

# Clinical Pharmacodynamics and Pharmacokinetics of Antimanic and Mood-Stabilizing Medications

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**Background:** A number of medications are now available or are in development as antimanic and/or mood-stabilizing agents. We reviewed the clinical pharmacodynamics and pharmacokinetics of these agents to provide a summary of these properties relevant to clinical practice. **Method:** We conducted a MEDLINE search augmented by a manual search of bibliographies and a review of textbooks to identify articles regarding the clinical pharmacology of lithium, valproate, carbamazepine, oxcarbazepine, olanzapine, clozapine, risperidone, ziprasidone, quetiapine, lamotrigine, and topiramate. **Results:** Not surprisingly, there are a number of clinically relevant pharmacodynamic and pharmacokinetic differences among these medications, and these differences are discussed. **Conclusion:** Knowledge of the clinical pharmacology of established and putative antimanic and mood-stabilizing medications is important in administering these agents safely and effectively. (*J Clin Psychiatry* 2002;63[suppl 4]:3-11)

A growing number of medications have established efficacy or are in active development for the treatment of acute bipolar mania or long-term mood stabilization.<sup>1</sup> These compounds are diverse in their chemical, pharmacokinetic, and pharmacodynamic properties. These properties, in turn, have important clinical implications regarding choice of agent, dosing, and drug-drug interactions. The purpose of this review is to provide a summary of the pharmacodynamics and pharmacokinetics (Table 1) of antimanic and mood-stabilizing agents relevant to clinical practice.

## LITHIUM

### Pharmacodynamics

Lithium is a simple monovalent cation. Lithium formulations have been used in the treatment of acute bipolar mania and in maintenance treatment for patients with bipolar disorder for over 50 years.<sup>2</sup> Lithium is indicated for the treatment of manic episodes of bipolar disorder and as maintenance treatment. The precise mechanism of action of lithium in the treatment of bipolar disorder is unknown. The effects of lithium on depolarization-provoked and calcium-dependent release of dopamine and norepinephrine from nerve terminals in the central nervous system (CNS),<sup>3</sup> neuronal second messenger signaling pathways, CNS cytoprotective proteins,<sup>4</sup> and the distribution of Na<sup>+</sup>, Ca<sup>2+</sup>, and Mg<sup>2+</sup> across neuronal membranes all have been suggested to contribute to its therapeutic effects.<sup>5</sup>

### Pharmacokinetics

Lithium is available as lithium carbonate capsules and tablets, in slow release tablets, and as lithium citrate syrup (8 mmol/5 mL).<sup>6</sup> Lithium is readily and nearly completely absorbed in the gastrointestinal tract. Peak concentrations occur within 2 to 4 hours of administration of immediate release formulations. Slow release formulations are associated with later and lower peak concentrations.<sup>6</sup> Lithium is not metabolized; approximately 95% is renally excreted. Renal excretion is biphasic, with rapid clearance of up to two thirds of an acute dose within 6 to 12 hours followed by a slower elimination over the next 12 hours.<sup>5</sup> The overall elimination half-life is approximately 24 hours with a corresponding time to steady-state concentrations of 4 to 5 days.

Hyponatremia, fluid volume depletion, and use with diuretics or angiotensin converting enzyme (ACE) inhibitors may reduce lithium renal clearance and lead to toxicity.<sup>7</sup> Lithium has a low therapeutic index, and toxicity is proportional to concentrations just above the therapeutic range, although some patients may display signs of toxicity at the upper end of the therapeutic range. Recommended target therapeutic plasma concentrations range from 0.8 to 1.5 mmol/L for acute mania and from 0.6 to 1.2 mmol/L for maintenance therapy.<sup>8</sup> Toxic reactions and common lithium side effects have been summarized in many excellent reviews.<sup>5,6</sup> Lithium overdoses can be fatal; hemodialysis is the treatment of choice for severe intoxication. Gastric lavage, correction of fluid and electrolyte imbalances, and regulation of kidney function are important interventions.<sup>7</sup> Urea, mannitol, and aminophylline all produce significant increases in lithium excretion.<sup>7</sup>

## VALPROATE (DIVALPROEX SODIUM)

### Pharmacodynamics

Divalproex sodium is indicated for the treatment of acute manic episodes in patients with bipolar disorder, as monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures, simple and complex absence seizures, adjunctively in patients with multiple seizure types that include absence seizures, and for prophylaxis of migraine headaches.<sup>7</sup>

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Table 1. Selected Pharmacokinetic Parameters of Antimanic and Mood-Stabilizing Agents<sup>a</sup>

Medication	Protein Binding (%)	Metabolism	Active Metabolites	Mean Elimination Half-Life
Lithium	0	95% renal excretion	None	24 h
Divalproex	70–95	β-oxidation CYP450 system Glucuronidation	Many	16 h
Olanzapine	93	CYP1A2, 2D6 Glucuronidation	None	30 h (po)
Carbamazepine	75–90	Oxidation Hydroxylation Conjugation	10,11-Epoxyde	18–55 h, then 2–17 h
Oxcarbazepine	40	Hydroxylation CYP450 system	10-Hydroxy	OXC 2 h, 10-OH 9 h
Clozapine	97	N-Oxidation N-Demethylation CYP1A2, 3A4, 2D6	Norclozapine	12 h
Risperidone	90	Hydroxylation CYP2D6, 3A4	9-Hydroxy	RSP 3 h, 9-OH 20 h
Ziprasidone	99	Aldehyde oxidase CYP3A4	None	7 h (po) 2–4 h (IM)
Quetiapine	83	CYP3A4 sulfoxidation and oxidation	None	2–3 h
Lamotrigine	55	Glucuronidation CYP450 system	None	13 h
Topiramate	13–17	Hydroxylation Hydrolysis Glucuronidation	None	21 h

<sup>a</sup>Abbreviations: 9-OH = 9-hydroxy metabolite, 10-OH = 10-hydroxy metabolite, OXC = oxcarbazepine, RSP = risperidone.

