

Fluoxetine

Olanzapine Symbyax™

Description: Fluoxetine; olanzapine (SYMBYAX™) is a combination of an atypical antipsychotic, olanzapine, with a selective serotonin reuptake inhibitor (SSRI), fluoxetine. This drug combination is the first FDA-approved combination medication for the depressive phase of bipolar I disorder. Clinically, atypical antipsychotics have been frequently used off-label in combination with SSRIs for a variety of psychotropic disorders. Olanzapine, as a single agent, is useful for patients with a diagnosis of bipolar I disorder with manic or mixed episodes. The addition of fluoxetine helps to alleviate bipolar depression better than the use of olanzapine alone. The FDA approved fluoxetine; olanzapine (SYMBYAX™) for the treatment of the depressive phase of bipolar disorder on December 24, 2003. On October 15, 2004 the FDA directed manufacturers of all antidepressants to include a Black Box warning, expanded warning statements, and clinical trial results detailing the increased risk of suicidality in children and adolescents. A Patient Medication Guide (MedGuide) will also accompany all prescriptions for antidepressants. The FDA is currently assessing the risk of suicidality in adults taking antidepressants and a final report is expected by mid- to late 2006. In September 2003, the FDA requested all manufacturers of atypical antipsychotics to include product label warnings about the potential for an increased risk of hyperglycemia and diabetes with the use of atypical antipsychotics. On April 11, 2005 the FDA issued a public health advisory noting that the unapproved use of atypical antipsychotics for the treatment of behavioral disorders in the elderly with dementia has been associated with a higher death rate vs. placebo. All manufacturers of atypical antipsychotics (including SYMBYAX™) will be required to include a boxed warning in their labeling noting this risk.

Quetiapine

Seroquel®

Description: Quetiapine is an atypical antipsychotic agent structurally similar to clozapine, a dibenzodiazepine antipsychotic. Clinical trials indicate that quetiapine is effective as monotherapy for the management of bipolar mania; treatment may also be delivered in combination with standard mood stabilizers (i.e., lithium, divalproex). Quetiapine trials also suggest effectiveness in the treatment of the depressive phase of bipolar disorder. Quetiapine received FDA approval for management of the manifestations of psychotic disorders in September 1997. Quetiapine (as monotherapy or in combination with lithium or divalproex) received FDA approval for manic episodes associated with bipolar disorder on January 13, 2004.

Children: Safe and effective use of combination therapy is not established.

Patients with hepatic impairment: Patients with hepatic impairment have a 30% lower mean clearance of quetiapine than normal subjects; dosage adjustment is necessary.

Patients with renal impairment: Specific guidelines for dosage adjustments in renal impairment are not available. Although patients with severe renal impairment (CrCl 10–30 ml/min) have a 25% lower mean clearance than normal subjects, plasma quetiapine concentrations are still within the range of concentrations seen in normal subjects receiving the same dose. Therefore, it appears that no dosage adjustment is needed in patients with a CrCl above 10 ml/min.

Ziprasidone

Geodon®

Description: Ziprasidone is an atypical antipsychotic, pharmacologically distinct from traditional agents like the phenothiazines or haloperidol. Atypical antipsychotics are deemed to be the standard of care for schizophrenia and related disorders, and with the exception of clozapine, may be considered as first-line treatment options for the management of psychosis. Ziprasidone's unique pharmacology offers advantages in the areas of antipsychotic-induced weight gain and possibly the treatment of depressive symptoms in patients with schizophrenia or schizoaffective disorder. However, serious side effects may occur; ziprasidone has been associated with QTc interval prolongation and should not be combined with other medications that may produce this effect. Geodon® capsules received final FDA approval on February 5, 2001. Intramuscular (IM) Geodon® injection was FDA-approved June 24, 2002 for the treatment of acute agitated behavior and acute psychotic symptoms in patients with acute exacerbations of schizophrenia; open studies comparing the drug to haloperidol IM have shown comparable efficacy, and data have suggested IM ziprasidone may be less likely to induce movement disorders. On August 23, 2004 ziprasidone monotherapy was approved by the FDA for use in acute bipolar mania.

