A PRIMARY CARE APPROACH TO BIPOLAR DISORDER*

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ABSTRACT

Many patients with bipolar disorder can be successfully managed in primary care if the physician uses the tools and information available. Bipolar disorder treatment encompasses far more than pharmacotherapy. Nonpharma-cologic interventions are vital. Numerous medications are effective in treating this disorder but they do not exhibit class effects. Anticonvulsants and antipsychotic drugs, in particular, have very different efficacy and safety profiles. This article discusses the types of nonpharmacologic therapies that have shown success in bipolar disorder management, pharmacotherapy goals and options, clinical pearls for using atypical antipsychotics in bipolar disorder (including off-label usage), and medical comorbidities as potential treatment confounders (namely obesity and diabetes). With messages of hope, direction, and the importance of adherence, primary care physicians can have a dramatic impact on the outcomes of their patients with bipolar disorder.

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Beyond the challenges in diagnosing bipolar disorder lie the numerous considerations for treating and managing bipolar disorder. To maximize chances of treatment success, the primary care physician (PCP) needs to understand and embrace several important principles in bipolar disorder management. First, multiple treatment modalities will be necessary, including nonpharmacologic interventions. Several "classes" of medications are used to treat bipolar disorder, some of which are approved by the US Food and Drug Administration (FDA) and some of which are used off-label. Although clinicians may speak of a class effect with these drugs in other disorders, in bipolar disorder, there are substantial differences in mechanism of action, efficacy, side effect profile, and use in different phases of the disorder. Also, not all drugs in each class are effective for this disorder. Although antidepressants are a foundation of unipolar depression, they should be avoided in bipolar depression if possible. Finally, to avoid or to minimize the known metabolic complications with antipsychotic agents, clinicians should follow the recently published guidelines from the American Diabetes Association (ADA) and the American Psychiatric Association (APA). In fact, side effects are the main reason patients discontinue use of antipsychotic medications prematurely.

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PSYCHOTHERAPY

Psychotherapy is a critical component of bipolar disorder management. It should be initiated at the time of diagnosis and reviewed throughout the patient's lifetime. Psychotherapy should ideally include at least some aspects of each of the following: psychoeducation, cognitive-behavior therapy, family-focused therapy, interpersonal therapy, and interpersonal social rhythm therapy. There is considerable overlap between the approaches; their common themes are outlined in Table 1.[1]

Psychoeducation involves teaching patients about the illness and its treatment, including ways to identify early warning signs of relapse and, especially important early after diagnosis, information to reduce the stigma surrounding this disorder. Many patients may be surprised and/or upset when they are diagnosed with bipolar dis-

order, perhaps even feeling ashamed. The more information they have on the causes of the disorder and a realistic prognosis, the better they are able to deal with the diagnosis and take part in their own treatment plan. Group education and support are often very effective venues for psychoeducation.

Cognitive-behavior therapy (CBT) is a type of structured psychotherapy the helps the patient modify the detrimental thought patterns and behaviors that accompany bipolar disorder and its diagnosis as well as the negative perceptions of the medication used to treat the disorder. Importantly, CBT can also help the patient identify high-risk situations that may trigger relapse or switching. CBT is more often reimbursed by health insurance companies than other types of psychotherapy.

Family focused therapy is essentially psychoeducation for the patient's family members. It aims to reduce the distress among family members that may accompany the diagnosis of their loved and helps the family members to accept and provide support for the patient. It also reinforces the message that bipolar disorder is a medical illness, not the fault of the patient or any family member, and is not indicative of the patient simply being "crazy."

Table 1. Common Themes in Psychological Treatments for Bipolar Disorders

Psychological therapies may use some or all of the following interventions:

1. Facilitate adjustment to the disorder and its treatment
2. Enhance medication adherence
3. Improve self-esteem and self-image
4. Reduce maladaptive or high-risk behaviors
5. Recognize and modify psycho-bio-social factors that destabilize the individual's day-to-day functioning and mood state
6. Help the individual recognize and manage psychosocial stressors and interpersonal problems, including within the family
7. Teach strategies to cope with the symptoms of depression, hypomania, and any cognitive and behavioral problems
8. Teach early recognition of relapse symptoms and develop effective coping techniques
9. Identify and modify attitudes and beliefs about the disorder and its treatment
10. Improve self-management through homework assignments

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Interpersonal therapy focuses back on the patient and ways to improve relationships with family, friends, neighbors, and the community, particularly those that may have been damaged during severe manic or depressive episodes. The goal of this therapy is to improve communication skills and increase self-esteem during a short period of time. The therapy is usually limited to 3 or 4 months' duration. Unlike CBT, it usually does not involve challenges to self-defeating thoughts, but patients learn tools and techniques to help them in social situations, and their faulty thinking may be corrected by the therapist.

Finally, interpersonal social rhythm therapy helps the patient to establish daily routines, which is a very important part of preventing relapse or switching. For example, I often tell my patients with bipolar disorder that they should go to bed at the same time during the weekend as they do during the week, to maintain circadian rhythms.

As reviewed by Scott and Gutierrez, the published literature on these therapies illustrates numerous benefits in bipolar disorder, including reduced relapse rates, reduced length of hospitalization, increased time between episodes, shorter recovery time from depression, improved social functioning, and higher medication compliance.[1]

Many of these therapies have manuals for both clinician and patient to guide them through treatment. Ideally, patients with bipolar disorder should be referred to a psychologist with experience in this area, but the PCP should be aware of the types of therapy available, local psychologists who specialize in these treatments, and ways that some of these messages can be incorporated into the primary care office visit (also discussed later in this article).

Lifestyle Changes

Along with psychotherapy, lifestyle changes are an inherent and essential part of bipolar disorder management. The concept of lifelong treatment should be discussed with the patient at the time of diagnosis. Although the recommended lifestyle changes are not extreme, they can be difficult for patients during an episode and especially for patients with comorbid substance use. These changes include elimination of alcohol, caffeine, nicotine, and illegal drugs; incorporation of regular exercise into their routine; and eating a balanced diet. Mood charts are an essential component of man-

agement, as much for the patient as for the physician. Figure 1 is an example of the mood chart we use in our clinic.[2] Note that we ask patients to evaluate their mood twice a day (morning and night) and that manic and depressive symptoms are divided into 3 levels of severity. This reinforces the message to patients that everyone has normal “ups and downs” in mood. Many patients use these charts to monitor their moods and to identify potential episode triggers.