Valproic acid is a simple branched-chain carboxylic acid. Valproate inhibits pentylenetetrazol-induced and maximal electroshock seizures in animals and suppresses secondarily generalized seizures without affecting focal activity in cortical cobalt- and alumina-lesioned animals.<sup>8</sup> Valproate also has anticonvulsant properties and neuroprotective effects similar to those of lithium; these properties may be more directly relevant to the antimanic and mood-stabilizing properties of valproate.<sup>4,8</sup>

### Pharmacokinetics

Valproate is commercially available in the United States in 5 oral preparations: valproic acid, sodium valproate, divalproex sodium, divalproex sodium sprinkle capsules, and divalproex sodium extended-release tablets. Divalproex sodium, valproic acid, and divalproex sodium extended release are not bioequivalent and, therefore, not interchangeable. Valproate is also available intravenously and in suppository form for rectal administration.<sup>7</sup> In Europe, valpromide, the amide of valproic acid, is available.

The bioavailability of valproate is nearly complete with all formulations.<sup>9</sup> Peak plasma concentrations are usually achieved within 2 hours for valproic acid and sodium valproate oral formulations; divalproex sprinkle has an earlier onset but slower rate of absorption; divalproex and divalproex extended release reach peak plasma concentrations within 3 to 8 hours. The divalproex extended-release formulation requires a 20% upward dosage adjustment for equivalence with the non-extended-release formulation.<sup>7</sup> Absorption can be delayed if the oral formulations

are taken with food. Valproate is highly protein bound, primarily to serum albumin. Only the unbound drug crosses the blood-brain barrier and exerts pharmacologic activity. When protein bound valproate is displaced by other drugs competing for binding sites, the total drug concentration may not change. However, the amount of pharmacologically active drug does increase and may produce signs and symptoms of toxicity. Furthermore, when the plasma concentration of valproate increases with dosage titration, the amount of unbound valproate increases disproportionately and is metabolized more rapidly, at times producing lower-than-expected total plasma concentrations.<sup>9</sup> Protein binding sites are usually saturated at plasma valproate concentrations of approximately 45 to 55 μg/mL. Valproate protein binding is increased by low-fat diets and decreased by high-fat diets.

Valproate is metabolized hepatically by 3 primary pathways to a large number of metabolites that have pharmacologic activity. These 3 pathways are mitochondrial β-oxidation to 3-OH-valproate, 3-oxo-valproate, and 2-en-valproate; cytochrome P450 metabolism to the toxic 4-en- and 2,4-en-valproate metabolites; and glucuronidation to a number of inactive metabolites.<sup>9</sup> The 2-en-valproate metabolite is pharmacologically active and has a long half-life.<sup>10</sup> The mean elimination half-life of valproate is approximately 16 hours, but can be altered by drugs that affect its metabolic pathways. Mitochondrial β-oxidation is the primary metabolic pathway, especially when valproate is administered alone. However, when administered with other agents that induce the P450 system, P450 metabolism is increased, increasing the risk of adverse effects, including, very

rarely (but especially in children), hepatic necrosis.<sup>10</sup> Valproate formulations are not recommended for administration to patients with clinically significant hepatic disease or dysfunction. Elderly patients may be particularly susceptible to the sedative effects of valproate. In addition to rare hepatotoxicity, valproate formulations also received boxed warnings for teratogenicity and rare cases of pancreatitis.<sup>7</sup>

Plasma concentration-response data from one large, randomized, acute treatment trial<sup>11</sup> indicated a therapeutic range of 50 to 125 µg/mL, with increasing likelihood of response the higher the plasma concentration within that range.<sup>12</sup> One advantage of valproate in the treatment of acute mania rests with its ability to be administered via rapid-loading strategies (e.g., 30 mg/kg/day for 2 days, followed by 20 mg/kg/day<sup>13,14</sup> or 20 mg/kg/day at the initiation of treatment<sup>15,16</sup>) that achieve therapeutic plasma concentrations within 24 hours and may produce more rapid antimanic activity. Compared with lithium, valproate has a wider therapeutic index. Nevertheless, substantial overdose can produce toxicity and death. Naloxone has been used to reverse CNS depressant effects.<sup>17</sup> Since the unbound fraction of valproate is high in overdose, hemodialysis or tandem hemodialysis and hemoperfusion may remove significant amounts of the drug.<sup>17</sup>

