Introduction

Bipolar disorder is a devastating disease that has a severe impact on patients, their family members, and society. The prevalence of bipolar disorder is estimated at 1 to 2 percent of the adult population. However, the true prevalence is thought to be much higher when misdiagnosis and a broader spectrum of the disease is taken into account. Bipolar disorder is the sixth leading cause of disability in the world.

The economic burden of bipolar disorder is significant. It is estimated that the lifetime cost to care for patients who developed bipolar disorder in 1998 was 24 billion dollars. In that study, the average lifetime cost per case ranged from $11,720 for people with a single manic episode to $624,785 for those with chronic episodes. Lost employment and use of the criminal justice system contribute to the economic and societal impact of bipolar disease.

Bipolar depression is the most difficult phase of bipolar disorder to treat. It causes greater morbidity and mortality than the manic phase. According to DSM-IV, bipolar depression is defined as a major depressive episode in a person who has had at least one manic episode (bipolar I), or a hypomanic episode (bipolar II). In general, patients spend far more time in the depressed phase than the manic phase of the disease. As many as 15 percent of people with bipolar disorder will commit suicide. Patients are nearly 35 times more likely to commit suicide during depressive episodes.

Pharmacotherapy for bipolar depression is different than pharmacotherapy for unipolar depression. Antidepressant medications are not recommended as monotherapy in bipolar depression due to the risk of precipitating an affective switch into mania and increased mood-cycling. The current American Psychiatric Association (APA) guidelines, last revised in 2002, recommend using lithium or lamotrigine (Lamictal®) as first-line treatment for bipolar depression. According to the APA guideline, adding paroxetine (Paxil®), sustained-release bupropion (WellbutrinSR®), or lamotrigine to a mood stabilizer may be considered in patients that have breakthrough symptoms on optimal doses of a mood stabilizing agent alone. In contrast to unipolar depression, the recommendation is to discontinue the antidepressant upon symptom relief. Long-term continuation of the antidepressant may induce rapid cycling.

Symbyax® is a combination of the atypical antipsychotic olanzapine (Zyprexa®) and the antidepressant fluoxetine (Prozac®). Symbyax® (olanzapine/fluoxetine) is the first medication
mine, and alpha1 receptors may explain some of the side effects of olanzapine, including anticholinergic actions, somnolence, and orthostatic hypotension, respectively. Olanzapine binds weakly to GABA1, benzodiazepine and alpha-adrenergic receptors.10

Fluoxetine inhibits the reuptake of serotonin by antagonizing the serotonin transporters of the presynaptic neurons. Fluoxetine is also a weak inhibitor of norepinephrine and dopamine reuptake.10

Peak serum concentrations of olanzapine and fluoxetine occur at approximately 4 and 6 hours, respectively.10 Olanzapine has linear pharmacokinetics over the therapeutic dosing range. The mean half-life of olanzapine is 30 hours; once daily dosing leads to steady-state concentrations in approximately 1 week. The half-life of olanzapine is 1.5 times longer in the elderly population. Olanzapine is primarily metabolized by glucuronidation and cytochrome P450 1A2 (CYP1A2). Cigarette smoking induces the CYP1A2 enzyme and may decrease serum concentrations of olanzapine. Metabolism via CYP2D6 is a minor pathway of olanzapine. Fluoxetine is a potent inhibitor of CYP2D6. Con-
sequently, there is a small decrease in olanzapine clearance that does not appear to be clinically important. Fluoxetine and its active metabolite norfluoxetine reach steady-state concentrations in 2 to 4 weeks. The half-life of fluoxetine is 2 to 3 days, while the half-life of norfluoxetine is 7 to 9 days. Hepatic impairment can affect the elimination of fluoxetine. For instance, in patients with cirrhosis the half-life of fluoxetine and norfluoxetine are prolonged to 8 and 12 days, respectively. Hepatic impairment can affect the elimination of fluoxetine.

Clinical Trials

Olanzapine and other atypical antipsychotics have demonstrated efficacy in treating acute mania. There is evidence to suggest that fluoxetine’s efficacy is augmented by concomitant treatment with olanzapine. The efficacy of olanzapine/fluoxetine in bipolar depression was demonstrated in an eight-week, double-blind, parallel, randomized controlled trial. Notably, there were no statistically significant differences in treatment-emergent mania among treatment and placebo groups.

The clinical trial was designed to compare the efficacy and safety of olanzapine monotherapy to placebo in depressed bipolar I patients, but olanzapine/fluoxetine was also tested in an exploratory analysis. Patients were randomized in a 4:4:1 allocation to receive olanzapine monotherapy 5 to 20mg/d (n=370); placebo (n=377); or olanzapine/fluoxetine, 6 and 25, 6 and 50, or 12 and 50mg/d in a flexible dosing schedule (n=86). All patients were 18 years or older and met DSM-IV criteria for diagnosis of bipolar I depression. Of the 833 patients, 13 percent were inpatients, 82.6 percent were white, and 63 percent were female. The primary outcome was the change in Montgomery-Asberg Depression Rating Scale (MADRS) from baseline to week 8. The MADRS is a 10-item clinician-rated scale with total scores ranging from 0 to 60.