Pharmacotherapy Goals and Options

For effective management of bipolar disorder in primary care, clinicians should consider the following. First, decide your comfort zone for treatment. As discussed later in this article, therapy often includes the use of drugs that can have complicated adverse effect profiles, particularly in the context of comorbid medical illness (frequently seen in these patients). As shown in Figure 2, treatment of individuals with bipolar disorder often requires simultaneous treatment of comorbid conditions.[3,4] Also, off-label usage of these drugs is frequent. The PCP must decide whether he or she feels comfortable working with drugs that are not frequently prescribed in primary care. If not, the patient should be referred to a psychiatrist. Second, know your referral options. As mentioned earlier, the PCP should know not only local psychotherapists but also psychiatrists to

Figure 1. Sample Mood Chart

Name/Month/YR																																																													
Date: AM/PM	1	1	2	2	3	3	4	4	5	5	6	6	7	7	8	8	9	9	10	10	11	11	12	12	13	13	14	14	15	15	16	16	17	17	18	18	19	19	20	20	21	21	22	22	23	23	24	24	25	25	26	26	27	27	28	28	29	29	30	30	31	31
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We developed this mood chart for our clinic. It can be personalized to fit the patient's specific needs and profile.
Reprinted with permission from Kaye. *J Am Board Fam Pract.* 2005;18:271-281.[2]

whom they can refer patients for treatment, preferably with immediate availability when necessary.

Treatment goals for a bipolar disorder patient vary, depending on the current symptoms of the disturbance. However, in general, any pharmacotherapy should aim to reduce cycling, treat the acute episode of mania or depression, control agitation, resolve psychosis (if present), offer a favorable risk/benefit ratio, and not impose significant treatment barriers.

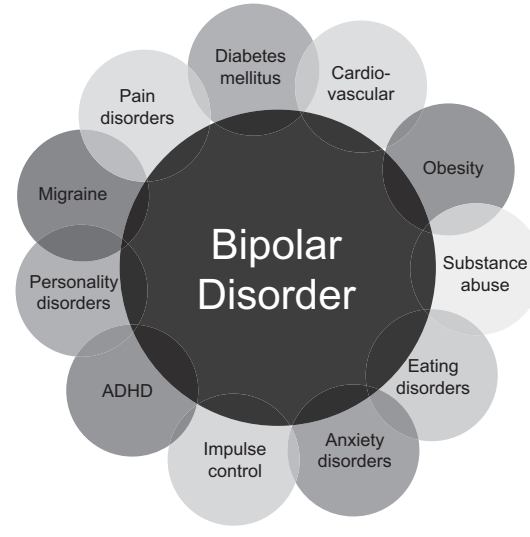
Medication options for bipolar disorder include mood stabilizers that prevent cycling, antimanic agents, antidepressants, and atypical antipsychotics. Some of these drugs are used off label for bipolar disorder and/or as adjunctive therapy. As shown in Figure 3, patients with bipolar disorder typically take 2 or more psychotropic drugs at any given time. One of these may be considered the foundation, to provide mood stabilization over time, while the others are added for symptomatic control as needed.[5,6] One concern of using traditional antipsychotics to treat acute mania is that they can push a patient's mood down too far and cause depression. Conversely, some antidepressants may induce rapid cycling or drive the patient to switch from depression into a full-blown manic episode. If a medication inadvertently complicates symptoms, the relationship between the clinician and patient could be put in jeopardy. Also, some drugs are used for different phases of the disorder, as shown in Figure 4.[7] Antidepressants are used only during depressive phases and only in combination with a mood stabilizer.

Polypharmacy is the rule rather than the exception with bipolar disorder. A voluntary registry of 457 subjects with bipolar disorder highlighted the frequency of polypharmacy. Less than 20% of the patients received monotherapy, and more than 80% received 2 or more medicines, of whom nearly 50% received 3 or more medicines. Among the entire group, nearly 25% were taking 4 or more medications.[8] These data underscore the need for the clinician to perform a risk-benefit analysis for each drug added to the treatment plan—for bipolar disorder and for any other comorbid illness (psychiatric or medical).

Mood Stabilizers

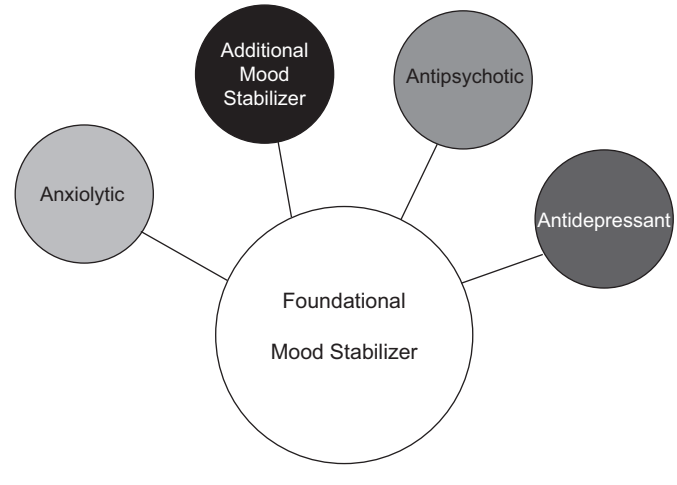
A liberal definition of a mood stabilizer is a medication that treats the acute phase of the illness without causing a switch to the opposite phase.[9] A more conservative and accepted definition of a mood stabilizer includes the ability of the medication to show

Figure 2. Multidimensionality of Bipolar Disorder



Reprinted with permission from McIntyre et al. *Hum Psychopharmacol*. 2004;19:369-386.[3]

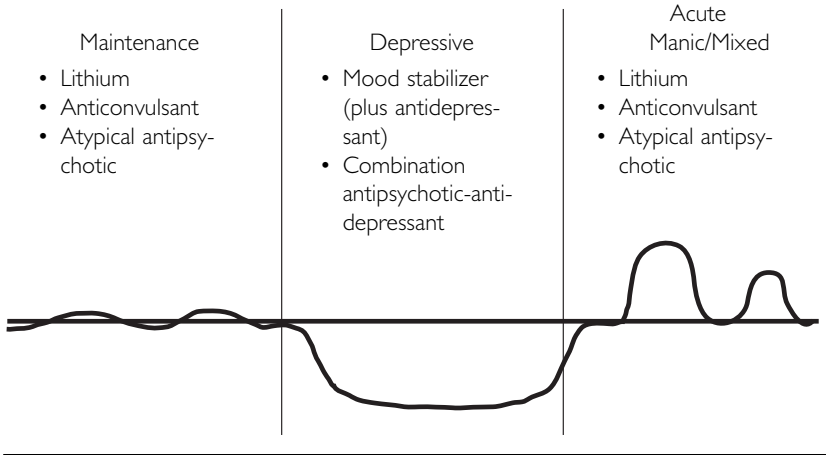
Figure 3. Bipolar Treatment Paradigm



maintenance efficacy, to prevent recurrent episodes of this cyclical event. Under this definition, the true mood stabilizers include lithium, sodium valproate/valproic acid/divalproex, carbamazepine, and lamotrigine. Only lithium and lamotrigine have well-accepted, evidence-based data to show that they prevent the recurrence of both depressive and manic episodes, whereas the data for divalproex and carbamazepine are weaker, but supported by over 20 years of clinical experience. Note, many antiepileptics have not shown efficacy in bipolar disorder.