## OLANZAPINE

### Pharmacodynamics

Olanzapine is a thienobenzodiazepine compound with a high affinity for a number of serotonin (5-HT<sub>2A/2C</sub>, 5-HT<sub>3</sub>, and 5-HT<sub>6</sub>) and dopamine (D<sub>1</sub>, D<sub>2</sub>, D<sub>3</sub>, and D<sub>4</sub>) receptors.<sup>18</sup> Olanzapine also binds with high affinity to histamine H<sub>1</sub> and adrenergic α<sub>1</sub> receptors. Recent data suggest that it has weak postsynaptic muscarinic M<sub>1</sub> antagonism and that its presynaptic effects on M<sub>2</sub> and serotonin receptors actually enhance release of acetylcholine.<sup>19</sup> Although the precise mechanism of olanzapine's thymoleptic activity is not known, it is likely that its D<sub>2</sub> antagonist properties correspond to antimanic activity and that its serotonergic properties confer antidepressant activity.<sup>20</sup> Olanzapine's effects on α<sub>1</sub> receptors is associated with modest orthostatic changes, and its effects on H<sub>1</sub> receptors may contribute to sedation and appetite stimulation.<sup>21</sup> Olanzapine's procholinergic properties may explain its beneficial effects on cognition.

Olanzapine is indicated for the treatment of acute bipolar mania. In randomized, controlled clinical trials, olanzapine was superior to placebo<sup>22,23</sup> and comparable to lithium,<sup>24</sup> divalproex,<sup>25</sup> and haloperidol<sup>26</sup> in the treatment of acute bipolar manic (and mixed) episodes. In one trial,<sup>27</sup> olanzapine was superior to divalproex. In addition, the combination of olanzapine and fluoxetine was superior to either agent alone in patients with treatment-refractory nonpsychotic major depressive disorder.<sup>28</sup> Olanzapine was also superior to haloperidol in alleviating depressive symptoms in patients with schizophrenia and schizoaffective disorder.<sup>29,30</sup>

### Pharmacokinetics

Olanzapine is available in tablets, rapidly disintegrating oral tablets, and an intramuscular formulation.<sup>7</sup> Both oral formula-

tions are bioequivalent. Olanzapine is well absorbed and reaches peak plasma concentrations in approximately 6 hours after oral dosing.<sup>17</sup> It is extensively eliminated by first-pass metabolism with approximately 40% of an oral dose metabolized before reaching systemic circulation. Food does not affect the rate or extent of olanzapine absorption.

Olanzapine exhibits linear kinetics over the clinical dosing range (2.5–20 mg/day). Its mean elimination half-life is approximately 30 hours with steady-state concentrations occurring in 5 to 7 days. Olanzapine is extensively distributed throughout the body and is 93% bound to plasma proteins, binding primarily to albumin and α<sub>1</sub>-glycoprotein. Glucuronidation and P450 (1A2 and 2D6)-mediated oxidation are the primary metabolic pathways for olanzapine. CYP2D6 metabolism appears to be a minor pathway because olanzapine's clearance is not significantly diminished in individuals lacking this enzyme.<sup>17</sup> In pharmacokinetic studies, neither renal nor hepatic impairment had a significant impact on olanzapine pharmacokinetics.<sup>7</sup> The mean elimination half-life in elderly patients is increased approximately 1.5-fold. Olanzapine clearance is increased by approximately 40% in smokers and decreased by approximately 30% in women, although dosage adjustment in smokers or women is not routinely recommended.<sup>7</sup>

Olanzapine has a comparatively wide therapeutic index, and doses above 20 mg/day may be needed to achieve efficacy in patients who have not responded but otherwise tolerate lower doses. In premarketing trials involving over 3100 patients, overdose of olanzapine was identified in 67 patients. In the patient taking the highest dosage, 300 mg, reported signs and symptoms included drowsiness and slurred speech.<sup>17</sup> In patients who were evaluated in hospitals, there were no observations indicating an adverse change in laboratory values or electrocardiogram. Activated charcoal binds to olanzapine in the gut and can significantly reduce absorption of the drug as can use of a laxative.<sup>17</sup> Appropriate supportive care is indicated. Rare cases of neuroleptic malignant syndrome have been reported.<sup>31</sup>

The pharmacokinetics of the intramuscular (IM) formulation of olanzapine differ from those of the oral formulation primarily in that the IM formulation has a more rapid rate of absorption.<sup>32</sup> The C<sub>max</sub> of IM olanzapine is approximately 4 to 5 times greater than with oral olanzapine. Time to peak concentration for IM olanzapine ranges from 15 to 45 minutes compared with 3 to 6 hours for oral olanzapine.

## CLOZAPINE

### Pharmacodynamics

Clozapine is a dibenzodiazepine derivative and is indicated for the management of severely ill patients with schizophrenia who fail to respond adequately to standard antipsychotic agents.<sup>7</sup> Although there are no double-blind, randomized, controlled trials of clozapine in the treatment of acute mania, data from numerous clinical reports suggest that clozapine has antimanic and mood-stabilizing properties.<sup>33</sup> Clozapine binds to dopamine (D<sub>1-5</sub>) and serotonin receptors (5-HT<sub>1A/1C</sub>, 5-HT<sub>2A/2C</sub>, 5-HT<sub>3</sub>, and

5-HT<sub>6</sub>) with moderate-to-high affinity. It also has affinity for  $\alpha_1$ - and  $\alpha_2$ -adrenergic, H<sub>1</sub>, and M<sub>1</sub> receptors.<sup>34-38</sup> As with olanzapine, D<sub>2</sub> receptor antagonism may be one mechanism of clozapine's antimanic activity, and its serotonergic and  $\alpha_2$ -adrenergic effects may confer antidepressant activity.<sup>20</sup> Its  $\alpha_1$  antagonism is associated with orthostatic effects, H<sub>1</sub> antagonism with sedative and appetite stimulating effects, and M<sub>1</sub> antagonism with anticholinergic side effects.

