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29.29 Serotonin–Dopamine Antagonists and Similarly Acting Drugs (Second-Generation or Atypical Antipsychotics)

Comprehensive Textbook of Psychiatry. 9th ed. Vol. 2. Philadelphia: Lippincott Williams & Wilkins; 2009:3190. Thase ME, Haight BR, Richard N, Rockett CB, Mitton M. Remission rates following antidepressant therapy with bupropion or selective reuptake inhibitors: A meta-analysis of original data from 7 randomized controlled trials. J Clin Psychiatry. 2005;66:974. Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, STAR*D Study Team. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: Implications for clinical practice. Am J Psychiatry. 2006;163:28. Weissman AM, Levy BT, Hartz, AJ, Bentler S, Donohue M. Pooled analysis of antidepressant levels in lactating mothers, breast milk, and nursing infants. Am J Psychiatry. 2004;161:1066. 29.29 Serotonin–Dopamine Antagonists and Similarly Acting Drugs (Second-Generation or Atypical Antipsychotics) The serotonin–dopamine antagonists (SDAs), also known as second-generation or atypical antipsychotic drugs, are a group of pharmacologically diverse drugs that have largely supplanted the older dopamine receptor antagonists (DRAs). The term atypical is used because these drugs differ in their side effect profiles, most notably a lower risk of extrapyramidal side effects (EPS), and have spectra of action that are broader than those of

the DRAs. In contrast to the earlier antipsychotic drugs, the SDAs have significant effects on both the dopamine and serotonin systems. Their pharmacology is complex, with individual drugs in this group having multiple neurotransmitter effects. All SDAs are indicated for the treatment of schizophrenia. Most of these secondgeneration antipsychotic drugs have also received approval as monotherapy or adjunctive therapy in the treatment of bipolar disorder. Some have also been approved as adjuncts for treatment of major depression. As of 2013, ten second-generation antipsychotic drugs were approved by the Food and Drug Administration (FDA). These include the following: risperidone (Risperdal), risperidone IM long acting (Consta), olanzapine (Zyprexa), olanzapine for extendedrelease injectable suspension (Zyprexa, Relprevv), quetiapine (Seroquel), quetiapine XR (Seroquel XR), ziprasidone (Geodon), aripiprazole (Abilify), paliperidone (Invega), paliperidone palmitate (Invega, Invega Sustenna), asenapine (Saphris), lurasidone (Latuda), iloperidone (Fanapt), and clozapine (Clozaril). It is arguable whether the SDAs represent an improvement in overall tolerability than the DRAs. Although there is improvement with respect to a lowered, but not absent, risk of EPS, most of the drugs in this group often produce substantial weight gain, which in turn increases the potential for development of diabetes mellitus. Olanzapine and clozapine appear to account for most cases of weight gain and drug-induced diabetes mellitus. The other agents pose a smaller risk of these side effects; nevertheless, the FDA has requested that all SDAs carry a warning label that patients taking the drugs be monitored closely, and has recommended the following factors be considered for all

patients prescribed second-generation antipsychotics.

1. Personal and family history of obesity, diabetes, dyslipidemia, hypertension, and cardiovascular disease
2. Weight and height (so that body mass index can be calculated)
3. Waist circumference (at the level of the umbilicus)
4. Blood pressure
5. Fasting plasma glucose level
6. Fasting lipid profile Patients with preexisting diabetes should have regular monitoring, including hemoglobin A1C (HgA1C) and in some cases insulin levels. Among these drugs, clozapine sits apart. It is not considered a first-line agent because of side effects (hematological) and need for weekly blood tests. Although highly effective in treating both mania and depression, clozapine does not have an FDA indication for these conditions. MECHANISMS OF ACTION The presumed antipsychotic effects of the SDAs are blockade of D2 dopamine receptors. Where the SDAs differ from older antipsychotic drugs is their higher ratio interactions with serotonin receptor subtypes, most notably the 5-HT2A subtype, as well as with other neurotransmitter systems. It is hypothesized that these properties account for the distinct tolerability profiles associated with each of the SDAs. All SDAs have different chemical structures, receptor affinities, and side effect profiles. No SDA is identical in its combination of receptor affinities, and the relative contribution of each receptor interaction to the clinical effects is unknown. THERAPEUTIC INDICATIONS Although initially approved for the treatment of schizophrenia and acute mania, some of these drugs have also been approved as adjunctive therapy in treatment-resistant depression and as adjunctive therapy in major depressive disorder. They are also useful in posttraumatic stress disorder and anxiety disorders, and although clinicians tend to use them in behavioral disturbances associated with dementia, all SDAs carry an FDA boxed

