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Review



# Special considerations in the treatment of patients with bipolar disorder and medical co-morbidities

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## Abstract

**Background:** The pharmacological treatment of bipolar disorder has dramatically improved with multiple classes of agents being used as mood-stabilizers, including lithium, anticonvulsants, and atypical antipsychotics. However, the use of these medications is not without risk, particularly when a patient with bipolar disorder also has comorbid medical illness. As the physician who likely has the most contact with patients with bipolar disorder, psychiatrists must have a high index of suspicion for medical illness, as well as a basic knowledge of the risks associated with the use of medications in this patient population.

**Methods:** A review of the literature was conducted and papers addressing this topic were selected by the authors.

**Results and discussion:** Common medical comorbidities and treatment-emergent illnesses, including obesity, diabetes mellitus, dyslipidemia, cardiac disease, hepatic disease, renal disease, pulmonary disease and cancer are reviewed with respect to concomitant use of mood stabilizers. Guidance to clinicians regarding effective monitoring and treatment is offered.

**Conclusions:** Mood-stabilizing medications are necessary in treating patients with bipolar disorder and often must be used in the face of medical illness. Their safe use is possible, but requires increased vigilance in monitoring for treatment-emergent illnesses and effects on comorbid medical illness.

## Background

Patients with bipolar disorder are among the most challenging to treat pharmacologically, especially in the presence of medical comorbidity. Although the rates of medical comorbidity are high in patients with bipolar disorder (20–80%), medical illnesses are frequently underdiagnosed and inadequately treated in psychiatric patients. For example, Cradock-O'Leary and colleagues reviewed centralized Veterans Affairs data and examined the use of medical services by 175,653 veterans during fiscal year 2000 [1]. They identified 3,694 veterans with a primary diagnosis of bipolar disorder and compared the care that these veterans received to that of all veterans. Among all veterans with diabetes and hypertension, those with a comorbid diagnosis of bipolar disorder (as well as those with diagnoses of anxiety disorder, schizophrenia, post-traumatic stress disorder, or a substance use disorder) were less likely to have more than one medical visit

in one year. This is especially concerning given that veterans are afforded medical and psychiatric treatment within one comprehensive health care system, seemingly making care more accessible. Patients with bipolar disorder in the general population are likely receiving even less medical care. The significance of this finding is that the psychiatrist may be the only physician caring for these patients on a regular basis. Therefore, psychiatrists must have a high index of suspicion for medical illness, as well as a basic knowledge of the risks associated with the use of medications in this patient population.

The purpose of this paper is to identify common medical comorbidities in bipolar disorder, including those that are treatment–emergent, and to offer guidance to clinicians regarding effective monitoring and treatment.

## Material and methods

An extensive review of effective pharmacotherapies is beyond the scope of this paper which will perform a selective review the psychotropic medications often prescribed to patients with bipolar disorder, with an emphasis on their use in patients with medical comorbidity. More specifically, the review results include papers concerning bipolar patients with obesity, diabetes mellitus, dyslipidemia, cardiac, hepatic, renal and pulmonary disease and cancer.

It is essential to keep in mind that benefit cannot be deleted from the risk:benefit analysis. In some cases a medication with greater side effects or medical risk may be the preferred treatment because of the documented efficacy of the agent either in general, or in a particular patient.

This paper will perform a selective review of the psychotropic medications often prescribed to patients with bipolar disorder, with an emphasis on their use in patients with medical comorbidity. Currently, lithium, valproate, olanzapine, lamotrigine, risperidone and quetiapine are indicated for use in bipolar disorder by the US Food and Drug Administration (FDA). Aripiprazole has recently been submitted to the FDA for approval in the treatment of bipolar disorder. Other agents are also used as adjuncts, despite limited efficacy data. As such, mention of a medication in this article does not necessarily imply efficacy, and the reader is referred to the American Psychiatric Association practice guideline for Bipolar Disorder (2002).