Lithium is used for long-term treatment of bipolar disorder and remains the gold standard treatment. It is 1 of only 2 drugs (the other being clozapine) that have shown a significant preventive effect on suicide.[10,11] Lithium has also shown some success in maintenance treatment for rapid-cycling bipolar disorder.[12] Although some patients may be concerned about taking lithium because of a stigma associated with it, they may be comforted to know (especially those who embrace holistic medicine) that lithium is a naturally occurring crystal. For the physician, serum lithium levels, blood chemistry, and thyroid hormone levels need to be monitored (lithium can induce hypothyroidism, although this is relative easy and inexpensive to treat with thyroid hormone, as needed). Also, because lithium has a narrow therapeutic index, it can be fatal in overdose. Slow-release forms are often better tolerated, and are now available generically.

Figure 4. Bipolar Disorder Treatments by Phase



National Institute of Mental Health (NIMH). *Bipolar Disorder.* NIH publication 02-3679, 2001-2002. Available at: http://www.nimh.nih.gov/publicat/NIMHbipolar.pdf. Accessed January 15, 2006.[7]

Although it tends to be used more frequently in Europe, carbamazepine (an anticonvulsant) has established efficacy as a mood-stabilizing agent in bipolar disorder. The most serious side effects are rash, hyponatremia, and blood dyscrasia (which is rare). However, drug-drug interactions can be common. Serum levels, liver enzymes, and serum sodium levels will need to be monitored.

Valproate (or valproic acid/divalproex) is promoted for rapid-cycling bipolar disorder.[13] However, its side effects often complicate its long-term use: weight gain, tremor, sedation, and hepatotoxicity. In fact, valproate has limited long-term efficacy data. It is also associated with more severe adverse events such as polycystic ovaries and neural tube defects in pregnancy.[14] Serum levels and liver enzymes also need to be monitored with its use. The newest data suggest that better efficacy is achieved with higher serum levels (71.4–85.0 ng/mL at least and better control with levels of >94 ng/mL), but higher dosing, of course, correlates with more side effects.[15]

Lamotrigine, one of the more recently approved drugs for bipolar disorder, appears to be more effective at relieving depression, with milder efficacy in attenuating manic episodes. This has an advantage because patients with bipolar disorder tend to spend the majority of their time or their episodes in the depressive state: depression is 3 times more common than mania in bipolar I disorder and up to 37 times more common in bipolar II disorder. It also offers minimal weight gain and minimal sedation in its side-effect profile. Folate supplementation is suggested as well as slow titration, with 25-mg increments every 3 to 7 days. Caution should be exercised with concomitant use of valproate as the risk of rash increases. The most worrisome adverse events is a benign rash; the most serious adverse event is the rare occurrence of Stevens-Johnson syndrome (0.05%).

Antidepressants have traditionally been avoided in bipolar disorder out of concern of increased cycling; however, they are used in a subset of patients who do require them during depressive episodes. As mentioned earlier in this article, they should only be used with a true mood stabilizer in these patients. Of the antidepressant classes, selective serotonin

reuptake inhibitors (SSRIs) and bupropion have lower switch rates than other types of antidepressants; venlafaxine appears to have the highest switch rate and should generally be avoided.[16]

ANTIPSYCHOTICS

There is considerable symptomatic and syndromic overlap between different mood and psychotic disorders (Figure 5). Thus, antipsychotics (specifically, atypical antipsychotics) are frequently used adjunctively in bipolar disorder treatment. They include risperidone, olanzapine, ziprasidone, quetiapine, aripiprazole, and (as a last resort) clozapine. Although these drugs are collectively referred to as a class, they do not show a class effect in bipolar disorder. In fact, they have strikingly different receptor binding profiles, as shown in Figure 6, which may explain their differences in efficacy and side effects.[17-20] For example, olanzapine and quetiapine have high binding affinity for muscarinic receptors and histamine receptors, thus they may be sedating or may impair cognition. Olanzapine has been associated with development of the metabolic syndrome at a higher rate than any of the other agents in this class.

Antipsychotic agents are primarily used to treat manic symptoms and to prevent cycling; however, Gao et al, in a recent literature review, state that there are "no convincing data [to] support the impression that the typical antipsychotic agents worsen bipolar depression."[21] Evidence that monotherapy with atypical antipsychotics for the long-term management of bipolar disorder is lacking, despite US FDA approval of some of these compounds, with additional approvals expected.[22] However, the use of atypical antipsychotics in addition to the standard mood stabilizers—lithium, divalproex, lamotrigine, and carbamazepine—is certainly within the standard of care.

CLINICAL PEARLS FOR USING ATYPICAL ANTIPSYCHOTICS FOR BIPOLAR DISORDER

Risperidone is used as an antimanic agent. It incurs a higher risk of tardive dyskinesia than some of the other atypical antipsychotics, thus the dose should be kept below 4 mg if possible. It is available in several formulations: oral, elixir, and intramuscular injection (both short- and long-acting).

Olanzapine is also used as an antimanic agent and is US FDA approved for this indication. It has solid evidence of efficacy as monotherapy or adjunctive therapy for mania.[23-29] It has significant anticholinergic side effects (including sedation) and is associated with significant weight gain, metabolic syndrome, and diabetes. As a result, it is no longer considered to be a first-line agent.

Quetiapine is an antimanic agent with excellent data to suggest efficacy in bipolar depression (new drug indication submitted by AstraZeneca to US FDA December 30, 2005, for bipolar depression).[30] Trials are under way evaluating quetiapine as monotherapy in unipolar depression. Similar to olanzapine, quetiapine has antihistaminic and muscarinic properties, thus sedation can be a problematic side effect. Higher doses are often needed for the treatment of mania and schizophrenia, but doses up to 800 mg can be achieved in the first week of therapy by increasing the dose by 100 mg/day for the first 4 days, and then by up to 200 mg/day on days 5 and 6 to a maximum of 800 mg/day.[31] It is only available in oral formulation. At higher doses, alpha-1 antagonism may cause hypotension.