All groups were moderately to severely depressed at baseline, with mean MADRS scores of 31.3, 32.6, and 30.8 for the placebo, olanzapine, and olanzapine/fluoxetine groups, respectively. Starting at week 1 and continuing throughout the study, the olanzapine monotherapy and olanzapine/fluoxetine groups showed significantly greater mean improvements in MADRS scores versus placebo (P<0.001) (Figure 1). Beginning at week 4 and continuing to week 8, olanzapine/fluoxetine demonstrated significantly greater mean improvement in total MADRS scores compared to olanzapine monotherapy and placebo (P<0.02). Table 1 summarizes the mean improvement in total MADRS scores at 8 weeks.

Safety/Monitoring

In the clinical trial there were no statistically significant differences in treatment-emergent mania among the groups. (Table 2) Table 3 lists the adverse events associated with olanzapine/fluoxetine. The adverse event profile for olanzapine/fluoxetine was similar to that for olanzapine monotherapy; however, olanzapine/fluoxetine was associated with significantly higher rates of nausea and diarrhea compared to olanzapine alone (Table 3).

Olanzapine is associated with metabolic side effects, including weight gain, hyperglycemia, and dyslipidemia. In some cases, the hyperglycemia has resulted in ketoacidosis and death. All patients taking atypical antipsychotics should be monitored for hyperglycemia. People who already have diabetes should be monitored more frequently. Before beginning olanzapine/fluoxetine, clinicians should collect baseline weight, lipids, and measures of glucose control.

Olanzapine/fluoxetine may cause orthostatic

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Change in MADRS Score Mean ± SE (95%CI)</th>
<th>vs Placebo P Value</th>
<th>vs Olanzapine P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-11.9 ± 0.8 (-13.4 to -10.4)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>-15.0 ± 0.7 (-16.4 to -13.6)</td>
<td>.002</td>
<td>NA</td>
</tr>
<tr>
<td>Olanzapine/fluoxetine</td>
<td>-18.5 ± 1.3 (-21.1 to -16.0)</td>
<td>&lt;.001</td>
<td>.01</td>
</tr>
</tbody>
</table>
hypotension, which can induce tachycardia, dizziness, and rarely syncope. For this reason, caution should be used in patients with cardiovascular disease, cerebrovascular disease, and in patients predisposed to hypotension. This is most likely to occur during initial dose-titration.

Olanzapine/fluoxetine should not be taken with a monoamine oxidase inhibitor (MAOI) or within 14 days of discontinuing a MAOI. An MAOI should not be started for at least 5 weeks after discontinuing olanzapine/fluoxetine in order to allow sufficient time for fluoxetine and its metabolites to be eliminated.

**Dosing/Cost**

Olanzapine/fluoxetine is taken once daily in the evening to minimize the consequences of somnolence. Olanzapine/fluoxetine comes in capsules containing 6 or 12 mg of olanzapine and 25 to 50 mg of fluoxetine (table 4). The starting dose of olanzapine/fluoxetine is 6 mg/25 mg. Dose adjustments can be made based on efficacy and tolerability. The safety for doses above 18 mg/75 mg has not been evaluated, nor has the efficacy of olanzapine/fluoxetine been proven after 8 weeks of therapy. Therefore, 18 mg/75 mg is the maximum recommended daily dose. No adjustments for renal impairment are required. Dose adjustments for hepatic impairment may be needed depending on the severity of impairment, but there are no specific recommendations available. Olanzapine/fluoxetine has not been evaluated in children < 18 years old or in the elderly ≥ 65 years of age. Unlike unipolar depression, there are no guidelines for how long depressive episodes should be treated with antidepressant medications in patients with bipolar disorder.

Olanzapine/fluoxetine is not more expensive than taking olanzapine and fluoxetine separately (Table 4). Taking the two drugs separately would allow greater flexibility in dose titration. However, for some patients, taking one pill may be convenient and foster improved adherence.

**Summary**

The depressive phase of bipolar disorder is difficult to treat and associated with higher morbidity and mortality than the manic phase of the disease. Olanzapine/fluoxetine is the first FDA-approved medication indicated for depressive episodes in people with bipolar disorder. One randomized controlled trial demonstrated that olanzapine/fluoxetine significantly reduced depressive symptoms over 8 weeks as measured by MADRS. The efficacy of olanzapine/fluoxetine treatment longer than 8 weeks has not been evaluated. There are no guidelines for how long depressive episodes should be treated with antidepressant medications in patients with bipolar disorder. Olanzapine/ fluoxetine is not more expensive than taking olanzapine and fluoxetine separately and may be less expensive. Common side effects include somnolence, diarrhea, orthostatic hypotension, weight gain, and dry mouth. There is concern that using the fixed doses of olanzapine/fluoxetine may lead to overuse of olanzapine. In addition to weight gain, olanzapine has been associated with dyslipidemia and diabetes. Practitioners should be cognizant of these adverse effects and closely monitor weight, lipids, blood glucose, and HbA1C. It is likely that different atypical antipsychotic and antidepressant combinations will be investigated for the treatment of bipolar disorder in the future.