## Results and discussion

### *Obesity*

Obesity is a leading cause of preventable death in the United States, with an estimated 300,000 people dying annually of obesity-related causes [2]. Although the general population in the United States is increasingly more overweight and obese, 64.5% and 30.5%, respectively, in a 1999–2000 survey, individuals with bipolar I disorder are still slightly more likely to be obese [3]. Fagiolini and colleagues found that 35.4% of patients with bipolar disorder were obese. Pharmacotherapy and affective episodes both influence appetite and physical activity, thereby increasing the risk for obesity. Obesity in bipolar patients is correlated with a greater number of lifetime depressive and manic episodes, a more severe and difficult-to-treat index episode, and a greater risk of developing an affective recurrence, most often depression [4].

Persons with bipolar disorder are more likely to be overweight (body mass index [BMI] of 25–29.99 kg/m2) or obese (BMI of 30 kg/m2 or greater) even when mood is euthymic. Elmslie and colleagues found the prevalence rates for obesity and being overweight in euthymic female bipolar patients were 1.5 and 1.8 times greater, respectively, when compared to the reference group [5]. Obesity was also more prevalent in male euthymic patients compared with the reference group. In both male and female bipolar patients, truncal obesity was most prominent. This pattern of obesity reflects fat that is distributed centrally between the thorax and pelvis and is associated with increased risk of type 2 diabetes mellitus, dyslipidemia, hypertension, stroke, ischemic heart disease and early mortality [6-9]. The authors concluded that the prevalence of obesity in this study of outpatients was related to the use of antipsychotics, but less so lithium or anticonvulsants. Of those persons prescribed no psychotropics, less than 10% were obese, suggesting that bipolar disorder itself does not cause obesity, and that pharmacologic treatment and gender are greater influences [10].

Important factors influencing obesity in bipolar patients include nutrient intake and physical activity. In assessing the nutrient intake of persons with bipolar disorder, Elmslie and colleagues found that they had increased intake of carbohydrates and sweets, especially non-alcoholic sweetened drinks [5]. The intake of sucrose was higher in patients, particularly females, receiving antipsychotics than in those receiving other or no medications. Patients with bipolar disorder were also more sedentary, exercising less frequently and with less intensity than reference subjects. Medication side effects such as dry mouth and increased thirst may lead to increased consumption of sweetened drinks. Sedation, decreased motivation and impaired coordination may promote physical inactivity.

Obesity in patients with bipolar disorder should not be the only factor used to inform selection of psychotropics. In fact, patients who are obese at baseline may be less likely to have significant weight gain than those with a lower baseline body mass index. At the same time,

though, use of certain psychotropic medications may make it more difficult for those patients to lose weight. Patients should be weighed at baseline and again two weeks after beginning treatment. If the patient gains four pounds or more, behavioral interventions of diet and exercise and a consultation with a nutritionist should be considered. Specific dietary modifications should include avoidance of refined carbohydrates, including sweetened drinks, increased intake of omega-3 fatty acid, and small amounts of protein with each meal [11]. Behavioral interventions can lead to significant loss of weight gained while taking atypical antipsychotics, and the modifications of eating and exercise habits help patients maintain the weight loss [12].

Pharmacologic treatment of obesity should be avoided if at all possible, given the risk of side effects and drug interactions. Pharmacologic agents should be reserved for those patients with a BMI of 30 kg/m2 or greater, or a BMI of 27 kg/m2 or greater and risk factors for weight related medical illnesses [12]. Agents associated with weight loss include metformin [13-15], topiramate [16], sibutramine [12], amantadine [18,19], nizatidine [19] and orlistat [20]. Centrally acting agents have a theoretical risk of exacerbating psychosis or mood disorders and should be used with caution [22,23].

Gastric restrictive surgical interventions may be considered for patients whose BMI exceeds 40 kg/m2 and who have not responded to behavioral interventions or pharmacologic treatment [12].

### *Diabetes mellitus*

Cassidy and colleagues reported the prevalence of diabetes mellitus in hospitalized bipolar patients to be approximately three times the national average [24]. Further, bipolar patients with diabetes mellitus had more lifetime psychiatric hospitalizations than non-diabetic bipolar patients. It is prudent, therefore, for psychiatrists to be aware of the risk factors associated with diabetes, including treatment-emergent diabetes. Recent publications linking atypical antipsychotics with treatment-emergent diabetes are numerous, but often contradictory. There are reports of hyperglycemia associated with risperidone, quetiapine and ziprasidone, and more frequently with clozapine and olanzapine [26,27].