warning regarding adverse effects when used in elderly persons with dementiarelated psychoses, because elderly patients with dementia-related psychoses are at an increased risk (1.6 to 1.7 times) of death compared with placebo. All of these agents are considered first-line drugs for schizophrenia except clozapine, which may cause adverse hematological effects that require weekly blood sampling. SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDER The SDAs are effective for treating acute and chronic psychoses such as schizophrenia

and schizoaffective disorder, in both adults and adolescents. SDAs are as good as or better than typical antipsychotics (DRAs) for the treatment of positive symptoms in schizophrenia and superior to DRAs for the treatment of negative symptoms. Compared with persons treated with DRAs, persons treated with SDAs have fewer relapses and require less frequent hospitalization, fewer emergency department visits, less phone contact with mental health professionals, and less treatment in day programs. Because clozapine has potentially life-threatening adverse effects, it is appropriate only for patients with schizophrenia who are resistant to all other antipsychotics. Other indications for clozapine include treatment of persons with severe tardive dyskinesia— which can be reversed with high dosages in some cases—and those with a low threshold for EPS. Persons who tolerate clozapine have done well on long-term therapy. The effectiveness of clozapine may be increased by augmentation with risperidone, which raises clozapine concentrations and sometimes results in dramatic clinical improvement. Mood Disorders All of the SDAs (except clozapine) are FDA approved for treatment of acute mania. Some of these agents, including aripiprazole, olanzapine, quetiapine, and quetiapine XR, are also approved for the maintenance treatment in bipolar disorder as monotherapy or adjunctive therapy. The SDAs improve depressive symptoms in schizophrenia, and both clinical experience and clinical trials show that all of the SDAs augment antidepressants in the acute management of major depression. At this time, olanzapine in combination with fluoxetine has been approved for treatment-resistant depression, and aripiprazole and quetiapine XR are indicated for adjunctive therapy to antidepressants in major depressive disorders (MDDs). Quetiapine and quetiapine XR are also approved in bipolar depression. A fixed combination of olanzapine and fluoxetine (Symbyax) is approved as a treatment for acute bipolar depression. Other Indications About 10 percent of patients with schizophrenia exhibit outwardly aggressive or violent behavior, and the SDAs are effective for treatment of such aggression. Other off-label indications include acquired immunodeficiency syndrome (AIDS) dementia, autistic spectrum disorders, Tourette’s disorder, Huntington’s disease, and Lesch–Nyhan syndrome. Risperidone and olanzapine have been used to control aggression and selfinjury in children. These drugs have also been coadministered with sympathomimetics, such as methylphenidate (Ritalin) or dextroamphetamine (Dexedrine), to children with attention-deficit/hyperactivity disorder who are comorbid for either oppositional– defiant disorder or conduct disorder. SDAs—especially olanzapine, quetiapine, and clozapine—are useful in persons who have severe tardive dyskinesia. The SDAs are also effective for treating psychotic depression and for psychosis secondary to head trauma, dementia, or treatment drugs. Treatment with SDAs decreases the risk of suicide and water intoxication in patients with schizophrenia. Patients with treatment-resistant obsessive-compulsive disorder

