with bipolar affective disorder. Models of therapy that focus on cognitive behavioral (Lam et al., 2003), psychoeducational (Colom & Vieta, 2004; Simon et al., 2005), interpersonal/social rhythms (Frank et al., 1994), and family (Miklowitz & Goldstein, 1997) interventions have been developed and tested, with most studies yielding positive results with effect sizes that match or exceed those of recently approved pharmacotherapies. Among these therapies, the family-focused therapy model of Miklowitz et al. (2000; Miklowitz, George, Richards, Simoneau, & Suddath, 2003) is particularly relevant to the treatment of teenagers and young adults with bipolar depression, whose financial and emotional well-being is often inextricably tied to their relations with their families of origin.

Although these focused therapies clearly have value for relapse prevention, their utility as an "add-on" strategy (i.e., in combination with pharmacotherapy) for acute phase treatment of bipolar depression remains uncertain. In fact, in the only large-scale RCT completed to date that examined the acute phase antidepressant efficacy of interpersonal social rhythms therapy, psychotherapy did not have a significant additive effect compared to a relatively intensive supportive clinical management condition during the first 12 to 16 weeks of the study (Frank et al., 2005). Receiving interpersonal social rhythms therapy during the acute phase of therapy did make a difference in longer term outcomes, although this effect took several years to emerge (Frank et al., 2005).

Conclusions

Bipolar affective disorder usually begins during adolescence or young adulthood and, much more often than not, irrevocably alters the life course of both the person with the illness and his or her significant others. It is the more numerous, longer lasting, and more difficult to treat depressive episodes that ultimately take a greater toll on the life of the average person with bipolar disorder than the sometimes fulminate and almost always more colorful manias; this toll is expressed in more days spent ill, greater impairment of vocational and cognitive functioning, reduced quality of life, and a greater risk of suicide. As only a small proportion of people treated for bipolar I disorder are accurately diagnosed and appropriately treated during the initial several lifetime episodes, and only a similarly small proportion will remain on prophylactic pharmacotherapy for an indefinite period thereafter, for most who first become ill during adolescence, bipolar disorder becomes recurrent and potentially disabling illness. The principal treatments during the acute phase are mood stabilizers and atypical antipsychotics; when these are ineffective, antidepressants may be used judiciously with heightened scrutiny for signs of TEAS. When compared to major depressive disorder or schizophrenia, the amount of empirical evidence to guide treatment selection is meager. For most, no single therapy is highly effective, and often treatments that are incompletely effective must be used in combinations. Strong evidence is emerging from longer term studies to suggest that focused forms of adjunctive psychotherapy can significantly reduce the risk of relapse and prolong recoveries. Until better forms of therapy are developed, the best hope to reduce the toll of bipolar depression is more prompt recognition and accurate diagnosis, followed by implementation of conscientious yet, at times, creative treatment plans that draw upon both pharmacological and psychotherapeutic strategies.

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