Of note, those with baseline risk factors for diabetes mellitus are more likely to develop treatment-emergent diabetes (TED). Sowell identified risk factors for patients who entered clinical trials and later developed TED [28]. At study entry these patients had higher random glucose levels, were older, more obese and more likely to possess multiple risk factors for DM. Neither treatment-emergent weight gain nor treatment group significantly impacted the risk for TED. Established risk factors for diabetes include: family history, ethnicity, increasing age, central obesity, physical inactivity, low HDL/high triglycerides, fasting glucose of 110 mg/dL or greater, gestational diabetes, hypertension, and polycystic ovary syndrome.

Though questions remain about the pathophysiology of treatment-emergent diabetes, guidelines are being formulated to aid clinicians in identifying patients at risk. Screening for diabetes should include questioning patients about symptoms such as excessive thirst and urination, nocturia, unexplained weight loss, fatigue, frequent infections, and blurred vision. Recommendations for fasting glucose screening at baseline and follow-up for patients receiving atypical antipsychotics are presented in Table 1[29].

### *Dyslipidemia*

The effects of atypical antipsychotics on lipid levels have been reported primarily in patients with schizophrenia. Studies of patients on atypical antipsychotics, as well as high potency neuroleptics, show a significant association between weight gain and cholesterol and triglyceride elevation in patients with schizophrenia. This association is most commonly observed in patients prescribed clozapine and olanzapine, reaching statistical, though not necessarily clinical significance [26,30-33]. Olanzapine, risperidone and quetiapine have also been shown to decrease mean low-density lipoprotein (LDL) levels, and olanzapine may also lower mean high-density lipoprotein (HDL) levels [30]. Some studies indicate that ziprasidone may lower cholesterol and serum triglycerides [27]. As such, some authors recommend monitoring body weight, fasting cholesterol and triglycerides at baseline and every six months in routine clinical practice with all antipsychotics [26].

**Table 1: Diabetes Mellitus Screening Recommendations For Patients Treated with Atypical Antipsychotics [29]**

| | |
|---|---|
| Initiation of Treatment | • Baseline fasting glucose level |
| First Year of Treatment | • Fasting glucose level every 3–4 months<br>• Observe for signs of hyperglycemia |
| Duration of Treatment | • Fasting glucose level every 6 months in high-risk patients<br>• Fasting glucose level every 12 months in patients with normal glucose levels during first year of therapy |

The effects of anticonvulsants on serum lipid and cholesterol levels have been studied primarily in patients with seizure disorders. Carbamazepine-induced increase in total cholesterol is primarily due to an increase in HDL [34]. This occurs during the initial weeks of therapy, persists throughout treatment and reverses in the first few weeks after discontinuation. A 5-year prospective study of patients treated with carbamazepine also revealed a transient increase in LDL cholesterol and triglycerides in the first year of treatment [35]. When carbamazepine was replaced with oxcarbazepine in patients with seizure disorders, total serum cholesterol levels decreased, but HDL cholesterol and triglyceride levels remained unchanged [36].

Women with obesity and polycystic ovaries or hyperandrogenism treated with valproate have also been shown to have elevations in serum triglycerides and low HDL to total cholesterol ratios [37,38]. This is consistent with insulin resistance in this population. Valproate does not appear to contribute to clinically significant dyslipidemia across other populations [38,39]. The effects of lamotrigine and topiramate on serum cholesterol and triglyceride levels have been reported in small studies and case reports [16,38]. Neither of these anticonvulsants appears to affect lipid levels.

Currently there are no published recommendations for monitoring serum lipids in patients receiving anticonvulsants. In patients identified as having polycystic ovaries or hyperandrogenism, monitoring of lipid levels is warranted.