**References**


### Table 4. Retail Price

<table>
<thead>
<tr>
<th>Drug</th>
<th>Strength</th>
<th>Cost*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Avg</td>
</tr>
<tr>
<td><strong>Symbyax®</strong> (Olanzapine/fluoxetine)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 mg/25 mg</td>
<td>$265.82</td>
<td>$242.88 – $293.99</td>
</tr>
<tr>
<td>6 mg/50 mg</td>
<td>$265.82</td>
<td>$242.88 – $293.99</td>
</tr>
<tr>
<td>12 mg/25 mg</td>
<td>$396.68</td>
<td>$362.46 – $446.69</td>
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<tr>
<td>12 mg/50 mg</td>
<td>$396.68</td>
<td>$362.46 – $446.69</td>
</tr>
<tr>
<td>7.5 mg</td>
<td>$254.15</td>
<td>$239.68 – $273.79</td>
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<td>20 mg</td>
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<td>Total</td>
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<tr>
<td><strong>Zyprexa®</strong> + Fluoxetine (average generic)</td>
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<td>15 mg</td>
<td>$79.79</td>
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<tr>
<td>Total</td>
<td>$552.81</td>
<td>$516.46 – $609.29</td>
</tr>
</tbody>
</table>

*Cost for a 30-day supply at three community pharmacies and one online.

15. Jin H, Meyer JM, Jeste DV. Phenomenology of and risk factors for new-onset diabetes mellitus and diabetic ketoacidosis associated with atypical antipsychotics: an

### New Drugs and Dosage Forms

- Gabapentin tablets (Neurontin®) will now be formulated with a “functional score” in the 600 and 800 mg strength. Tablets that have been split must be administered within “several” days.
- Metformin hydrochloride extended release (Fortamet®), now available in 500 and 1000 mg tablets, incorporates single-composition osmotic technology (SCOT). It is indicated as monotherapy or combination therapy with a sulfonylurea or insulin, in addition to diet and exercise. The recommended starting dose is 1000 mg daily as a single dose with the evening meal. The dose can be titrated in 500 mg increments to the maximum of 2500 mg/d.
- Rifaximin tablets (Xifaxan™), a rifampin analogue, is indicated for the treatment of patients age 12 years or older with traveler’s diarrhea due to noninvasive strains of *Escherichia coli*; rifaximin is essentially unabsorbed.
We reviewed the treatment and prevention of Lyme disease in January of 2003. The review was based upon guidelines endorsed by the Infectious Disease Society of America (IDSA). Subsequently, the International Lyme and Associated Disease Society (ILADS) developed a working party to evaluate current practices and establish new standards of care for patients with Lyme disease. In November of 2003, ILADS released guidelines for the management of Lyme disease. There is some inconsistency between the two sets of guidelines that merit mention. The purpose of this report is to alert readers to the existence of the ILADS guidelines and succinctly contrast them with those from IDSA.

ILADS classifies “chronic Lyme disease” as persistent fatigue, cognitive dysfunction, headaches, sleep disturbance, neuropsychiatric presentations, cardiac presentations, or musculoskeletal problems. ILADS recognizes and defines chronic Lyme disease whereas IDSA attributes persistent symptomatology to an immune mediated response. ILADS places less emphasis on the specific antibiotic chosen, recognizing amoxicillin, azithromycin, cefuroxime, clarithromycin, doxycycline, or tetracycline as acceptable oral therapies. Likewise, ceftriaxone, cefotaxime, penicillin, imipenem, azithromycin, and doxycycline are all credited with antispirochetal activity and identified as appropriate intravenous therapies. In contrast, IDSA is more specific in its recommendations regarding antibiotic therapy.

ILADS endorses a broader application of antibiotics, including longer courses of therapy, compared to IDSA. ILADS acknowledges that some of their recommendations are predicated upon expert opinion (when controlled trials are not available).

Both IDSA and ILADS recognize the importance of Lyme disease and a disturbing increase in the number of cases annually. The lack of a consensus opinion is a testament to the need for further research. Until such time, optimal management of Lyme disease will remain a goal for all practitioners.

References

FDA-approved labeling changes
- Warfarin was added as a Precaution in the labeling for pantoprazole sodium (Protonix®) to alert providers to the need for more vigilant monitoring.