Patients with hepatic impairment: Ziprasidone AUC and half-life have been increased in those with cirrhosis. The manufacturer has not recommended oral dosage adjustments for patients with hepatic impairment. Ziprasidone IM has not been evaluated in patients with hepatic dysfunction.

Patients with renal impairment: The manufacturer has not recommended oral dosage adjustments for patients with renal impairment. Ziprasidone IM contains a cyclodextrin excipient that is cleared by renal filtration; this dosage form should be administered with caution in patients with impaired renal function.

Intermittent hemodialysis: See dosage in renal impairment. Ziprasidone is not removed by hemodialysis.

Aripiprazole Abilify®

Description: Aripiprazole (OPC-14597) is the first in a new class of atypical antipsychotic drugs known as ‘dopamine system stabilizers’ (DSSs). Aripiprazole is a partial dopamine agonist, in contrast to other antipsychotic agents that are full dopamine antagonists, and thus the drug has a distinct mechanism of action. Compared to other traditional antipsychotics, aripiprazole has a very low incidence of cardiovascular reactions; it does not lengthen the QT interval. Aripiprazole has not been found to affect prolactin. In the monotherapy treatment of acute mania associated with bipolar I disorder, 40—53% of aripiprazole-treated patients have exhibited a 50% or greater reduction in the Young Mania Rating Scale (Y-MRS) at endpoint. FDA approval for aripiprazole was granted November 15, 2002 for the treatment of schizophrenia; in September 2003, the FDA approved aripiprazole for maintenance treatment of schizophrenia. On September 29, 2004 the FDA approved aripiprazole for the treatment of acute bipolar mania, including manic and mixed episodes associated with bipolar disorder. Aripiprazole was FDA-approved for bipolar disorder maintenance treatment (after a 6-week period of stabilization) on March 7, 2005. An oral solution of aripiprazole was FDA-approved on December 10, 2004.

Patients with hepatic impairment: Specific guidelines for dosage adjustments in hepatic impairment are not available; it appears that no dosage adjustments are necessary.

Patients with renal impairment: Specific guidelines for dosage adjustments in renal impairment are not available; it appears that no dosage adjustments are necessary.

Intermittent hemodialysis: Hemodialysis is unlikely to be effective in removing aripiprazole since the drug is highly bound to plasma proteins.

Carbamazepine Carbatrol®, Eptitol®, Equetro™, Tegretol® | Tegretol®-XR

Description: Carbamazepine is an oral anticonvulsant drug, structurally similar to tricyclic antidepressants. Carbamazepine is used in the treatment of partial seizures, both simple and complex, and for tonic-clonic seizures. Carbamazepine is preferred over phenobarbital for children because it has fewer adverse effects on behavior and alertness. Carbamazepine is also effective in treating pain of neurologic origin such as trigeminal neuralgia. Finally, carbamazepine has been shown to be effective in the treatment of certain psychiatric disorders including manic-depressive illness and aggression due to dementia in the elderly, although these are not FDA-approved indications. Carbamazepine was originally approved by the FDA in 1968. Two extended-release dosage forms, Tegretol-XR® tablets and Carbatrol® capsules, were approved in May 1996 and September 1997, respectively. In December 2004, the FDA approved Equetro™, an extended-release (multi-phasic) formulation of carbamazepine, for the treatment of Bipolar I Disorder. Carbamazepine should be used with caution in patients with blood dyscrasia caused by drug therapies or hematological disease because of the potential increased risk of hematologic toxicity. Although uncommon, carbamazepine can cause hematological toxicity consisting of transient leukopenia, neutropenia, thrombocytopenia, or more severe reactions like agranulocytosis or aplastic anemia. Serum concentrations of 4—12 mcg/ml are considered to be therapeutic in the treatment of seizure disorders. Carbamazepine is a potent enzyme inducer and can induce its own metabolism; this appears to be mediated via its effects on the hepatic CYP3A4 isoenzyme. Onset of enzyme induction is at about 3 days, with maximum effect at about 30 days.