#### *Cardiac disease*

As discussed above, patients with bipolar disorder have a higher prevalence of cardiac risk factors, such as obesity, glucose dysregulation and dyslipidemia. It is not surprising, therefore, that patients with bipolar disorder also have greater mortality from cardiovascular disease compared with the general population [40]. Further, many of the medications that treat bipolar disorder may have cardiac side effects or toxicity. Underlying cardiac disease may also affect the pharmacokinetics of psychotropics.

Congestive heart failure (CHF) can affect pharmacokinetics in various ways. Diminished cardiac output results in a shift of blood flow to vital organs. This may lead to decreased perfusion of the gastrointestinal tract and skeletal muscle with resultant erratic absorption of oral and intramuscular medications, increased drug delivery to brain tissue, reduced blood flow to kidneys with resultant slowed clearance and prolonged elimination half-lives. Though studies supporting dosing guidelines for psychotropics in CHF are lacking, it has been recommended that medication doses be reduced by 50% in patients with CHF [41].

Lithium has been shown to both induce and ameliorate CHF. In therapeutic doses, lithium probably does not decrease cardiac contractility. However, if CHF symptoms worsen, lithium should be discontinued [42]. Patients with CHF are also at increased risk for orthostatic hypotension, specifically with medications that antagonize alpha-1 receptors [43]. Medications with significant alpha-1 blockade include low-potency neuroleptics and atypical antipsychotics (quetiapine > risperidone > olanzapine/ziprasidone). Lithium and anticonvulsants are not alpha-1 antagonists [44].

Patients with preexisting intraventricular conduction delays are at increased risk for complete heart block when given medications with quinidine-like properties, including carbamazepine and tricyclic antidepressants [45]. Valproate has no known adverse cardiac effects [46]. Lithium is associated with sinus node dysfunction, which is usually reversible with discontinuation of medication [42]. There is sparse evidence for first-degree atrial-ventricular (AV) block and rare reports of aggravation of ventricular arrhythmias with lithium at therapeutic levels. However, lithium toxicity may be associated with sinoatrial block, AV block, AV dissociation, bradyarrhythmias, ventricular tachycardia, and ventricular fibrillation. T-wave flattening or inversion with therapeutic lithium levels are of uncertain clinical significance and are usually reversible upon discontinuation of lithium therapy [42].

Prolongation of the QTc interval on electrocardiograph (ECG) in the context of antipsychotic medication use has received increased attention in recent years. Prolongation of the QT interval greater than 500 ms increases the risk of torsade de pointes, a polymorphic ventricular tachycardia that is associated with syncope and sudden death. Several antipsychotics have been documented to cause torsade de pointes and sudden death, including pimozide, sertindole, droperidol, haloperidol, and thioridazine, which has the greatest risk [47]. Risperidone-induced QT prolongation has been observed, including one fatality, though torsade de pointes was not reported [48]. Ziprasidone has also been associated with prolongation of the QT interval; however, to date, no cases of ziprasidone-associated torsade de pointes or sudden death have been reported in the literature or to the Federal Drug Administration. It should be pointed out, though, that most of the safety data on ziprasidone to date originates from clinical trials, with selective entry criteria likely to exclude patients who are susceptible to torsade de pointes and sudden death.

A study of the effects of six antipsychotics on the QT interval found that thioridazine produced the most prolonga-

**Table 2: Cardiovascular Considerations in the Treatment of Bipolar Disorder**

| Drug + | EKG or Conduction Changes | Congestive Heart Failure | Orthostatic Hypotension | Post-Myocardial Infarction |
|---|---|---|---|---|
| Lithium * (therapeutic level) | Sinus node dysfunction; T wave flattening/inversion; rare 1st degree AV block & aggravation of ventricular arrhythmias | May exacerbate symptoms of CHF; monitor level due to fluid/electrolyte changes | None | Monitor for electrolyte aberrations; in combination with ACE inhibitors, increased risk of arrhythmia |
| (toxicity) | Sinoatrial block; AV block/dissociation bradyarrhythmias; ventricular tachycardia/fibrillation | | | |
| Valproate * | Unlikely | May require decrease in valproate dose | None | Risk of liver injury in conjunction with lipid-lowering agents; risk of bleeding complications in conjunction with antiplatelet agents, warfarin, niacin |
| Carbamazepine | Quinidine-like properties increase risk of complete heart block | May require decrease in carbamazepine dose | None | Induction of CYP3A4 increases metabolism of some anticoagulant & cardiovascular drugs |
| Olanzapine * | Unlikely | May require decrease in olanzapine dose | Minimal | Increased cardiac risk factors: weight gain, metabolic changes and hyperlipidemia |
| Ziprasidone | QT prolongation; risk of torsade de pointes | May require decrease in ziprasidone dose | Minimal | Should be avoided due to increased risk of arrhythmia |
| Risperidone * | Unlikely | May require decrease in risperidone dose | Some orthostatic hypotenstion | Increased cardiac risk factors: some weight gain |
| Quetiapine * | Unlikely | May require decrease in quetiapine dose | Significant orthostatic hypotension | Increased cardiac risk factors: weight gain |