### Pharmacokinetics

Clozapine is well absorbed after oral administration with a mean peak plasma concentration occurring 2.5 hours after dosing following first-pass metabolism. Food does not appear to affect absorption.<sup>17</sup>

The liver extensively metabolizes clozapine, mainly by N-oxidation and N-demethylation.<sup>39</sup> The systemic clearance of clozapine is mediated primarily by metabolism through the CYP1A2 enzyme. The major metabolite of clinical relevance is N-desmethylclozapine (norclozapine).<sup>40</sup> Norclozapine is a potent 5-HT<sub>1C</sub> receptor antagonist and has similar affinities to D<sub>2</sub> and 5-HT<sub>2</sub> receptors as clozapine.<sup>41</sup> In addition, norclozapine was toxic to hematopoietic precursors at serum concentrations only 3 to 6 times the normal concentration for clozapine.<sup>42</sup> Fortunately, most studies of clozapine pharmacokinetics found that norclozapine concentrations were lower than clozapine concentrations.<sup>40</sup> However, coadministered agents that induce CYP1A2 and 3A4 enzymes (e.g., carbamazepine or smoking) could accelerate the conversion of clozapine to norclozapine and increase the risk of hemotoxicity.<sup>39,40,43-45</sup> Clozapine is also metabolized by the CYP2D6 enzyme and can have its metabolism inhibited by agents that are also metabolized by this isoenzyme (e.g., fluoxetine, risperidone).<sup>40,45</sup> The mean elimination half-life of clozapine after a single dose was 8 hours, but increased to 12 hours at steady-state. Smoking had a greater effect on plasma clozapine concentrations in men than in women.<sup>40</sup> Women and the elderly have a slower clearance of clozapine. Ethnicity also exerts an important influence on clozapine metabolism.<sup>46,47</sup> Clozapine is 97% protein bound, and interactions with other protein-bound drugs may be clinically significant.

At steady-state, clozapine metabolism appears to follow linear kinetics. A significant correlation between plasma clozapine concentration and response has been reported in a number of studies.<sup>48-54</sup> A threshold plasma concentration ranging from > 350 to 420 ng/mL was identified in these studies.

Clozapine has boxed warnings for agranulocytosis (necessitating frequent white blood cell count monitoring), seizures, and acute cardiac and respiratory events. Rare cases of neuroleptic malignant syndrome have been reported.<sup>31</sup> The most common signs and symptoms of clozapine overdose were altered consciousness, including drowsiness, delirium, and coma; tachycardia; hypotension; respiratory depression or failure; and sialorrhea. Aspiration pneumonia, seizures, and cardiac arrhythmias also have been reported. Fatal overdoses have been reported with clozapine at doses > 2500 mg. However, some patients have recovered from overdoses > 4000 mg.<sup>7</sup>

## RISPERIDONE

### Pharmacodynamics

Risperidone, a benzisoxazole derivative, is indicated for the management of the manifestations of psychotic disorders. Data from 2 randomized, controlled clinical trials suggest that risperidone has antimanic efficacy.<sup>55,56</sup> In addition, risperidone was superior to haloperidol in alleviating depressive symptoms in patients with schizoaffective disorder in a randomized, controlled trial.<sup>57</sup> Risperidone has high affinity for the D<sub>2</sub>, 5-HT<sub>2A/2C</sub>,  $\alpha_1$ - and  $\alpha_2$ -adrenergic, and H<sub>1</sub> receptors. It has low-to-moderate affinity for 5-HT<sub>1C/1D</sub> and 5-HT<sub>1A</sub> receptors, weak affinity for D<sub>1</sub> receptors, and no significant affinity for M<sub>1</sub> or  $\beta$ -adrenergic receptors.<sup>58</sup> As with other atypicals, risperidone's D<sub>2</sub> receptor antagonism may confer antimanic activity and its serotonergic effects, antidepressant activity. In addition,  $\alpha_2$  antagonism may also confer antidepressant activity.<sup>20</sup>  $\alpha_1$ -Adrenergic antagonism is associated with orthostatic changes and H<sub>1</sub> antagonism with sedation and appetite stimulation.

### Pharmacokinetics

Risperidone is nearly completely absorbed following oral administration. Approximately one third of risperidone is metabolized via first-pass effect in the liver before reaching systemic circulation. 9-OH-risperidone is the primary metabolite and is nearly equipotent with risperidone as a 5-HT<sub>2</sub> and D<sub>2</sub> antagonist.<sup>40</sup> Thus, the absolute bioavailability of risperidone and 9-OH-risperidone is combined to be nearly 100% after oral administration. Time to peak plasma concentration ranged between means of 0.8 to 1.4 hours. Food has no effect on the absorption of risperidone.