Valproic Acid, Divalproex Sodium

Depacon™ | Depakene® | Depakote® | Depakote® ER

Description: Valproic acid and divalproex sodium are anticonvulsants that are chemically unrelated to other anticonvulsants. Valproic acid was synthesized over a century ago, but its anticonvulsant properties were not discovered until 1963. Both regular valproate sodium and a sustained-release form (divalproex sodium) are commercially available; these dosage forms share the same pharmacology. Valproic acid was licensed by the FDA in 1978. In May 1995, valproic acid was approved for treatment of bipolar disorder and in March 1996 it was approved for migraine prophylaxis. An intravenous dosage form of valproate sodium (Depacon®) was approved in January 1997. A once-daily Depakote® ER tablet was approved by the FDA in August 2000 for use in migraine prophylaxis. In December 2002 the once-daily formulation was approved for adults and in September 2003 for children ≥ 10 years of age as single and adjunctive therapy for the treatment of complex partial seizures and simple and complex absence seizures. On December 6, 2005 divalproex sodium extended-release (Depakote® ER) was approved for adults as monotherapy in the treatment of acute manic or mixed episodes associated with bipolar I disorder, with or without psychotic features. A small pilot study indicates that divalproex is effective in reducing the symptoms of depression and anxiety in bipolar depression; however, larger multi-site trials are needed for this indication. A 20 month clinical trial of valproate compared to lithium for treatment of adult patients with rapid-cycling bipolar disorder (n=60) did not demonstrate superiority of divalproex over lithium. The rates of relapse into any mood episode for those given lithium versus divalproex were 56% and 50%, respectively; the rates were 34% and 29% for a depressive relapse and 19% and 22% for a hypomania/mania relapse.

Patients with hepatic impairment: Because of the severe hepatotoxicity that may occur with valproic acid, avoid use in those with active hepatic disease/impairment. Drug clearance may be decreased by 50% in cirrhosis. Because liver dysfunction associated with valproic acid is likely dose-related, titrate dose slowly in susceptible patients. Periodic liver function tests should be performed. Discontinue if significant hepatic dysfunction is suspected or confirmed.

Patients with renal impairment: In patients with severe renal impairment or renal failure, uremia can cause an increase in the free fraction of the drug, resulting in possible toxicity. Also, unbound valproic acid in the blood may be cleared more rapidly than bound drug. Close monitoring of valproic acid serum concentrations may be warranted to ensure adequate dosage, ensure efficacy and limit toxicity.

Therapeutic Drug Monitoring: As with all anticonvulsants, dosage should be individualized and adjusted to patient response and the indication for therapy. Therapeutic valproic acid serum concentrations for epilepsy are generally considered to be between 50–100 mcg/ml, although some epileptic patients may require higher serum concentrations for proper seizure control. A clinical response in mania is generally observed with trough serum concentrations between 50–125 mcg/ml. Toxicity may be seen with concentrations exceeding 100–125 mcg/ml.

Risperidone

Risperdal® | Risperdal® Consta™ | Risperdal® M-Tab™

Description: Risperidone is an antipsychotic agent that, along with other atypical agents is deemed to be the standard of care for schizophrenia and related disorders, and with the exception of clozapine, may be considered as first-line treatment options for the management of psychosis. Psychotic disorders, including acute and chronic schizophrenic psychoses, and affective symptoms associated with schizophrenia have responded to treatment with risperidone. Selected data suggest advantages of atypical antipsychotics over typical antipsychotic agents (e.g., phenothiazines) such as a possible reduction in the negative symptoms of schizophrenia and a reduced incidence of extrapyramidal symptoms. Unlike clozapine, the first serotonin-dopamine blocking agent marketed, risperidone is not associated with agranulocytosis. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study evaluated the effectiveness of selected atypical antipsychotics and perphenazine in schizophrenic patients (see Atypical Antipsychotic Overview). The primary outcome measure was discontinuation of treatment for any cause, with secondary outcomes evaluating drug efficacy (determined via the PANSS and CGI scale), adverse event profiles, and reasons for drug discontinuation. For the primary outcome measure, 74% of patients discontinued study medication before 18 months. The olanzapine group demonstrated a slightly longer time to discontinuation of treatment for any cause compared to the quetiapine or risperidone groups. Secondarily, the duration of successful treatment was significantly longer in the olanzapine and risperidone groups, compared to other atypicals or perphenazine. The PANSS and CGI scores improved and were similar in all groups. However, discontinuation due to adverse events was greater in the olanzapine group, primarily due to weight gain and metabolic effects. Among treatment groups, risperidone had the lowest rate of treatment discontinuation due to intolerable side effects. Risperidone