EKG = Electrocardiogram AV = Atrial-Ventricular CHF = Congestive Heart Failure ACE = Angiotensin Converting Enzyme CYP = Cytochrome P450 + Not all agents are appropriate for monotherapy. Inclusion in this table does not necessarily imply efficacy. * Currently FDA approved for use in Bipolar Disorder.

tion (mean change of 35.6 ms), followed by ziprasidone (20.3 ms), quetiapine (14.5 ms), risperidone (11.6 ms), olanzapine (6.8 ms), and haloperidol (4.7 ms) [47,49,50]. These findings are difficult to interpret given that quetiapine and olanzapine have not been implicated in cases of torsade de pointes or sudden death, but produced greater prolongation than haloperidol, which has been associated with the fatal arrhythmia.

At this time, routine ECG screening and monitoring has not been recommended before initiating treatment with antipsychotics. However, a careful medical history should be taken for symptoms of cardiac pathology, such as recurrent syncope. A family history of early sudden death should be obtained and serum electrolyte imbalances should also be corrected as these may predispose patients to arrhythmias. It has been suggested that ECG monitoring be undertaken in patients at higher risk, including those with cardiovascular disease, a history of QT prolongation, polypharmacy (metabolic inhibitors or other drugs known to affect the QT interval), high doses of antipsychotics, or symptoms possibly related to arrhythmias (syncope, palpitations, dizziness, etc.). The QTc interval may not reliably predict the risk for arrhythmia; however, an examination of the ECG by a cardiologist for other signs of arrhythmia may facilitate a more useful assessment of risk [50].

Patients with recent myocardial infarction (MI) are at increased risk for arrhythmias, heart failure and sudden death and are frequently treated with numerous medications, thereby increasing the likelihood for drug interactions with psychotropic medications. Lithium may be used after MI, but care must be taken to monitor for and correct any electrolyte aberrations. Of note, lithium in combination with angiotensin converting enzyme (ACE) inhibitors may produce an increased risk of arrhythmia [42,51]. Valproate has an increased risk of liver injury in conjunction with lipid-lowering agents, as well as risk of bleeding complications when taken with antiplatelet agents, warfarin or niacin. Carbamazepine acts as an inducer of cytochrome 3A4, which may increase the metabolism of some anticoagulant and cardiovascular medications. Olanzapine may induce or worsen cardiac risk factors such as obesity, metabolic derangements and hyperlipidemia. Quetiapine and risperidone may also contribute to obesity. Ziprasidone should be avoided due to increased risk of arrhythmia [51]. Cardiovascular condsiderations in the treatment of bipolar disorder are reviewed in Table 2.

### *Hepatic disease*

Patients with pre-existing liver disease are at increased risk for liver toxicity due to psychotropic medications. Hepatic insufficiency increases blood levels and half-lives of all psychotropic medications, except lithium. Possible mechanisms include: decreased oxidative metabolism through cytochrome enzymes; possible reduction of conjugation pathways for medications that predominantly undergo glucuronidation; decrease in hepatic blood flow because

of portacaval shunting, thereby decreasing first pass metabolism; decrease in quantities and affinity of plasma proteins, thereby increasing free-drug levels; increase in volume of distribution in patients with ascites [52].