Ziprasidone is US FDA approved for bipolar mania and mixed states but its approval as maintenance treatment is expected. In order for ziprasidone to act as an antimanic agent, it must be prescribed at doses of 120 mg/day or higher, the dose at which it achieves the minimum of 60% D_2 receptor blockade needed for efficacy.[32-34] In vitro, at doses of 20 mg/day to 80 mg/day, ziprasidone is a potent sero-

Figure 5. Overlap of Mood Disorders and Psychotic Disorders

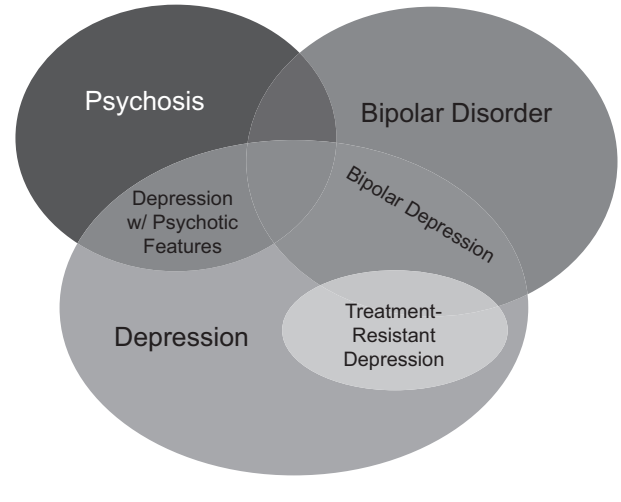
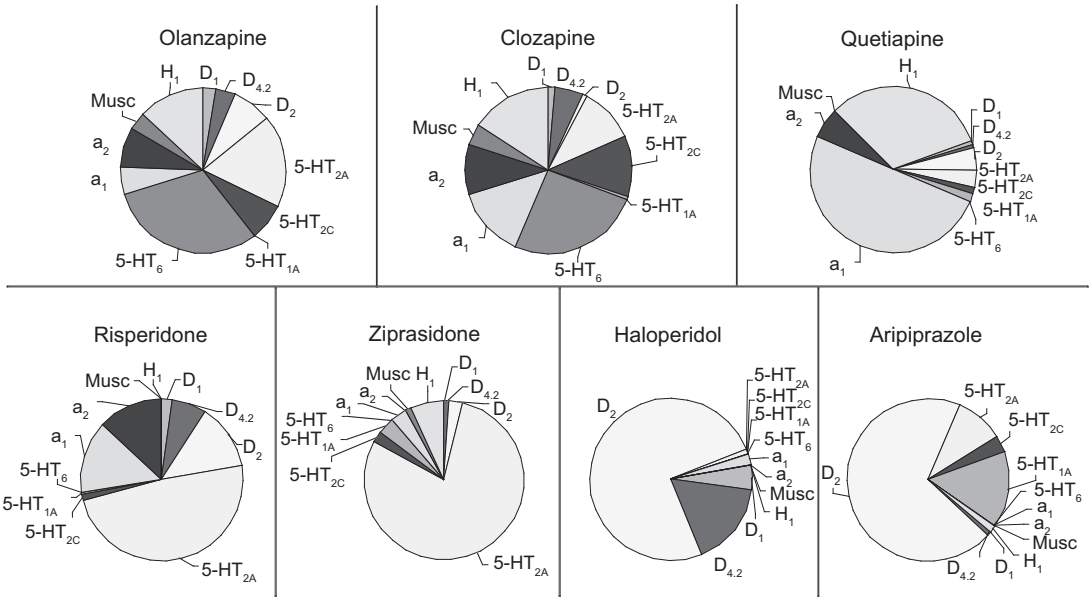


Figure 6. Different Antipsychotic Drugs Act Differently on Brain Receptors



Atypical antipsychotics typically exert their antipsychotic effects through dopamine receptor (D_2) antagonism. However, these drugs also have lower binding affinities to other types of receptors, such as serotonergic (5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_5), dopaminergic (D_1), histaminic (H_1), muscarinic (Musc), and alpha-adrenergic (a_1, a_2). Shown here is the relative receptor binding for each drug and receptor type.
Data from Bymaster et al[17]; Corbett et al[18]; Lawler et al[19]; Schotte et al.[20]

tonin and norepinephrine reuptake inhibitor, on the same order of magnitude as imipramine or amitriptyline.[35,36] It, too, has emerging data as an antidepressant in vivo and has been used as an augmenting agent in treatment- resistant depression.[37] Ziprasidone has a fast onset of action and is well tolerated. It has minimal anticholinergic, antihistaminic, or α-adrenergic effects, and it is not affected by nicotine (an important consideration in this patient population, in which smoking is very common). It is metabolized primarily by aldehyde oxidase. This is important because there are no known clinically relevant inhibitors or inducers of aldehyde oxidase, thus this drug is unlikely to be affected by drug-drug interactions. In fact, ziprasidone is a useful adjunctive treatment. Higher doses may be needed to achieve desired levels of efficacy, but its short serum half-life allows for rapid titration; however, the "half-life" in the brain is 18 to 24 hours, which allows for once-a-day dosing. It is available in oral and intramuscular formulations, and it readily dissolves, thus an "elixir" can be made. Efficacy studies show that it is one of the fastest-acting antimanic agents, when dosed at 80 mg on day 1 and 120 mg or 160 mg on day 2, with food.[38,39]

Aripiprazole is the newest antipsychotic to become available. It has antimanic properties with US FDA approval for maintenance treatment. It functions as a partial agonist at the dopamine D_2 and the serotonin 5-HT_{1A} receptors, and as an antagonist at serotonin 5-HT_{2A} receptor. Because of its very high D_2 agonism, it is associated with higher rates of extrapyramidal symptoms and akathisia than the other atypical antipsychotics and there is some concern that it may induce tardive dyskinesia.[40] Also, it requires CYP450 2D6 and 3A4 for its metabolism, thus drug-drug interactions should be a consideration, especially if used in children, geriatric patients, or in patient populations in which hepatic impairment may be an issue. Its efficacy for bipolar disorder is in a limited dose range.