(OCD) have responded to the SDAs; however, a few persons treated with the SDAs have been noted to develop treatment-emergent symptoms of OCD. Some patients with borderline personality disorder may improve with the SDAs. Some data suggest that treatment with conventional DRAs

has protective effects against the progression of schizophrenia when used during the first episode of psychosis. Ongoing studies are looking at whether the use of SDAs in at-risk patients with early evidence of disease prevents deterioration, thus improving long-term outcome. ADVERSE EFFECTS The SDAs share a similar spectrum of adverse reactions, but differ considerably in terms of frequency or severity of their occurrence. Specific side effects that are more common with an individual SDA are emphasized in the discussion of each drug in subsequent text. RISPERIDONE (RISPERDAL) Indications Risperidone is indicated for the acute and maintenance treatment of schizophrenia in adults and for the treatment of schizophrenia in adolescents age 13 to 17 years. Risperidone is also indicated for the short-term treatment of acute manic or mixed episodes associated with bipolar I disorder in adults and in children and adolescents age 10 to 17 years. The combination of risperidone with lithium or valproate is indicated for the short-term treatment of acute manic or mixed episodes associated with bipolar I disorder. Risperidone is also indicated for the treatment of irritability associated with autistic spectrum disorder in children and adolescents age 5 to 16 years, including symptoms of aggression toward others, deliberate self-injuriousness, temper tantrums, and quickly changing moods. Pharmacology Risperidone is a benzisoxazole. It undergoes extensive first-pass hepatic metabolism to 9-hydroxy risperidone, a metabolite with equivalent antipsychotic activity. Peak plasma levels of the parent compound occur within 1 hour for the parent compound and 3 hours for the metabolite. Risperidone has a bioactivity of 70 percent. The combined half-life of risperidone and 9-hydroxy risperidone averages 20 hours, so it is effective in once-daily dosing. Risperidone is an antagonist of the serotonin 5-HT2A, dopamine D2, α1adrenergic and α2-adrenergic, and histamine H1 receptors. It has a low affinity for αadrenergic and muscarinic cholinergic receptors. Although it is as potent an antagonist of D2 receptors, as is haloperidol (Haldol), risperidone is much less likely than haloperidol to cause EPS in humans when the dose of risperidone is below 6 mg per day.

Dosages The recommended dose range and frequency of risperidone dosing has changed since the drug first came into clinical use. Risperidone is available in 0.25, 0.5, 1, 2, 3, and 4 mg tablets and a 1 mg/mL oral solution. The initial dosage is usually 1 to 2 mg at night, which can then be increased to 4 mg per day. Positron emission tomography (PET) studies have shown that dosages of 1 to 4 mg per day provide the required D2 blockade for a therapeutic effect. At first it was believed that because of its short elimination halflife, risperidone should be given twice a day, but studies have shown equal efficacy with once-a-day dosing. Dosages above 6 mg a day are associated with a higher incidence of adverse effects, particularly EPS. There is no correlation between plasma concentrations and therapeutic effect. Dosing guidelines for adolescents and children are different from those for adults, requiring lower starting dosages; higher dosages are associated with more adverse effects. Side Effects The EPS of risperidone are largely dosage dependent, and there has been a trend to using lower doses than initially recommended. Weight gain, anxiety, nausea and vomiting, rhinitis, erectile dysfunction, orgasmic dysfunction, and increased pigmentation are associated with risperidone use. The most common drug-related reasons for discontinuation of risperidone use are EPS, dizziness, hyperkinesias, somnolence, and nausea. Marked elevation of prolactin may occur. Weight gain occurs more commonly with risperidone use in children than in adults. Risperidone is also available as an orally disintegrating tablet (Risperdal M-Tab), which is available in 0.5, 1, and 2 mg strengths, and in a depot formulation (Risperdal Consta), which is given as an intramuscular (IM) injection formulation every 2 weeks. The dose may be 25, 50, or 75 mg. Oral risperidone should be coadministered with Risperdal Consta for the first 3 weeks before being discontinued. Drug Interactions Inhibition of

CYP2D6 by drugs such as paroxetine and fluoxetine can block the formation of risperidone's active metabolite. Risperidone is a weak inhibitor of CYP2D6 and has little effect on other drugs. Combined use of risperidone and selective serotonin reuptake inhibitors (SSRIs) may result in significant elevation of prolactin, with associated galactorrhea and breast enlargement. PALIPERIDONE (INVEGA) Indications Paliperidone is indicated for the acute and maintenance treatment of schizophrenia. Paliperidone is also indicated for the acute treatment of schizoaffective disorder as monotherapy, or as an adjunct to mood stabilizers or antidepressants.