Hepatitis C virus (HCV) infection is a leading cause of cirrhosis and liver transplantation in the United States, with an estimated prevalence of 3 million Americans [53]. There is a high comorbidity between hepatitis C and psychiatric illness. Computerized chart reviews of HCV-infected veterans revealed that 86.4% had at least one past or present psychiatric, drug or alcohol-abuse disorder, and 31% had active disorders as defined by recent hospitalizations to psychiatric or drug-detoxification units [54]. Given the high comorbidity of HCV and psychiatric illness, we must use caution in prescribing psychotropics with known hepatotoxicity, especially anticonvulsants. However, these medications are not necessarily contraindicated.

Some authors have reported that alanine aminotransferase (ALT) elevation was not significantly greater when starting treatment with valproate as compared to antidepressants, lithium or gabapentin in patients with HCV [55]. These findings suggest that valproate can be used for some patients with HCV without adversely affecting ALT levels. Obtaining pretreatment baseline ALT levels in patients with HCV is recommended as well as monitoring of levels during treatment. Discontinuation of valproate when aminotransferase levels are "clearly increased above the normal pretreatment baseline" is recommended [55].

Many patients (10–40%) receiving valproate will experience a reversible increase in aminotransferases. Valproate-induced liver injury occurs with a frequency of approximately 1 per 37,000 persons exposed [56]. Certain groups have an increased risk of 1 per 500, including those with personal or family history of mitochondrial enzyme deficiency, Reye's syndrome, Friedreich's ataxia, a sibling affected by valproate hepatotoxicity, or multiple drug therapy, as well as children younger than 3 years of age [57].

Several anticonvulsants have been associated with anticonvulsant hypersensitivity syndrome (reactive metabolite syndrome), including carbamazepine, phenytoin, phenobarbital, and lamotrigine. The triad of hypersensitivity includes fever, rash and internal organ involvement with onset of symptoms within 1 to 8 weeks of exposure. The frequency of the syndrome is estimated at 10–100 per 100,000 persons exposed. Risk of serious hypersensitivity reactions among first-degree relatives of those who have had a reaction to one of these anticonvulsants is about 1 in 4 [57-59].

There are case reports of hepatic injury associated with other drugs that are commonly used in bipolar disorder. There have been a few case reports linking olanzapine with acute hepatocellular injury and one of acute hepatitis accompanied by hallmarks of a hypersensitivity syndrome [57]. Risperidone may cause transient increases in aminotransferases as well as cholestatic hepatitis [57], but hepatic disease does not appear to modify drug pharmacokinetics [60]. Topiramate has been associated with one case report of acute hepatic failure in a woman who was also treated with carbamazepine, as well as one case of reversible ALT elevation [57].

Recognizing early symptoms of hepatic toxicity and discontinuing treatment are important in optimizing recovery. Early symptoms of hepatic toxicity include apathy, malaise, fever, diminished appetite, nausea, and vomiting [63]. Regular monitoring of aminotransferases may also

**Table 3: Recommended Dosage Adjustments for Patients with Comorbid Hepatic and Renal Disease**

| Drug + | Hepatic Disease | Renal Disease |
|---|---|---|
| Lithium * | May need to increase dose with ascites due to fluid shifts | Contraindicated in Acute Renal Failure. HD dosing: 300–600 mg in singe post-HD dose |
| Valproate * | Reduce dose with elevated transaminases | None |
| Carbamazepine | Reduce dose with elevated transaminases | Reduce dose with symptoms of toxicity due to reduced clearance of toxic metabolite |
| Olanzapine * | None | None |
| Risperidone * | May need to reduce dose | Reduce dose by 50–60% due to diminished clearance |
| Quetiapine * | May need to reduce dose | None |
| Ziprasidone | None | Use intramuscular formulation with caution |
| Lamotrigine * | May need to reduce dose due to prolonged half-life | May need to reduce dose |
| Gabapentin | None | Dose reduction proportional to rise in creatinine |
| Topiramate | May need to reduce dose as clearance of drug may be decreased | Reduce dose by half |

HD = hemodialysis + Not all agents are appropriate for monotherapy. Inclusion in this table does not necessarily imply efficacy. * Currently FDA approved for use in Bipolar Disorder.

help identify patients with "silent" hepatotoxicity. Referral to an internist or hepatologist, following discontinuation of the offending agent, is warranted if treatment-induced liver injury is suspected. If symptoms of anticonvulsant hypersensitivity syndrome are apparent, the patient should be referred for emergency treatment. Dosage adjustments for patients with hepatic disease are shown in Table 3.