has also been effective in patients with acute mania or with refractory bipolar disorder. Risperidone was approved for the initial treatment of schizophrenia by the FDA in December 1993. An oral solution was approved in June 1996. On March 3, 2002, the drug received FDA-approval for the longer-term management of schizophrenia; the continued use of the drug has been shown to delay relapse of the disease. The fast-dissolving Risperdal® M-tab™ was approved by the FDA in early 2003. Risperdal Consta®, a long-acting injectable depot formulation of risperidone, was FDA-approved for schizophrenia on October 31, 2003. On December 8, 2003 risperidone was approved for treatment of bipolar I disorder (also known as bipolar mania), either as monotherapy or in combination with lithium or valproate.

Olanzapine

Zyprexa® | Zyprexa® Zydis®

Description: Olanzapine is an atypical antipsychotic agent similar in chemical structure and in mechanism of action to clozapine. Atypical antipsychotics (excluding clozapine) are deemed to be the standard of care for schizophrenia and related disorders. Compared to typical antipsychotics, olanzapine appears to have a lower potential for extrapyramidal side effects, neutropenia, and hyperprolactinemia. Clinically, olanzapine is effective for the positive and negative symptoms of schizophrenia. Olanzapine is also approved for the treatment of acute bipolar mania. Controlled studies have also established the efficacy of olanzapine monotherapy for prevention of relapse into mania during the maintenance phase of treatment. Compared to haloperidol or lithium, olanzapine is equally effective in achieving remission in bipolar mania, but a switch to depression occurred more frequently in the haloperidol group. The risk for serious extrapyramidal symptoms is present with conventional antipsychotics, but weight gain can be problematic for olanzapine patients. Olanzapine has been shown to be superior to valproate in a 3-week study of acute bipolar patients with mixed or manic episodes, but the decrease in the Hamilton Depression scores were similar. FDA approval was granted October 1, 1996 for the treatment of schizophrenia. The company withdrew an additional NDA in 1999 for the treatment of symptoms related to Alzheimer's and other dementias pending the FDA review of criteria relating to clinical drug trials in demented subjects. In March of 2000 the FDA approved olanzapine for monotherapy of acute manic or mixed episodes associated with bipolar disorder. An orally-disintegrating tablet (i.e., Zyprexa® Zydis®), bioequivalent to the regular tablets, was approved in April 2000. On July 16, 2003 olanzapine was FDA-approved for use in combination with lithium or valproate to treat acute manic episodes of bipolar I disorder. An IM formulation (Zyprexa® IntraMuscular) was approved in the US on March 30, 2004 for the treatment of acute agitation in patients with schizophrenia and bipolar disorder.

Lamotrigine

Lamictal® | Lamictal® Chewable

Description: Lamotrigine is an oral anticonvulsant agent developed based on the observation that some antiepileptic drugs possess antifolate activity. Although derived from agents which inhibit dihydrofolate reductase, lamotrigine has relatively little antifolate activity. Due to life-threatening rashes (including Stevens-Johnson syndrome and toxic epidermal necrolysis), lamotrigine carries a Black-Box warning stating the drug should be discontinued if a rash appears at any time during treatment. Factors to predict a serious rash are not available; however, children appear to be at greater risk. Lamotrigine was found to be an effective anticonvulsant and is used as adjunctive treatment for refractory partial seizures with or without secondarily generalized tonic-clonic seizures. In adults, lamotrigine may be used for monotherapy of partial seizures in patients currently on single-drug therapy with an enzyme-inducing anti-epileptic drug. Improvements in quality of life, when compared to placebo, have been seen with lamotrigine; patients noted improvements in rating of seizure severity, mastery, and happiness. Lamotrigine was originally approved by the FDA on December 28, 1994. Lamotrigine is also effective for the adjunctive treatment of Lennox-Gastaut syndrome and was approved for this use in pediatric and adult patients in September 1998. A chewable tablet was FDA-approved in August 1998. In January 2003, the FDA approved lamotrigine tablets as adjunctive therapy for partial seizures in children 2 years of age and older. On January 16, 2003, lamotrigine was approved for monotherapy treatment for partial seizures in patients \geq 16 years when converting from valproate therapy. Lamotrigine was FDA-approved for the long-term maintenance treatment of bipolar I disorder on June 23, 2003; phase III trials demonstrated that the drug helps delay the time to occurrence of mood disorders in stabilized patients, including both depression and mania, although the findings were more robust for depression. Carbamazepine, phenytoin, phenobarbital and primidone can decrease lamotrigine half-life. Valproic acid decreases the clearance of lamotrigine and more than doubles elimination half-life, whether given with or without the other antiepileptic drugs.