Risperidone is cleared primarily by 9-hydroxylation via CYP2D6 and 3A4 isoenzymes.<sup>40,58,59</sup> 9-OH-risperidone is cleared primarily by renal excretion. In poor CYP2D6 metabolizers, the mean elimination half-life of risperidone was approximately 19 hours compared with about 3 hours in extensive CYP2D6 metabolizers.<sup>58</sup> Mean half-life for 9-OH-risperidone was 19 to 23 hours. The combined elimination half-life of risperidone and the 9-OH metabolite was approximately 20 hours in both poor and extensive metabolizers.<sup>58</sup> Coadministration with medications that compete for 2D6 metabolism can significantly increase risperidone plasma concentrations. In contrast, risperidone and 9-OH-risperidone do not appear to significantly block the 2D6 metabolism of other agents. Time to steady-state for risperidone ranged from 1 to 7 days, and 5 to 6 days for 9-OH-risperidone.<sup>40</sup> Most studies have demonstrated linear kinetics for risperidone and 9-OH-risperidone. Risperidone protein binding is approximately 90%; the 9-OH metabolite is approximately 77% protein bound. Neither compound significantly displaces the other from protein binding sites and other agents only weakly displace risperidone and 9-OH-risperidone.<sup>58</sup> Risperidone clearance is significantly reduced in patients with renal or hepatic impairment and in the elderly. Corresponding dosage adjustments are required for patients with these characteristics.

In premarketing studies, there were 8 reports of risperidone overdose.<sup>7</sup> Doses ranged from 20 to 300 mg with no fatalities.



Reported signs and symptoms included drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. One case of overdose of approximately 240 mg was associated with hypokalemia, hyponatremia, and QTc prolongation and widened QRS. Another case of overdose of 36 mg was associated with a seizure. Postmarketing reports have been consistent with the signs and symptoms reported in clinical trials. Appropriate supportive care is indicated for risperidone overdose.<sup>7</sup> Like other atypicals, risperidone has been reported in association with rare cases of neuroleptic malignant syndrome.<sup>31</sup>

## ZIPRASIDONE

### Pharmacodynamics

Ziprasidone is a benzothiazolylpiperazine indicated for the treatment of psychosis. Ziprasidone has high affinity for 5-HT<sub>2A/2C</sub>, 5-HT<sub>1D</sub>, 5-HT<sub>7</sub>, and D<sub>2</sub> receptors as an antagonist and for 5-HT<sub>1A</sub> receptors as an agonist.<sup>60</sup> Ziprasidone exhibits modest antagonism of  $\alpha_1$ -adrenergic and H<sub>1</sub> receptors and of the serotonin and norepinephrine transporters.<sup>60</sup> Ziprasidone's D<sub>2</sub> antagonism may confer antimanic properties as demonstrated to date in one randomized, placebo-controlled trial.<sup>61</sup> Its effects on the 5-HT<sub>2</sub>, 5-HT<sub>1A</sub>, and 5-HT<sub>1D</sub> receptors and inhibition of serotonin and norepinephrine reuptake suggest multiple antidepressant actions.<sup>60</sup> Ziprasidone's antidepressant effects have been demonstrated in patients with schizophrenia and schizoaffective disorder.<sup>62-64</sup> Ziprasidone's  $\alpha_1$  antagonism is associated with modest orthostatic effects and H<sub>1</sub> antagonism with sedation. Ziprasidone was also associated with mean QTc prolongation of 6 to 10 msec in fixed-dose trials.<sup>65</sup>

### Pharmacokinetics

The absorption of ziprasidone is substantially increased when taken with food. Peak plasma concentrations occurred 6 to 8 hours postdose in multiple dosing studies.<sup>66</sup> The mean elimination half-life was approximately 7 hours, and steady-state concentrations were achieved within 1 to 3 days with b.i.d. dosing. Over the 40 to 160 mg/day therapeutic dosage range, ziprasidone exhibited linear kinetics at steady-state.<sup>67</sup> Age, gender, and mild-to-moderate renal or hepatic impairment had no clinically significant effects on ziprasidone metabolism.

Ziprasidone is highly protein bound (>99%) and is extensively metabolized by the liver. The primary metabolic pathway of ziprasidone is via aldehyde oxidase. Metabolism via CYP3A4 is also an important secondary pathway. Ziprasidone's metabolites are not known to be clinically active.<sup>60</sup> Ziprasidone does not appear to significantly interfere with the metabolism of other agents via interactions at the 3A4 or 2D6 isoenzymes. Ketoconazole, a potent 3A4 inhibitor, increased peak-dose peak plasma ziprasidone concentrations by up to 35%.<sup>68</sup> Coadministration with carbamazepine produced 27% to 36% increases in ziprasidone clearance.<sup>69</sup> Since ziprasidone is not metabolized by CYP1A2 (induced by smoking), smoking is unlikely to significantly affect ziprasidone kinetics. In other studies, ziprasidone had no clinically significant interactions with lithium,

aluminum and magnesium antacids, and combination oral contraceptives.<sup>60</sup>

An IM formulation of ziprasidone is in development and intended for the management of acute agitation in patients with psychosis. The formulation is completely bioavailable after administration with an elimination half-life of 2 to 4 hours. In single-dose pharmacokinetic studies, C<sub>max</sub> of ziprasidone 20 mg IM was approximately comparable to 80 mg p.o. b.i.d., with peak concentrations of the IM dose occurring within 1 hour of administration.<sup>70</sup>

## QUETIAPINE

### Pharmacodynamics

Quetiapine is a dibenzothiazepine derivative indicated for the management of manifestations of psychotic disorders. There are no data from randomized, controlled trials indicating efficacy of quetiapine monotherapy in acute mania, although anecdotal evidence suggests that it may have efficacy in reducing manic symptoms.<sup>71,72</sup> Quetiapine was superior to placebo as combination therapy with divalproex in the treatment of adolescents with acute bipolar mania.<sup>73</sup>

Quetiapine has weak affinity for D<sub>2</sub>, D<sub>1</sub>, M<sub>1</sub>, and 5-HT<sub>1A</sub> receptors and modest affinity for H<sub>1</sub>, 5-HT<sub>2A/2C</sub>, and  $\alpha_1$ - and  $\alpha_2$ -receptors.<sup>74</sup> Its D<sub>2</sub> receptor antagonism may confer antimanic effects, and its serotonergic and  $\alpha_2$ -adrenergic actions may confer antidepressant activity.<sup>20</sup> Quetiapine's  $\alpha_1$  and H<sub>1</sub> antagonism correlate with orthostatic, sedative, and appetite-stimulating properties.