### *Renal disease*

The prevalence of chronic kidney disease in the adult population of the United States is 11% (19.2 million people) [64], and as death rates from heart disease, cancer and pneumonia decrease, deaths from renal disease are on the rise [65]. As more of our patients develop renal disease, psychiatrists must be aware of the effects of psychotropics on the kidneys, as well the effects of decreased renal functioning on the pharmacokinetics of medications prescribed.

Of all the medications used to treat bipolar illness, lithium has the greatest effect on the kidney. Lithium is associated with an impaired urinary concentrating capacity resulting in polyuria that can, rarely, become permanent due to irreversible structural tubular damage [42,66]. Glomerular function is less affected by lithium. Nephrotic syndrome occurs rarely at therapeutic lithium levels. If this does occur, lithium discontinuation alone or in combination with diuretics, hemodialysis, or steroids generally results in improvement [67]. Renal tubular acidosis (RTA) has also been associated with lithium use and is more likely in patients with other conditions (medullary sponge kidney, carbonic anhydrase B deficiency, tubulointerstitial nephropathy), medications producing acidosis (amphotericin B, non-steroidal anti-inflammatory drugs [NSAIDs]), or urinary acidification defects [42].

Patients with preexisting kidney disease are at increased risk for lithium toxicity and possibly the nephrotoxic effects of lithium. Lithium is contraindicated in acute renal failure, though chronic renal failure is not an absolute contraindication with close monitoring. It has been recommended to maintain lithium levels between 0.6 and 0.8 mEq/L in this setting [42]. Lithium may be used in patients on hemodialysis (HD) and should be administered in a single post-dialysis dose of 300–600 mg. Lithium levels should be checked pre-dialysis and 2–3 hrs following the post-dialysis dose. There is a case report in which lithium levels were maintained in the therapeutic range by intraperitoneal administration of lithium during continuous peritoneal dialysis [68].

Lithium has been used safely in post-renal transplant patients. Living-related-donor allograft recipients show near normal renal function within hours after transplant and lithium dose may be increased by the first post-transplant day. Cadaveric allograft recipients frequently develop acute tubular necrosis (ATN) with fluctuating renal function causing inconsistent serum levels and increased risk of toxicity [69]. Antirejection drugs also affect lithium levels: methylprednisolone decreases tubular reabsorption of lithium and cyclosporine decreases excretion of lithium [42].

Pharmacokinetics of some medications are altered by nephrotic syndrome due to low levels of serum albumin and higher levels of unexcreted metabolites competing for protein binding sites, resulting in increased bioavailability of free, active highly protein-bound drugs. Accumulation of active hydroxylated metabolites of carbamazepine may lead to symptoms of drug toxicity despite therapeutic drug levels [70].

Renal insufficiency and failure result in decreased drug clearance for many psychotropics. Valproate clearance is diminished by 27% in renal failure; however, it is cleared by hemodialysis (HD) so no dose adjustment is recommended [71]. The elimination half-life of lamotrigine is prolonged in renal failure, and dosing may need to be modified based on the creatinine clearance [72,73]. Gabapentin clearance is linearly related to creatinine clearance and dose should be decreased accordingly [74]. Topiramate clearance is decreased and the elimination half-life is prolonged with renal impairment. It is recommended that half the usual adult dose be used in renally impaired patients. Further, topiramate is a weak carbonic anhydrase inhibitor and is associated with the development of renal calculi. In clinical trials, 1.5% of patients treated developed renal stones. This risk can be reduced with adequate hydration [75]. Risperidone clearance is decreased by 60% and half-life increased in moderate to severe renal disease, though it is cleared by HD. Dosage adjustment is recommended in renal disease [60]. The pharmacokinetics of olanzapine, quetiapine, and oral ziprasidone are not altered in renal disease [76,77]. Though the intramuscular formulation of ziprasidone has not been studied in patients with renal impairment, because the cyclodextrin excipient is renally cleared it is suggested that it be administered with caution to patients with renal impairment [78]. Suggested dosage adjustments for medications used in the context of renal disease are shown in Table 3.