Lithium

Eskalith® | Lithobid® | Eskalith CR® | Lithonate®

Description: Lithium is a monovalent cation similar to sodium and potassium. For clinical use, it is administered orally as the carbonate and the more water-soluble citrate salts. Lithium is the drug of choice in treating recurrent bipolar affective disorder (i.e., manic-depressive illness) and has also been used for unipolar disorder (depression). Nonpsychiatric uses of lithium include the syndrome of inappropriate secretion of ADH (SIADH), neutropenia, thyrotoxic crisis, and migraine and cluster headaches, although these are not FDA-approved uses. The use of lithium in clinical medicine dates back to 1841 when it was proposed to be an effective therapy for gout, but it was later found ineffective for this purpose. In the late 1940s, lithium chloride was used as a salt substitute. After several cases of lithium toxicity were associated with indiscriminate use, it was withdrawn from the market until 1949 when it was serendipitously discovered that lithium was beneficial in the management of mania. Lithium carbonate was approved by the FDA in 1970. The pharmacokinetics of the drug were not well understood until years later.

Mechanism of Action: Lithium competes at cellular sites with sodium, potassium, calcium, and magnesium ions. Lithium competes with these ions at intracellular binding sites, at protein surfaces, at carrier binding sites, and at transport sites. At the cell membrane, lithium readily passes through sodium channels, and high concentrations can block potassium channels. Although the mechanism of the antimanic and antidepressant action in the CNS is not known, evidence suggests that the drug interferes with the synthesis, storage, release, and reuptake of monoamine neurotransmitters. Lithium enhances the uptake of tryptophan, increases the synthesis of serotonin, and may also enhance the release of serotonin in the CNS. Lithium does not possess sedative, depressant, or euphoriant effects. Onset of the acute antimanic effect is usually seen in 5–7 days, and the full therapeutic effect is established in 10–21 days.

Lithium administration increases renal sodium and potassium clearance. These effects are attenuated by a compensatory increase in aldosterone after 2–3 days. Lithium does not affect sodium reabsorption in either the ascending limb of the loop of Henle or in the distal tubule. A decrease in renal concentrating ability occurs in 30–50% of patients while receiving lithium; it often produces a mild nephrogenic diabetes insipidus manifested as polyuria. Lithium-induced diabetes insipidus is thought to be due to inhibition of vasopressin-induced adenylate cyclase activity in the medullary collecting tubule of the nephron. Since lithium is more toxic and a less reliable agent than demeclocycline, lithium should be considered a last choice for the treatment of SIADH.

Lithium enhances granulocyte production via stimulation of monocyte colony stimulating factor production. Lithium produces an increase in the total neutrophil pool and each of its components in the bone marrow and circulation. Leukocytosis peaks within 7–10 days of initiating therapy and the WBC count will return to baseline 7–10 days after discontinuing lithium.

The actions of lithium on the heart generally give rise to adverse (i.e., not therapeutic) effects. The most common EKG changes include flattening or inversion of the T-waves. This manifestation is thought to be due to lithium-induced inhibition of potassium cellular reuptake leading to intracellular hypokalemia. Because lithium displaces potassium, an extracellular hyperkalemia is seen and, since the intracellular: extracellular potassium balance is shifted, cardiac arrest is possible at lower than usual degrees of hyperkalemia.