COMPARING ANTIPSYCHOTIC AGENTS

The first results of the Clinical Antipsychotic Trials of Intervention Effectiveness project have been published.[41] This trial is designed to examine the long-term effects and usefulness of antipsychotics in persons with schizophrenia. The study is a head-to-head comparison of the atypical antipsychotics (olanzapine, quetiapine, risperidone, clozapine, and ziprasidone) and the conventional antipsychotics (perphenazine and fluphenazine decanoate). The results from treating 1493 patients show that the drugs had similar outcomes in terms of time to discontinuation for side effects or due to the patient's decision, in addition to Positive and Negative Syndrome Scale and the Clinical Global Impressions scale scores. Differences were seen in the incidence of certain side effects and in other outcomes. For example, the time to discontinuation for lack of efficacy was longer in days in the olanzapine group than any other group, but not statistically significantly than for the ziprasidone group. Also, more patients in the olanzapine group gained weight (on average 2 pounds per month), gained 7% or more of their baseline weight (30% vs 7%–16%; $P < .001$), and discontinued because of weight gain or metabolic effects (9% vs 1%–4%) compared to the other treatment groups. In fact, olanzapine-treated patients had more metabolic changes than the other groups. Only ziprasidone-treated patients showed improvement in all metabolic parameters, cholesterol, hemoglobin A_{1c}, and triglycerides.[41]

There were no significant differences among the groups in the incidence of extrapyramidal side effects, akathisia, or movement disorders as reflected by rating-scale measures of severity. However, more patients discontinued due to extrapyramidal symptoms in the perphenazine group than the other treatment groups (8% vs 2%–4%). Only risperidone patients showed a substantial increase in prolactin levels, and there were no statistical differences among treatment groups with regard to QTc changes or incidence of new cataracts.[41]

POTENTIAL TREATMENT CONFOUNDERS: MEDICAL COMORBIDITIES

Patients with bipolar disorder frequently have not only comorbid psychiatric conditions but also comorbid medical conditions. In a sample of 1379 patients with bipolar I disorder seen in the outpatient clinics at Duke University Medical Center from 2001 to 2002, 44% had significant comorbid medical conditions: 26% had 1 comorbid medical condition, 13% had 2 comorbid medical conditions, 3% had 3 comorbid medical conditions, and 2% had 4 or more comorbid medical conditions. Also, the percentage of bipolar I patients who had at least 1 comorbid medical condition increased directly proportionally with age, as follows: 30% in their 20s, 50% in their 50s, and 67% in their 70s.[42]

One of the most common comorbid conditions with bipolar disorder is obesity, which has its own associated complications, namely higher risk for diabetes and metabolic disorder. Although bipolar disorder may increase the risk of obesity caused by medication exposure and disease-specific symptoms (eg, appetite increase and reduced energy expenditure), obesity is linked to relapse in bipolar disorder. A study of 175 patients with bipolar I disorder who were treated for an acute affective episode and followed through a period of maintenance treatment showed that obesity correlated with poorer outcome, was more predictive of depressive recurrence than manic or mixed recurrence, and could alter the distribution and elimination of drugs.[43]

As recently reviewed by McIntyre and Konarski, there is a growing confluence of data (particularly studies conducted within the current decade) that confirm the higher prevalence of diabetes in patients with bipolar disorder than the general population and the unequivocal association between comorbid bipolar disorder and diabetes with being overweight and obesity.[44] Weight gain of 1 body mass index (kg/m^2) corresponds to a relative risk for developing diabetes of 2.9 to 4.3 in women and 1.0 to 1.5 in men.[45] In fact, co-occurrence of obesity, diabetes, and bipolar disorder should be considered by health practitioners when providing individual and family psychoeducation. Patients need to be warned about their likelihood of weight gain and developing diabetes, which places the patient at increased risk for heart disease. Obtaining a family history of these comorbidities should be part of the routine examination with diagnosis.[44] Also, metabolic syndrome (Table 2) is not to be ignored because of its increased risk for developing into type 2 diabetes.

In November 2003, the ADA, APA, American Association of Clinical Endocrinologists, and North American Association for the Study of Obesity held a conference to hear testimony from the pharmaceutical manufacturers of antipsychotic drugs and the US FDA with regard to the metabolic complications associated with antipsychotic drug use. Table 3 summarizes the consensus findings from that conference with regard to

atypical antipsychotics.[46] They also provide guidelines on monitoring parameters and frequency for patients taking antipsychotics (Table 4).[46] The APA also recommends that initial monitoring should include those parameters listed in the table and a lipid panel, complete blood count, electrolytes, liver enzymes, thyroid function tests, renal function, RPR, fasting blood glucose, hemoglobin A_{1c}, screening for hyperprolactinemia, screening for extrapyramidal symptoms and tardive dyskinesia using the Abnormal Involuntary Movement Scale, and a clinical history for cataracts, change in distance vision, or blurred vision.[46]

Finally, clinicians often think that the use of antipsychotic agents places the patient at greater risk for Torsades; however, the increased risk is usually a concern only with conventional antipsychotics (chlorpromazine, haloperidol, mesoridazine, thioridazine, and pimozide).[47] In fact, the perception of adverse events with atypical antipsychotics is often quite different from reality (Figure 7). Diabetes, hyperlipidemia, weight gain, insulin resistance, and higher glucose levels are all much more likely in patients taking atypical antipsychotic medications. They are also highly associated with each other and place the patient at increased risk for coronary heart disease and stroke. QTc prolongation is an extremely rare occurrence and clinicians would be well advised to focus on the coronary artery disease in patients, which is a significant risk as opposed to the rare electrical abnormalities that have been brought to our attention through marketing forces.

Off-Label Use of Medications

Off-label use of medications in psychiatry is a frequent if underreported practice. This also holds true for the management of bipolar disorder. However, in primary care, it is recommended that physicians try to stay "on label" when possible, mindful that off-label use can be done in regards to not only drug choice but also dose, diagnosis, or patient age. If it is necessary to use a medication off label, proper documentation is critical. Understandably, many physicians are concerned about the legal implications of off-label drug usage. It is important to note that the first page of the *Physician's Desk Reference* states the following: "The FDA has also recognized that the FD&C Act does not, however, limit the manner in which a physician may use an approved drug. Once a product is approved for marketing, a physician may choose to prescribe it for uses or in treatment regimens or patient populations that are not included in approved drug labeling. The FDA also observes that accepted medical practice includes drug use that is not reflected in approved drug labeling."[48] The Sidebar lists other important comments from thought leaders and professional medical organizations on off-label use of drugs.[41,46,49]

Proper documentation also includes informed consent, which is an ongoing discussion, rather than a single

Table 2. The Metabolic Syndrome

Waist	
Men	>40 inches
Women	>35 inches
Triglycerides	≥150 mg/dL
HDL-C	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	≥130/85 mm Hg
Fasting glucose	100–110 mg/dL

HDL-C = high-density lipoprotein-cholesterol.