### Pharmacokinetics

Quetiapine fumarate is rapidly absorbed after oral administration, reaching peak plasma concentrations in approximately 1.5 hours.<sup>74,75</sup> The bioavailability of quetiapine is minimally affected by administration with food, with increases in C<sub>max</sub> of 25%, and area under the curve (AUC) of 15%. Quetiapine is 83% bound to plasma proteins. In vitro studies did not demonstrate significant protein binding displacement of warfarin or diazepam, nor did these agents alter quetiapine binding.<sup>7</sup>

The liver extensively metabolizes quetiapine via CYP3A4 sulfoxidation and oxidation. Both metabolites are pharmacologically inactive. The mean elimination half-life is 2 to 3 hours. Clearance of quetiapine was reduced by up to 40% in the elderly.<sup>74</sup> Patients with renal impairment had a reduction in quetiapine clearance of 25% but without clinically significant elevations in plasma concentrations.<sup>74</sup> In contrast, patients with hepatic impairment had reductions in quetiapine clearance of 30% but with clinically significant elevations in plasma concentrations. Thus, dosage adjustment downward is recommended for patients with hepatic impairment.<sup>7</sup> Age, gender, ethnicity, and smoking status have no significant effects on quetiapine pharmacokinetics. Quetiapine kinetics in adolescents were dose proportional and similar to those in adults.<sup>76</sup>

Quetiapine overdoses were reported in 6 cases during premarketing trials with estimated doses ranging from 1200 to 9600 mg and no fatalities. Signs and symptoms of overdose included

drowsiness, sedation, tachycardia, and hypotension. One case of an overdose of 9600 mg was associated with hypokalemia and first-degree heart block.<sup>7</sup> As with other atypicals, rare cases of neuroleptic malignant syndrome have been reported.<sup>31</sup>

## CARBAMAZEPINE

### Pharmacodynamics

Carbamazepine is an iminostilbene derivative with a tricyclic structure similar to that of the tricyclic antidepressant imipramine.<sup>9</sup> Carbamazepine's pharmacologic properties fall into 2 major areas: its effects on neuronal ion channels to retard high-frequency repetitive firing of action potentials and its effects on synaptic and postsynaptic transmission.<sup>9</sup> Carbamazepine blocks voltage-sensitive sodium channels and may also act on potassium channels to increase potassium conductance. It also affects a number of neurotransmitter systems implicated in the pathophysiology of mood disorders. Specifically, carbamazepine alters neurotransmission mediated by adenosine, dopamine, norepinephrine, serotonin, acetylcholine, GABA, glutamate, substance P, and aspartate.<sup>9</sup> To date, these mechanisms have not been clearly linked to carbamazepine's psychotropic effects. Carbamazepine is indicated for the treatment of partial seizures with complex symptomatology, generalized tonic-clonic seizures, mixed seizure patterns, which include partial or generalized tonic-clonic seizures, absence seizures, and trigeminal neuralgia.<sup>7</sup> Carbamazepine has been efficacious in the treatment of acute bipolar mania and depression and as maintenance therapy in randomized, controlled trials.<sup>77</sup>

### Pharmacokinetics

Carbamazepine solutions, suspensions, syrups, slow-release, and chewable formulations are available.<sup>7</sup> Slow-release formulations appear to produce more stable plasma concentrations.<sup>9</sup> The absorption of carbamazepine following oral administration is often slow and erratic. Peak plasma concentrations are usually reached 4 to 8 hours after ingestion with bioavailability of approximately 85%. Carbamazepine absorption may be slower in the evening than in the morning. It is rapidly distributed to all tissues, and 75% to 90% is protein bound, including proteins other than albumin.<sup>9</sup>

Carbamazepine undergoes extensive hepatic metabolism predominantly by conversion to a 10,11-epoxide. This metabolite is pharmacologically active and is associated with neurologic side effects. Its plasma concentration may reach 50% of the parent drug. The 10,11-epoxide, in turn, is metabolized further to inactive compounds, primarily by glucuronidation.<sup>9</sup> Conjugation and hydroxylation also inactivate carbamazepine. The elimination half-life ranges from 18 to 55 hours at the initiation of treatment, but usually falls to 2 to 17 hours during sustained treatment because of metabolic autoinduction. Carbamazepine is a potent inducer of the P450 system, and this induction can accelerate the metabolism of coadministered agents.<sup>9</sup> Recommended therapeutic plasma concentrations for carbamazepine range from 3 to 14  $\mu\text{g/mL}$ , but there has not been an established concentration-

response relationship within this range.<sup>78</sup> Carbamazepine has a narrow therapeutic index, and signs of toxicity (e.g., vertical nystagmus, ataxia) can occur at the upper end of the therapeutic range. Carbamazepine has boxed warnings of rare cases of aplastic anemia and agranulocytosis.<sup>7</sup> Severe dermatologic reactions including toxic epidermal necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome have been associated with carbamazepine. These reactions have been very rare. Carbamazepine is also teratogenic. Overdose with carbamazepine can be lethal. Activated charcoal can bind to carbamazepine remaining in the gut, and laxatives can facilitate elimination.<sup>17</sup> In cases of massive overdose, peak plasma concentrations may not occur for 2 to 3 days after ingestion.<sup>9</sup>