Pharmacology Paliperidone is a benzisoxazole derivative and is the major active metabolite of risperidone. Peak plasma concentrations (Cmax) are achieved approximately 24 hours after dosing, and steady-state concentrations of paliperidone are attained within 4 or 5 days. The hepatic isoenzymes CYP2D6 and CYP3A4 play a limited role in the metabolism and elimination of paliperidone, so no dose adjustment is required in patients with mild or moderate hepatic impairment. Dosage Paliperidone is available in 3, 6, and 9 mg tablets. The recommended dosage is 6 mg once daily administered in the morning. It can be taken with or without food. It is also available as extended-release tablets, which are also available in 3, 6, and 9 mg tablets administered once daily. It is recommended that no more than 12 mg should be administered per day. A long-acting formulation of paliperidone (Invega Sustenna) is given by injection once a month. Invega Sustenna is available as a white to off-white sterile aqueous extended-release suspension for intramuscular injection in dose strengths of 39 mg, 78 mg, 117 mg, 156 mg, and 234 mg paliperidone palmitate. The drug product hydrolyzes to the active moiety, paliperidone, resulting in dose strengths of 25 mg, 50 mg, 75 mg, 100 mg, and 150 mg of paliperidone, respectively. Invega Sustenna is provided in a prefilled syringe with a plunger stopper and tip cap. The kit also contains two safety needles (a 1½-inch 22-gauge safety needle and a 1-inch 23 gauge safety needle). It has a half-life of 25 to 49 days. Monthly injections of 117 mg are recommended, although higher or lower dosages can be used depending on the clinical situation. The first two injections should be in the deltoid muscle because plasma concentrations are 28 percent higher with deltoid versus gluteal administration. Subsequent injections can alternate between gluteal and deltoid sites. Side Effects The dose of paliperidone should be reduced in patients with renal impairment. It may cause more sensitivity to temperature extremes such as very hot or cold conditions. Paliperidone may cause an increase in QT (QTc) interval and should be avoided in combination with other drugs that cause prolongation of QT interval. It may cause orthostatic hypotension, tachycardia, somnolence, akathisia, dystonia, EPS, and parkinsonism. OLANZAPINE (ZYPREXA) Indications Olanzapine is indicated for the treatment of schizophrenia. Oral olanzapine is indicated for use as monotherapy for the acute treatment of manic or mixed episodes associated with bipolar I disorder and maintenance treatment of bipolar I disorder. Oral

olanzapine is also indicated for the treatment of manic or mixed episodes associated with bipolar I disorder as an adjunct to lithium or valproate, and olanzapine can also be used in combination with fluoxetine (Symbyax) for the treatment of depressive episodes associated with bipolar I disorder. Oral olanzapine and fluoxetine in combination (Symbyax) is indicated for the treatment of treatment-resistant depression. Olanzapine monotherapy is not indicated for the treatment of treatment-resistant depression. Pharmacology Approximately 85 percent of olanzapine is absorbed from the gastrointestinal (GI) tract, and about 40 percent of the dosage is inactivated by first-pass hepatic metabolism. Peak concentrations are reached in 5 hours, and the half-life averages 31 hours (range 21 to 54 hours). It is given in once-daily dosing. In addition to 5-HT2A and D2