Table 3. Atypical Antipsychotics and Metabolic Abnormalities

Drug	Weight gain	Risk for diabetes	Worsening lipid profile
Clozapine	+++	+	+
Olanzapine	+++	+	+
Risperidone	++	D	D
Quetiapine	++	D	D
Aripiprazole*	±	–	–
Ziprasidone*	±	–	–

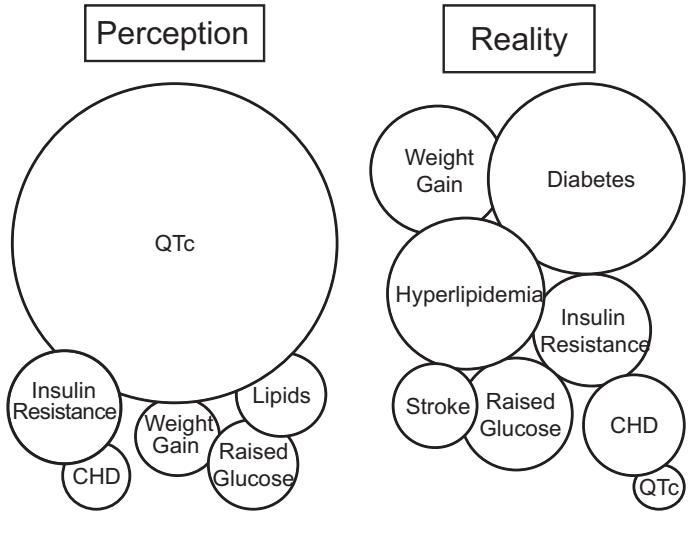
*Newer drugs with limited long-term data.
+ = increase effect; – = no effect; D = discrepant results.
Reprinted with permission from American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity. *Diabetes Care.* 2004;27:596-601.[46]

Table 4. Monitoring Guidelines for Patients Taking Atypical Antipsychotics

	Baseline	4 weeks	8 weeks	12 weeks	Quarterly	Annually	Every 5 years
Personal/family history	X					X	
Weight (BMI)	X	X	X	X	X		
Waist circumference	X					X	
Blood pressure	X				X	X	
Fasting plasma glucose	X				X	X	
Fasting lipid profile	X				X		X

More frequent assessments may be warranted based on clinical status.
BMI = body mass index.
Reprinted with permission from American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity. *Diabetes Care*. 2004;27:596-601.[46]

Figure 7. Perception Versus Reality Regarding Adverse Events with Atypical Antipsychotics



CHD = coronary heart disease.

signed document. The patient must be competent and noncoerced, showing comprehension of the warnings and asking questions. The patient must also understand the risks (most common and most dangerous potential side effects) and benefits associated with the treatment, treatment alternatives, the projected disease course without treatment, and the concept of off-label use. In the patient chart, I document discussions of informed consent, including off-label usage, with the following language: "I have explained to the patient the reasons for prescribing the above medication, the expected benefits and potential side effects, the treatment alternatives, and the expected course without treatment. The patient asked appropriate questions and appeared to understand the answers (I discussed off-label use). I provided information from the manufacturer. The patient has decided to try this medication and to be followed." This type of broad statement is more useful and simpler than trying to list everything drug/dose/option that was discussed. Remember, informed consent is an ongoing discussion with a patient and not simply a piece of paper that goes in a chart.

Patient Messages

Patient messages can play a critical part in determining whether a treatment will be successful. Patients look to their physicians for direction and hope, in both message content and delivery. For bipolar disorder, key

patient messages should warn against the patient adjusting medication dose or stopping the medication without first speaking to the physician. Patients also need to know that bipolar disorder, although increasingly diagnosed and discussed in the lay media, is unique to each individual, thus the medications that may be effective for their friend or relative may not work for them. Perhaps most importantly, though, the physician needs to deliver a message of hope, asking the patient not to get discouraged and to call with any questions or concerns they may have, and the doctor should return the call in a timely manner. Tell patients that they will get better if they take their medications and follow the nonpharmacologic interventions that you have prescribed for them. This also provides the opportunity to encourage patients to be involved in their own care, reminding them that they are responsible for their own health.

Clearly, these messages need to be tailored to the individual patient as some patients may be more motivated or adherent or have greater insight than others, and some may be less easily discouraged or influenced by outside sources (eg, family/friends and general news reports). PCPs often have a long-standing relationship with a patient and thus may better predict the potential barriers to treatment success for a particular patient.

Adherence Messages

With regard to pharmacotherapy, in particular, patients should understand and accept that the medication needs to be taken daily and should be continued even when they are feeling better. Also, the medications may need 2 to 4 weeks for effects to be felt. Mild side effects with these drugs are common and will usually abate in 7 to 10 days. Remind patients that they can call at any time with questions; however, this does require that we return our patients' calls. One of the most common reasons physicians are sued and lose is that they did not return the patients' phone calls.[50]

Conclusions

Bipolar disorder can be successfully managed in primary care if the PCP uses the tools and information available. Bipolar disorder treatment encompasses far more than pharmacotherapy. Nonpharmacologic interventions (psychotherapy, psychoeducation, and lifestyle management) are vital. Several medications are effective in treating this disorder, but they do not exhibit class effects. Anticonvulsants and antipsychotic drugs have very different efficacy and safety profiles, thus labeled usage should be followed when possible. If antidepressants need to be used, the duration should be limited to the depression cycle and they should always be administered with a mood stabilizer. Some atypical antipsychotics are associated with serious metabolic complications, thus the

THOUGHTS ON OFF-LABEL USE OF PRESCRIPTION DRUGS

Lieberman et al, CATIE study results:

"The dose range approved by the FDA for quetiapine and ziprasidone may be below their optimal therapeutic doses…"*

American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity:

"…are increasingly being used off label. In current practice, people who are likely to be treated with an SGA include those with schizophrenia spectrum disorders, bipolar disorder, psychotic depression, autism and developmental disorders, and to a lesser extent, individuals with conditions such as delirium, aggressive behavior, personality disorders, and PTSD. These conditions are common and often require lifelong treatment."†

Dr Norman Sussman:

"In general, dosages used in trials—the basis for labeling recommendations—are not necessarily optimal for clinical practice. In fact, opinion leaders such as those who present at CME symposia and drug manufacturers themselves are now advocating higher dosages of some new antipsychotics than those described in the PDR"‡

*Lieberman et al. *N Engl J Med.* 2005;353:1209-1223.[41]
†American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity. *Diabetes Care.* 2004;27:596-601.[46]
‡Sherman C. Higher-dose atypical regimens are becoming more common. *Clin Psych News.* 2003;31:29.[49]
CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness; CME = continuing medical education; FDA = Food and Drug Administration; PDR = *Physicians Desk Reference;* PTSD = post-traumatic stress disorder; SGA = second-generation antipsychotic.

guidelines put forth from the APA and ADA should be followed to minimize or hopefully reverse these complications. Side effects are the main reasons patients with bipolar disorder discontinue treatment. With our messages of hope, direction, and the importance of adherence, PCPs can have a dramatic impact on the outcomes of their patients with bipolar disorder.