Pharmacokinetics: Lithium salts are administered orally. Lithium is rapidly absorbed from the GI tract, and the rate of absorption is not significantly slowed by the presence of food. Lithium carbonate in tablets or capsules is 95–100% absorbed. Bioavailability from slow-release lithium carbonate tablets is 60–90%. Lithium citrate oral solutions are essentially 100% absorbed. Lithium carbonate is most commonly used because it has a longer shelf-life and contains more lithium on a weight basis than do other salts.

Peak serum concentrations after administration of lithium carbonate rapid-release formulations are reached in 0.5–3 hours, and absorption is complete within 6 hours. When extended-release tablets are used, peak lithium concentrations are observed 4–12 hours after the dose. Oral solutions of lithium citrate are extremely rapidly absorbed; peak serum levels are achieved in 15–60 minutes. Lithium has negligible protein binding and is distributed throughout the body, with slightly greater concentrations in thyroid, bone, and brain tissue. It is excreted unchanged in urine. A 300 mg dose of lithium carbonate tablets produces peak serum concentrations of 0.4–0.5 mEq/L. A similar dose in capsules gives

peak serum concentrations of 0.4—0.9 mEq/L. Serum lithium concentrations tend to fluctuate for 6—10 hours after dosing, so the 12-hour post-dose serum concentration is used for monitoring purposes. Data published in 1989 confirmed that serum concentrations of 0.8—1.0 mEq/L are more effective in preventing relapse in patients with bipolar disorder than are lower concentrations of 0.4—0.6 mEq/L. Steady-state serum lithium concentrations of 1—1.5 mEq/L are required to control acute mania. Toxicity is likely in most patients when levels exceed 1.5 mEq/L, although symptoms of lithium toxicity can appear in some patients with serum concentrations of 1 mEq/L or less. The narrow therapeutic ratio and interpatient variations make individual monitoring and dosage adjustment essential.

Approximately 90—95% of a dose of lithium is eliminated by the kidneys. The amount eliminated through sweat, saliva, and feces is negligible under normal circumstances. Lithium is freely filtered by renal glomeruli, but it also undergoes significant renal tubular reabsorption. Thus, any decrease in GFR will reduce lithium elimination. It was once thought that tubular reabsorption occurred only in the proximal tubule but interaction studies with HCTZ and furosemide revealed substantial lithium reabsorption also occurs in the ascending limb of the loop of Henle. In patients with normal renal function, biphasic elimination is observed. The initial half-life is 0.8—1.2 hours, and the terminal half-life is approximately 20—27 hours, although reported half-life values have ranged from 5—79 hours. In young adults, the half-life is 18—24 hours, and in the elderly, it is 30—36 hours. Many factors can affect lithium clearance including hyponatremia or hypernatremia, dehydration, and diuretic use.

In August 2004, the FDA requested all manufacturers of atypical antipsychotics to include revised product label warnings about the potential for an increased risk of hyperglycemia and diabetes with the use of atypical antipsychotics.

On April 11, 2005 the FDA issued a public health advisory noting that the unapproved use of atypical antipsychotics for the treatment of behavioral disorders in the elderly with dementia has been associated with a higher death rate vs. placebo. All manufacturers of atypical antipsychotics will be required to include a boxed warning in their labeling noting this risk.

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)

Initial results of phase one CATIE study have been published in the New England Journal of Medicine. The CATIE STUDY evaluated the effectiveness of selected atypical antipsychotics and perphenazine in schizophrenic patients. The primary outcome measure was discontinuation of treatment for any cause, with secondary outcomes evaluating drug efficacy (determined via the PANSS and CGI scale), adverse event profiles, and reasons for drug discontinuation. For the primary outcome measure, 74% of patients discontinued study medication before 18 months. It is clear that a real challenge exists for clinicians to improve adherence to medications. We urge you to review the published articles on CATIE and make your own decisions as to how this information impacts your practice. See: Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med.* 2005;353:1209—23

DISCLAIMER: The preceding documents are Description and Dosage excerpts from the complete drug monographs published by Gold Standard in Clinical Pharmacology. The excerpted information is not intended to be utilized as a source for drug information for patient care. Patient care should always be tailored to the individual circumstance of each patient. Therapeutic and safety monitoring should be done as per appropriate standards.

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