antagonism, olanzapine is an antagonist of the D1, D4, α1, 5-HT1A, muscarinic M1 to M5, and H1 receptors. Dosages Olanzapine is available in 2.5, 5, 7.5, 10, 15, and 20 mg oral and Zydis form (orally disintegrating) tablets. The initial dosage for treatment of psychosis is usually 5 or 10 mg, and for treatment of acute mania is usually 10 or 15 mg given once daily. It is also available as 5, 10, 15, and 20 mg orally disintegrating tablets that might be useful for patients who have difficulty swallowing pills or who “cheek” their medication. A starting daily dose of 5 to 10 mg is recommended. After 1 week, the dosage can be raised to 10 mg a day. Given the long half-life, 1 week must be allowed to achieve each new steady-state blood level. Dosages in clinical use ranges vary, with 5 to 20 mg a day being most commonly used, but 30 to 40 mg a day being needed in treatment-resistant patients. A word of caution, however, is that the higher dosages are associated with increased EPS and other adverse effects, and dosages above 20 mg a day were not studied in the pivotal trials that led to the approval of olanzapine. The parenteral form of olanzapine is indicated for the treatment of acute agitation associated with schizophrenia and bipolar disorder, and the IM dosage is 10 mg. Coadministration with benzodiazepines is not approved. Other Formulations Olanzapine is available as an extended-release injectable suspension (Relprevv), which is a long-acting atypical IM injection indicated for the treatment of schizophrenia. It is injected deeply in the gluteal region and should not be administered intravenously or subcutaneously, nor is it approved for deltoid administration. Before administering the injection, the administrator should aspirate the syringe for several seconds to ensure that no blood is visible. It carries a boxed warning for postinjection delirium sedation

syndrome (PDSS). Patients are at risk for severe sedation (including coma) and must be observed for 3 hours after each injection in a registered facility. In controlled studies, all patients with PDSS recovered, and there were no deaths reported. It is postulated that PDSS is secondary to increased levels of olanzapine secondary to accidental rupture of a blood vessel, causing extreme sedation or delirium. Patients should be managed as clinically appropriate and, if necessary, monitored in a facility capable of resuscitation. The injection can be given every 2 or 4 weeks depending on the dosing guidelines. Drug Interactions Fluvoxamine (Luvox) and cimetidine (Tagamet) increase, whereas carbamazepine and phenytoin decrease serum concentrations of olanzapine. Ethanol increases olanzapine absorption by more than 25 percent, leading to increased sedation. Olanzapine has little effect on the metabolism of other drugs. Side Effects Other than clozapine, olanzapine consistently causes a greater amount and more frequent weight gain than other atypicals. This effect is not dose related and continues over time. Clinical trial data suggest it peaks after 9 months, after which it may continue to increase more slowly. Somnolence, dry mouth, dizziness, constipation, dyspepsia, increased appetite, akathisia, and tremor are associated with olanzapine use. A small number of patients (2 percent) may need to discontinue use of the drug because of transaminase elevation. There is a dose-related risk of EPS. The manufacturer recommends “periodic” assessment of blood sugar and transaminases during treatment with olanzapine. There is an FDA-mandated warning about an increased risk of stroke among patients with dementia treated with SDAs, but this risk is small and is outweighed by improved behavioral control that treatment may produce. QUETIAPINE (SEROQUEL) Indications Quetiapine is indicated for the treatment of schizophrenia, as well as the acute treatment of manic episodes associated with bipolar I disorder, both as monotherapy and as an adjunct to lithium or divalproex. It is also indicated as monotherapy for the acute treatment of depressive episodes associated with bipolar disorder and maintenance treatment of bipolar I disorder as an adjunct to lithium or divalproex. Pharmacology Quetiapine is a dibenzothiazepine structurally related to clozapine, but it differs

markedly from that agent in biochemical effects. It is rapidly absorbed from the GI tract, with peak plasma concentrations reached in 1 to 2 hours. The steady-state half-life is about 7 hours, and optimal dosing is two or three times per day. Quetiapine, in addition