Discussion

Dr Treisman: Dr Kaye, because efficacy trials are often the basis of dosing in US FDA-approved uses, are these in fact the doses that are used for many patients in the real world? My view is skewed because I see many refractory cases. What doses would a primary care provider be likely to see you use in patients you are sharing?

Dr Kaye: Glenn, thank you for raising an important point. We all have heard the joke about specialists using the same medications as primary care doctors, but just at higher doses. To some degree, it ends up being true. As we share patients with PCPs, it is important for them to also realize that data derived from schizophrenia studies sometimes influences clinical psychiatrists when approaching difficult patients with bipolar disorder. Certainly, for ziprasidone and quetiapine, the doses needed for acute mania are often higher (240–320 mg for ziprasidone and 800–200 mg for quetiapine; Table 5).[25-28,30,38,39,49,51-92] Some experts, including the Cincinnati group headed by Dr Keck and some of the folks I know at Johns Hopkins Hospital, will start olanzapine at 40 to 60 mg on the first day and then reduce by 5 mg daily as the patient comes under control.

We have much less data to work with in terms of maintenance therapy and the role of atypicals in bipolar II disorder. Still, in the trenches, dosing above package insert is pretty common for ziprasidone, olanzapine, and quetiapine. Lower doses for treating both unipolar and bipolar depression are being used off label by psychiatrists and studied by manufacturers and institutions. However, the data in that area are limited to case reports or small case series. We keep trying to get direction from the depression data scores in bipolar studies (Montgomery-Asberg Depression Rating Scale/Hamilton Depression Rating Scale), but I caution about overinterpreting these data, as more often than not, the larger trials designed to look specifically at the depressive side of the disorder and at unipolar depression have not been able to substantiate much of an antidepressant effect for the class. High hopes, limited data, and lots of research going on, thus we will have to wait and see.

Dr Ostacher: Neil makes some good points. However, pharmaceutical companies often corrected the dosing mistakes they made in their schizophrenia trials by the time they did their mania trials, and I don't know any bipolar researchers who say that the recommended mania doses are inadequate. Other than for aripiprazole, the mania dosing of atypical antipsychotics is lower in range and maximum dose than for schizophrenia. Aripiprazole is routinely underdosed in bipolar disorder; it may well be that 2 mg or 5 mg works for mania (as suggested in Table 5), but the lowest dose ever studied for it is 15 mg. Psychiatrists using aripiprazole at low doses are open to their own liability. I can only imagine how much higher the liability is for a PCP who underdoses a drug for a serious mental illness that is usually treated by psychiatrists if it leads to a bad outcome.

Dr Moore: As a PCP, I would likely not exceed the evidence-based dosing. It is my feeling that I would want a specialist to evaluate for effects both positive and negative if higher dosing were needed. However, I am not sure that all of my colleagues would share my conservative approach. Although discussing these "real-world dosing recommendations" used by psychiatrists can bring some perspective to the PCP, especially in patients who do not respond, I would recommend that PCPs not attempt it on their own and refer to a specialist.

Dr Leibenluft: Yes, I'm not comfortable with recommending to PCPs drug doses that are outside the published, evidence-based ranges. Although we, as psychiatrists seeing patients with bipolar disorders, may feel comfortable extending those dose ranges based on our experience, I think that PCPs would be better off following the guidelines. If a PCP wants more expert clinical expertise, he/she really needs to get a consultation. That's a good opportunity for the psychiatrist-PCP relationship.

Dr Manji: I am also concerned about going beyond the PDR (*Physicians' Desk Reference*) guidelines, particularly if it is not based on controlled evidence. Indeed, we have examples of this in the treatment of mania. For many years, we heard about the use of high doses of haloperidol being used to treat mania by clinicians, but when it came to controlled trials, no advantage was seen by using this approach.[93] Although there are undoubtedly certain patients who require and can tolerate higher doses, I think that it would make sense for PCPs to consult with psychia-

Table 5. Doses of Drugs for Treating Bipolar Disorder Phases in Adults from Large Clinical Trials ($n \geq 200$)

	Bipolar Depression	Maintenance/ Continuation	Hypomania	Mania	Mixed	Comments on Real-World Use in Mania
Atypical Antipsychotics						
Aripiprazole	NA	15 or 30 mg/day[51] *	NA	30 mg/day starting dose; can be decreased to 15 mg to avoid side effects[52,53]	30 mg/day starting dose; can be decreased to 15 mg to avoid side effects[52,53]	Aripiprazole blocks 60% of dopamine D_2 receptors at 2 mg and 80% at 5 mg.† Thus, dosing in the range of 2–30 mg reflects current prescribing practices, but a clinician may consider trying lower doses to reduce akathisia.
Olanzapine	5–20 mg/day[28]	5–20 mg/day[54-57]	NA	5–20 mg/day[25-27,57-59]	5–20 mg/day [25,26,54,55,57]	Olanzapine is commonly used at 40 mg every day, and up to 60 mg every day is not unusual in clinical practice.[49,60]
Olanzapine/fluoxetine	6/25, 6/50, or 12/50 mg/day[28,61]	NA	NA	NA	NA	
Quetiapine	300 or 600 mg/day[30,62]	NA	NA	400–800 mg/day; mean 588 mg/day[63-67]	NA	Quetiapine is routinely dosed at 600–1200 mg/day and up to 1800 mg/day is common.[49,60,68,69]‡
Risperidone	NA	NA	NA	1–6 mg/day; mean 3.1–3.9 mg/day[70-75]	1–6 mg/day; mean 3.9 mg/day[71,72,74]	Risperidone at 6-mg blocks roughly 60% of dopamine D_2 receptors;† thus, doses below 6 mg are preferable. It has been used at doses up to 16 mg/day (original package insert). Ideal dosing may be 1–4 mg.
Ziprasidone	NA	NA	NA	40–80 mg twice daily[38,39]	40–80 mg twice daily[38,39]	Ziprasidone reaches 60% of D_2 receptors at 120 mg/day. In patients with severe, persistent mania, doses up to 320 mg every day is common.‡ Dosing once a day is supported by PET binding data, and taking ziprasidone with food is critical for absorption.[76-79]
Other Drugs						
Carbamazepine§	NA	NA	NA	200–1600 mg/day extended-release capsules[80,81]	200–1600 mg/day extended-release capsules[80,81]	
Lamotrigine‖	50–400 mg/day[82,83]	50–400 mg/day[82,84,85]	NA	NA	NA	
Lithium	0.8–1.1 mEq/L[82]	Mean 0.55–0.67 mEq/L[86]; mean 0.8–1.2 mmol/L[87]; 0.6–1.2 mEq/L[88-91]	NA	0.6–1.4 mEq/L[92]	0.6–1.4 mEq/L[92]	
Valproate	NA	71–125 µg/mL blood level[87]; 500–2500 mg/day[57]	NA	500–2500 mg/day[25,57]	500–2500 mg/day[25]	