## OXCARBAZEPINE

### Pharmacodynamics

Oxcarbazepine is the 10-keto analogue of carbamazepine. It has similar efficacy to carbamazepine in suppressing generalized tonic-clonic seizures and partial seizures with and without secondary generalization. Oxcarbazepine blocks voltage-sensitive sodium channels, stabilizing hyperexcited neuronal membranes, inhibiting repetitive firing, and decreasing the propagation of synaptic impulses.<sup>17</sup> It also increases potassium conductance and modulates the activity of high-voltage calcium channels. The relationship, if any, between these mechanisms and the drug's psychotropic effects is uncertain. Oxcarbazepine is indicated for use as monotherapy or adjunctive therapy in the treatment of partial seizures in adults with epilepsy and as adjunctive therapy in the treatment of partial seizures in children with epilepsy aged 4 to 16 years.<sup>7</sup> Like carbamazepine, oxcarbazepine may also be beneficial in the treatment of neuropathic pain.<sup>9</sup> Oxcarbazepine was comparable to haloperidol and lithium in the treatment of acute bipolar mania in 2 small randomized, controlled trials.<sup>79,80</sup>

### Pharmacokinetics

Oxcarbazepine has a distinctly different pharmacokinetic profile from carbamazepine. It is only a weak inducer of the P450 system and is not metabolized to an epoxide with neurologic side effects. Oxcarbazepine is completely absorbed and rapidly and extensively converted to a 10-hydroxy metabolite that is active and primarily responsible for the drug's antiepileptic activity.<sup>9</sup> Compared with carbamazepine, oxcarbazepine appears to have fewer drug-drug interactions and better overall tolerability. Nevertheless, like carbamazepine, oxcarbazepine is also associated with neurologic side effects, hyponatremia, and dermatologic reactions.<sup>7</sup>

The 10-hydroxy metabolite is approximately 40% protein bound. The elimination half-life of the parent compound is 2 hours, and 9 hours for the 10-hydroxy compound. The half-life of the 10-hydroxy metabolite is prolonged up to 19 hours in renally impaired patients.<sup>17</sup> The recommended dosage adjustment for patients with renal impairment is to initiate treatment at one half the usual starting dose to subsequently titrate slowly. Time to peak serum concentration is approximately 2 to 3 days.<sup>17</sup>

No fatalities from oxcarbazepine overdose have been reported. The maximum dose ingested among reported cases was 24,000 mg. All patients recovered with supportive and symptomatic treatment.<sup>7</sup>

## LAMOTRIGINE

### Pharmacodynamics

Lamotrigine is an antiepileptic drug of the phenyltriazine class. Its precise mechanism of action in epilepsy is unknown as is its thymoleptic mechanism(s). In vitro pharmacology studies indicate that lamotrigine inhibits voltage-sensitive sodium channels, thereby stabilizing neuronal membranes and modulating the presynaptic release of excitatory amino acids (e.g., glutamate, aspartate).<sup>81</sup> Lamotrigine also has weak affinity for the 5-HT<sub>3</sub> receptor. Data from randomized, controlled clinical trials suggest that lamotrigine may have efficacy in the treatment of bipolar depression and possibly as a maintenance agent.<sup>82,83</sup>

### Pharmacokinetics

Lamotrigine is available in tablet and chewable dispersible tablet formulations. Lamotrigine is rapidly and completely absorbed after oral administration with little first-pass metabolism. Its absorption is not affected by food. Peak plasma concentrations occur at a mean of 1.4 to 4.8 hours after oral administration. Both formulations obey similar kinetics.<sup>84</sup>

Lamotrigine is approximately 55% bound to plasma proteins and is not likely to interact significantly with other drugs with high protein binding. It is metabolized primarily by glucuronidation to an inactive 2-N-glucuronide conjugate.<sup>81</sup> Although the effects of lamotrigine on specific hepatic microsomal enzymes have not been well established, lamotrigine can induce its own metabolism. In multiple dose studies, the mean elimination half-life of lamotrigine was 13 hours. The kinetics of lamotrigine appear to be linear at steady-state within a dose range of 100 to 700 mg/day.<sup>81</sup> Lamotrigine clearance is significantly reduced in patients with hepatic or renal impairment. Age, gender, and smoking status do not appear to significantly affect lamotrigine pharmacokinetics. However, lamotrigine clearance was 25% lower in nonwhites compared with whites.<sup>81</sup> The most significant factor affecting lamotrigine clearance is coadministration with other antiepileptics, valproate in particular. Valproate more than doubles the elimination half-life of lamotrigine. Thus, if lamotrigine is administered with valproate, the lamotrigine dose must be lowered by half and the titration rate slowed.<sup>7</sup>