to being an antagonist of D2 and 5-HT2, also blocks 5-HT6, D1 and H1, and α1 and α2 receptors. It does not block muscarinic or benzodiazepine receptors. The receptor antagonism for quetiapine is generally lower than that for other antipsychotic drugs, and it is not associated with EPS. Dosages Quetiapine is available in 25, 50, 100, 200, 300, and 400 mg tablets. Quetiapine dosing should begin at 25 mg twice daily, with doses then increased by 25 to 50 mg per dose every 2 to 3 days, up to a target of 300 to 400 mg a day. Studies have shown efficacy in the range of 300 to 800 mg a day. In reality, more aggressive dosing is both tolerated and more effective. It has become evident that the target dose can be achieved more rapidly, and that some patients benefit from dosages of as much as 1,200 to 1,600 mg a day. When used at higher doses, serial ECG studies are required. Despite its short elimination half-life, quetiapine can be given to many patients once a day. This is consistent with the observation that quetiapine receptor occupancy remains even when concentrations in the blood have markedly declined. Quetiapine in doses of 25 to 300 mg at night has been used for insomnia. Other Formulations Quetiapine XR has a comparable bioavailability to an equivalent dose of quetiapine administered two or three times daily. Quetiapine XR is given once daily, preferably in the evening 3 to 4 hours before bedtime without food or a light meal to prevent an increase in Cmax. The usual starting dose is 300 mg, and it may be increased to 400 to 800 mg. It has all of the above indications and in addition is indicated for use as adjunctive therapy to antidepressants for the treatment of MDD. Drug Interactions The potential interactions between quetiapine and other drugs have been well studied. Phenytoin increases quetiapine clearance fivefold; no major pharmacokinetic interactions have been noted. Avoid use of quetiapine with drugs that increase the QT interval and in patients with risk factors for prolonged QT interval. The FDA has added a new warning about quetiapine cautioning prescribers about potential prolongation of the QT interval when above-recommended amounts of quetiapine are combined with specific drugs. The use of quetiapine should be avoided in combination with other drugs that are known to prolong QTc including class 1A antiarrhythmics (e.g., quinidine, procainamide) or class III antiarrhythmics (e.g., amiodarone, sotalol), antipsychotic medications (e.g., ziprasidone, chlorpromazine, thioridazine), antibiotics (e.g., gatifloxacin, moxifloxacin), or any other class of medications known to prolong the QTc interval (e.g., pentamidine, levomethadyl acetate, methadone). Quetiapine should also

be avoided in circumstances that may increase the risk of occurrence of torsade de pointes and/or sudden death including (1) a history of cardiac arrhythmias such as bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval. Postmarketing cases also show increases in QT interval in patients who overdose on quetiapine. Side Effects Somnolence, postural hypotension, and dizziness are the most common adverse effects of quetiapine. These are usually transient and are best managed with initial gradual upward titration of the dosage. Quetiapine is the SDA least likely to cause EPS, regardless of dose. This makes it particularly useful in treating patients with Parkinson’s disease who develop dopamine agonist–induced psychosis. Prolactin elevation is rare and both transient and mild when it occurs. Quetiapine is associated with modest transient weight gain in some persons, but some patients occasionally gain a considerable amount of weight. The relationship between quetiapine and the development of diabetes is not as clearly

established as are the cases involving the use of olanzapine. Small increases in heart rate, constipation, and a transient increase in liver transaminases may also occur. Initial concerns about cataract formation, based on animal studies, have not been borne out since the drug has been in clinical use. Nevertheless, it might be prudent to test for lens abnormalities early in treatment and periodically thereafter. ZIPRASIDONE (GEODON) Indications Ziprasidone is indicated for the treatment of schizophrenia. Ziprasidone is also indicated as monotherapy for the acute treatment of manic or mixed episodes associated with bipolar I disorder and as an adjunct to lithium or valproate for the maintenance treatment of bipolar I disorder. Pharmacology Ziprasidone is a benzisothiazole piperazine. Peak plasma concentrations of ziprasidone are reached in 2 to 6 hours. Steady-state levels ranging from 5 to 10 hours are reached between the first and the third days of treatment. The mean terminal half-life at steady state ranges from 5 to 10 hours, which accounts for the recommendation that twice-daily dosing is necessary. Bioavailability doubles when ziprasidone is taken with food, and therefore it should be taken with food. Peak serum concentrations of IM ziprasidone occur after approximately 1 hour, with a half-life of 2 to 5 hours. Ziprasidone, similar to the other SDAs, blocks 5-HT2A and D2 receptors. It is also an