This table is meant to act as a guide for PCPs treating bipolar disorder. The doses provided here are doses used in large clinical trials in which the drug of interest has shown efficacy. The column "Comments on Real-World Use in Mania" reflects Dr Kaye's clinical experience with these drugs and thus the doses are not necessarily evidence based. The panel members strongly encourage PCPs to follow the evidence-based dosing recommendations.

*This study had 161 patients.

†Comments on D_2-receptor activity are relevant to side effects, not efficacy.

‡"The dose range approved by the US FDA for quetiapine and ziprasidone may be below their optimal therapeutic doses…" (Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;353:1209-1223.)

§Carbamazepine auto-induces hepatic enzymes, which can affect blood levels of carbamazepine and the other medications (eg, oral contraceptives).

‖Clinicians should be cautious with lamotrigine dosing when it is coadministered with valproate/divalproex

NA = no studies performed or no studies that included adults or had at least 200 patients; PET = positron emission tomography.

trists in these cases, rather than using higher than recommended doses.

Dr Adams: I would not feel comfortable going outside recommended dose ranges. In fact, my goal is to get the patient to a psychiatrist. I may have to convince the patient why we should treat this, and then why I am referring them to a psychiatrist. I tell my patients, "If you broke your bone, I'd send you to an orthopedist. I think you've got bipolar disorder; I want you to see a psychiatrist."

Referral for Psychiatric Care

Dr Treisman: The resistance of payors to help primary caregivers make this happen is insane, especially given the pharmacoeconomic and psychoeconomic data of the impact of psychiatric care on primary care cost.

Dr Adams: It's much more convenient for a patient to just see me, and then they can also tell me about their sinusitis, and their child's problem, and they can get their flu shot, and I can also treat their depression and give them something for sleep. They don't have to take time off from work, and they can get an appointment pretty quickly. However, I tell them, "I have to get you to a good therapist so they can help me figure this out."

Dr Moore: Yes, it's convincing them that making the correct diagnosis is critical, and that you're not handing them off to someone else permanently.

Dr Leibenluft: That's a common treatment model—for the psychiatrist to make the diagnosis and initiate treatment, and the PCP can do the follow-up care, with the psychiatrist available for future consultation.

Dr Moore: That's a good model, but there's a culture that's evolved, at least in Washington, in which the psychiatrists are in a black box and there's really not a lot of communication between the psychiatrist and the primary care doctors.

Dr Treisman: That's a model that has to be fought. It is a big problem. In my first study as a clinician and nonbasic scientist, we referred 100 patients in the HIV clinic for follow-up care to a variety of different settings (eg, psychiatrists and specialty clinics). None of the 100 patients went to their appointments. Now, this is a special population of very psychiatrically ill patients. I don't think it's generalizable, but it does tell you that patients tend not to go. And, it also tells you that the psychiatrists tend not to push too hard to get them to come. The community psychiatry program at Johns Hopkins, which I was a part of at that time, never once called me to say the patient didn't show, called the patient, or did anything else. It's a big issue.

At the other end of the spectrum, our most recent study shows that integrated psychiatric and medical care in the HIV clinic has a mortality advantage.[94] That is, patients who have seen a psychiatrist in the AIDS clinic were expected to have higher mortality because they had a psychiatric diagnosis, but they have lower mortality than those who haven't seen a psychiatrist. The study was controlled for several factors. However, it shows that, in terms of positive predictive value, if you have a psychiatric diagnosis and have at least one visit with a psychiatrist, you're more likely to get HAART (highly active antiretroviral therapy). The data are very resilient. The data also show that those patients who see the psychiatrist at least once are more likely to stay on HAART and have reduced viral loads (although the data are less resilient, but still pretty good). There are several studies that show psychiatrically ill patients do more poorly in HIV settings, but the only thing that differentiates our clinic from those other clinics is that we have psychiatry on-site and they don't. It's truly integrated. Psychiatrists see patients in the clinic. I think it would be good if Dr Adams had a psychiatrist who was interested, excited, and very skilled, and said, "How about if I come to your office 2 days a month and see your psychiatrically ill patients with you and write in your charts, thus you know what's going on?" And, it's so good for patients. The healthcare system knows that, thus they're going to reimburse both of us for coming, and make it worth our while to do this together.

Dr Adams: It's also the primary care doctor believing that the mental health disorders are true medical problems and treating them with that model. It is also up to us—primary care doctors—to have a relationship with a psychiatrist. I have 3 or 4 whom I can call and say, "I'm sending you this person. This is what I think is going on with them." There are some things I've used to streamline this for patients. When I've been working with a patient and think they need to see a psychiatrist, I tell the patient to make the appointment, let me know who it's with, thus I can sign the record release and send something over saying the medications I've already tried. If I do that, I've gotten letters from the psychiatrist explaining the treatment plan. With that, I will refer indefinitely to that psychiatrist as long as what they said made a modicum of sense.

Dr Moore: But it's 1 in 10 psychiatrists that will do that.

Dr Adams: It is very rare, but sometimes they'll call, or sometimes I get cryptic notes. "Get an MRI (magnetic resonance image). You may want to try this."

Dr Ostacher: We're coming from very different cultural places. Primary care medicine does not have a psychoanalytic tradition to weigh them down.

Dr Leibenluft: And, many psychiatrists in private practice don't have the infrastructure.

Dr Ostacher: And, there are all sorts of payment problems. People have different insurances, and different psychiatrists take different insurances. That's a whole other, separate issue.

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