Lamotrigine has a boxed warning of serious rash which includes Stevens-Johnson syndrome.<sup>7</sup> The estimated risk of such rashes is approximately 1% in patients < 16 years old and 0.3% in adults. In patients < 16 years old, lamotrigine is approved for use only for those who have seizures associated with the Lennox-Gastaut syndrome.<sup>7</sup> The risk of rash may be increased when lamotrigine is administered with valproate formulations, at doses exceeding the initial dosage recommendations, and at titration rates exceeding the recommended schedule. Most

cases of life-threatening rash have occurred within 2 to 8 weeks of treatment initiation, although isolated cases have occurred after prolonged treatment. The appearance of rash is an indication for immediate discontinuation of lamotrigine.<sup>7</sup>

Overdoses with lamotrigine up to 15 g have been reported with some fatalities. Signs and symptoms of overdose included ataxia, nystagmus, increased seizures (in patients with epilepsy), delirium, coma, and intraventricular conduction delay.<sup>7</sup> Appropriate supportive care is indicated. Up to 20% of lamotrigine may be removable by hemodialysis.<sup>17</sup>

## TOPIRAMATE

### Pharmacodynamics

Topiramate is a sulfamate-substituted monosaccharide indicated for adjunctive therapy for adults and pediatric patients aged 2 to 16 years with partial onset seizures or primary generalized tonic-clonic seizures. Preliminary data suggest that topiramate may have antimanic and mood-stabilizing properties, but these observations require confirmation in randomized, controlled trials.<sup>85,86</sup> The precise antiepileptic and putative antimanic mechanism(s) of action of topiramate is unknown. In vitro studies indicate that topiramate blocks action potentials elicited by sustained depolarization, suggesting a state-dependent blockade of sodium channels; increases the frequency of  $\gamma$ -aminobutyric acid (GABA) activation of GABA<sub>A</sub> receptors and enhances GABA-induced chloride ion flux; antagonizes kainate/AMPA ( $\alpha$ -amino-3-hydroxy-5-methylisoxazole-4-propionic acid) subtype of glutamate receptors; and inhibits carbonic anhydrase (CA-II and CA-IV) isozymes.<sup>87</sup>

Topiramate blocks maximal electroshock seizures in rat and mouse experiments. It is only weakly effective in blocking pentylenetetrazol-induced clonic seizures. Topiramate exerts anticonvulsant activity in tonic and absence-like seizure models of epilepsy in rodents and clonic seizures induced by amygdala kindling or global ischemia.<sup>87</sup>

### Pharmacokinetics

Topiramate is available in tablets and sprinkle capsules. The 2 formulations are bioequivalent. Topiramate is rapidly absorbed with peak plasma concentrations occurring approximately 2 hours after oral administration. The bioavailability of topiramate is approximately 80% and is not affected by food.<sup>7</sup>

The pharmacokinetics of topiramate are linear over the dosage range of 200 to 800 mg/day. The mean plasma elimination half-life is 21 hours, and steady-state is reached in about 4 to 5 days. Topiramate is weakly (13%–17%) bound to plasma proteins. It is not extensively metabolized, and approximately 70% is eliminated unchanged in urine. Six metabolites are formed from hydroxylation, glucuronidation, and hydrolysis.<sup>87</sup> Topiramate undergoes some renal reabsorption through renal tubules. The clearance of topiramate was reduced by 42% in patients with moderate renal impairment and by 54% in patients with severe renal impairment. The use of half the usual dose is recommended in patients with significant renal compromise.<sup>7</sup> The clearance of topiramate

in patients with hepatic impairment may also be decreased. Age, gender, and ethnicity do not appear to affect topiramate clearance.

Topiramate is associated with a risk (approximately 1.5%) of nephrolithiasis probably due to its carbonic anhydrase inhibition, which increases urinary pH and decreases urinary citrate excretion. Use of topiramate with other carbonic anhydrase inhibitors or in patients on a ketogenic diet may further increase the risk of nephrolithiasis. Hydration is a recommended preventative measure.<sup>7</sup>

In topiramate overdose, gastric lavage or emesis is recommended following recent ingestion. Topiramate can be removed by hemodialysis. Appropriate supportive care is indicated.<sup>17</sup>

## DISCUSSION

The pharmacodynamics of the medications reviewed differ substantially. The pharmacologic mechanisms of action provide a basis of understanding the common and rare side effects of these medications as well as clues to their therapeutic actions. There are important pharmacologic differences, even among the atypical antipsychotic agents, that may affect their thymoleptic profiles. Similar pronounced differences exist in the pharmacokinetics of these agents. These differences are important to appreciate in day-to-day prescribing and in the administration of these medications in combination with other drugs.

*Drug names:* carbamazepine (Tegretol and others), clozapine (Clozaril and others), diazepam (Valium and others), divalproex sodium (Depakote), fluoxetine (Prozac and others), haloperidol (Haldol and others), lamotrigine (Lamictal), naloxone (Narcan and others), olanzapine (Zyprexa), oxcarbazepine (Trileptal), quetiapine (Seroquel), risperidone (Risperdal), topiramate (Topamax), valproic acid (Depakene), warfarin (Coumadin), ziprasidone (Geodon).

*Disclosure of off-label usage:* The authors of this article have determined that, to the best of their knowledge, carbamazepine, clozapine, lamotrigine, oxcarbazepine, quetiapine, risperidone, topiramate, and ziprasidone are not approved by the U.S. Food and Drug Administration for the treatment of bipolar disorder.

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