antagonist of 5-HT1D, 5-HT2C, D3, D4, α1, and H1 receptors. It has very low affinity for D1, M1, and α2 receptors. In addition, ziprasidone has agonist activity at the serotonin 5-HT1A receptors and is an SSRI and a norepinephrine reuptake inhibitor. This is consistent with clinical reports that ziprasidone has antidepressant-like effects in nonschizophrenic patients. Dosages Ziprasidone is available in 20, 40, 60, and 80 mg capsules. Ziprasidone for IM use comes as a single-use 20 mg/mL vial. Oral ziprasidone dosing should be initiated at 40 mg a day divided into two daily doses. Studies have shown efficacy in the range of 80 to 160 mg a day, divided twice daily. In clinical practice, doses as high as 240 mg a day are being used. The recommended IM dosage is 10 to 20 mg every 2 hours for the 10 mg dose and every 4 hours for the 40 mg dose. The maximum total daily dose of IM ziprasidone is 40 mg. Other than interactions with other drugs that prolong the QTc complex, ziprasidone appears to have low potential for clinically significant drug interactions. Side Effects Somnolence, headache, dizziness, nausea, and lightheadedness are the most common adverse effects in patients taking ziprasidone. It has almost no significant effects outside the central nervous system, is associated with almost no weight gain, and does not cause sustained prolactin elevation. Concerns about prolongation of the QTc complex have deterred some clinicians from using ziprasidone as a first choice. The QTc interval has been shown to increase in patients treated with 40 and 120 mg per day. Ziprasidone is contraindicated in combination with other drugs known to prolong the QTc interval. These include, but are not limited to, dofetilide, sotalol, quinidine, other class IA and III antiarrhythmics, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol, and tacrolimus. Ziprasidone should be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias. Aripiprazole (Abilify) Aripiprazole is a potent 5-HT2A antagonist and is indicated for the treatment of both schizophrenia and acute mania. It is also approved for augmentation of antidepressant agents in MDD. Aripiprazole is a D2 antagonist, but can also act as a partial D2 agonist. Partial D2 agonists compete at D2 receptors for endogenous dopamine, thereby producing a functional reduction of dopamine activity.

Indications Aripiprazole is indicated for the treatment of schizophrenia. Short-term, 4- to 6-week studies comparing aripiprazole with haloperidol and risperidone in patients with schizophrenia and

schizoaffective disorder have shown comparable efficacy. Dosages of 15, 20, and 30 mg a day were found to be effective. Long-term studies suggest that aripiprazole is effective as a maintenance treatment at a daily dose of 15 to 30 mg. Aripiprazole is also indicated for the acute and maintenance treatment of manic and mixed episodes associated with bipolar I disorder. It is also used as an adjunctive therapy to either lithium or valproate for the acute treatment of manic and mixed episodes associated with bipolar I disorder. Aripiprazole is indicated for use as an adjunctive therapy to antidepressants for the treatment of MDD. Aripiprazole is also indicated for the treatment of irritability associated with autistic disorder. Pharmacology Aripiprazole is well absorbed, reaching peak plasma concentrations after 3 to 5 hours. Absorption is not affected by food. The mean elimination half-life of aripiprazole is about 75 hours. It has a weakly active metabolite with a half-life of 96 hours. These relatively long half-lives make aripiprazole suitable for once-daily dosing. Clearance is reduced in elderly persons. Aripiprazole exhibits linear pharmacokinetics and is primarily metabolized by CYP3A4 and CYP2D6 enzymes. It is 99 percent protein bound. Aripiprazole is excreted in breast milk in lactating rats. Mechanistically, aripiprazole acts as a modulator, rather than a blocker, and acts on both postsynaptic D2 receptors and presynaptic autoreceptors. In theory, this mechanism addresses excessive limbic dopamine (hyperdopaminergic) activity, and decreased dopamine (hypodopaminergic) activity in frontal and prefrontal areas— abnormalities that are thought to be present in schizophrenia. The absence of complete D2 blockade in the striatal areas would be expected to minimize EPS. Aripiprazole is an α1-adrenergic receptor antagonist, which may cause some patients to experience orthostatic hypotension. Similar to the so-called atypical antipsychotic agents, aripiprazole is a 5-HT2A antagonist. Other Uses A study of aggressive children and adolescents with oppositional defiant disorder or conduct disorder found that there was a positive response in about 60 percent of the subjects. In this study, vomiting and somnolence led to a reduction in initial aripiprazole dosage. Drug Interactions