### *Pulmonary disease*

There are few reports of mood stabilizers and atypical antipsychotics contributing to respiratory depression or pulmonary disease. One case report of olanzapine-associated respiratory failure occurred in an elderly patient with chronic lung disease and the authors recommend careful observation of patients with chronic lung disease treated

with olanzapine [79]. In the clinical trials of quetiapine, hyperventilation was reported to occur in <1/1000 patients treated and case reports have appeared in the literature [80]. Lithium, anticonvulsants, risperidone and ziprasidone do not appear to alter respiratory drive.

### *Cancer*

Patients with cancer are particularly susceptible to the hematologic and cognitive effects of medications, due to both their illness and chemotherapeutic treatment. Lithium should be closely monitored as fluid and electrolyte intake may vary in patients with cancer. Close monitoring is also necessary when lithium is combined with nephrotoxic chemotherapeutic agents such as cisplatin. An increased risk of cognitive dysfunction with lithium, especially in patients with primary brain tumors or metastasis has been reported. Carbamazepine has a risk of marrow suppression, which may produce an additive effect when combined with chemotherapeutic agents that suppress blood marrow production. Valproate, risperidone and olanzapine have been safely used in patients with cancer [81]. Olanzapine has been studied in patients with cancer and has been found to have an antiemetic effect [82], as well as reducing pain scores and opioid requirements in patients with uncontrolled cancer pain associated with cognitive impairment or anxiety [83].

## Conclusions

The treatment of bipolar disorder is complicated in patients with medical comorbidity. Patients with psychiatric illness may not have routine general medical care and diagnosis of general medical conditions may be delayed. As the physician with the most (and often the only) contact with these patients, psychiatrists need to be vigilant in detecting early signs and symptoms of medical illness and facilitating referral for appropriate evaluation and intervention. Psychiatrists must also be aware of the medical risks of psychotropic medications and their use in the medically ill population. This paper has reviewed some of the medications commonly used in bipolar disorder and discussed their use with comorbid medical illness.

### *Drug names*

Amantadine (Symmetrel), amphotericin B (Amphocin and Fungizone), aripiprazole (Abilify), carbamazepine (Tegretal and others), clozapine (Clozaril), droperidol (Inapsine and others), gabapentin (Neurontin), haloperidol (Haldol and others), lamotrigine (Lamictal), lithium (Eskalith and others), metformin (Glucophage), nizatidine (Axid), NSAIDs (Ibuprofen, Naproxen and others), olanzapine (Zyprexa), orlistat (Xenical), oxcarbazepine (Trileptal), phenytoin (Dilantin and others), pimozide (Orap), quetiapine (Seroquel), risperidone (Risperdal), sibutramine (Meridia), thioridazine (Mellaril and others), topiramate (Topamax), valproate (Depakote), ziprasidone (Geodon).

## Competing interests

KM has declared no competing interests. LM receives grant/research support from the National Institute of Health (NIH), the Stanley Medical Research Institute, Cyberonics, Eli Lilly and Company and Abbott Laboratories; acts as a consultant to Bristol-Myers Squibb, Cyberonics, Eli Lilly and Company, Forest Laboratories, GlaxoSmithKline, Janssen, Novartis and Wyeth Pharmaceuticals; and has received honoraria from AstraZeneca, Bristol-Myers Squibb, Cyberonics, Eli Lilly and Company, Forest Laboratories, GlaxoSmithKline, Pfizer Inc., and Wyeth Pharmaceuticals.

## Authors' contributions

KM reviewed the literature and drafted the manuscript. LM identified the need for this review paper, participated in drafting the manuscript, and presented the findings, in part, at the American Psychiatric Association annual meeting in San Francisco, CA on May 18, 2003. Both authors read and approved the final manuscript.

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