Whereas carbamazepine and valproate reduce serum concentrations, ketoconazole, fluoxetine, paroxetine, and quinidine increase aripiprazole serum concentrations. Lithium and valproic acid, two drugs likely to be combined with aripiprazole when treating bipolar disorder, do not affect the steady-state concentrations of aripiprazole. Combined use with antihypertensives may cause hypotension. Drugs that inhibit CYP2D6 activity reduce aripiprazole elimination. Dosage and Clinical Guidelines Aripiprazole is available as 5, 10, 15, 20, and 30 mg tablets. The effective dosage range is 10 to 30 mg per day. Although the starting dosage is 10 to 15 mg per day, problems with nausea, insomnia, and akathisia have led to use of lower than recommended starting dosages of aripiprazole. Many clinicians find that an initial dose of 5 mg increases tolerability. Side Effects The most commonly reported side effects of aripiprazole are headache, somnolence, agitation, dyspepsia, anxiety, and nausea. Although it is not a frequent cause of EPS, aripiprazole does cause akathisia-like activation. Described as restlessness or agitation, it can be highly distressing and often leads to discontinuation of medication. Insomnia is another common complaint. Data so far do not indicate that weight gain or diabetes mellitus have an increased incidence with aripiprazole (Abilify). Prolactin elevation does not typically occur. Aripiprazole does not cause significant QTc interval changes. There have been reports of seizures. ASENAPINE (SAPHRIS) Indications Asenapine is approved for the acute treatment of adults with schizophrenia and acute treatment of manic or mixed episodes associated with bipolar I disorder with or without psychotic features in adults. Pharmacology Asenapine has an affinity for several receptors, including serotonin (5-HT2A and 5HT2C), noradrenergic (α2, and α1), dopaminergic (D3 and D4

receptors is higher than its affinity for D2 receptors), and histamine (H1). It has negligible affinity for muscarinic-1 cholinergic receptors and hence less incidence of dry mouth, blurred vision, constipation, and urinary retention. The bioavailability is 35 percent via sublingual (preferred) route and it achieves peak plasma concentration in 1 hour. Asenapine is metabolized through glucuronidation and oxidative metabolism by CYP1A2, so coadministration with fluvoxamine and other CYP1A2 inhibitors should be done cautiously.

Dosage Asenapine is available as 5 mg and 10 mg sublingual tablets, and should be placed under the tongue. This is because the bioavailability of asenapine is less than 2 percent when swallowed, but is 35 percent when absorbed sublingually. The agent dissolves in saliva within seconds and is absorbed through the oral mucosa. Sublingual administration avoids first-pass hepatic metabolism. Patients should be advised to avoid drinking or eating for 10 minutes after taking asenapine because this may lower the blood levels. The recommended starting and target dose for schizophrenia is 5 mg twice a day. In bipolar disorder, the patient may be started on 10 mg twice a day, and if necessary, the dosage may be lowered to 5 mg twice a day depending on the tolerability issues. In acute schizophrenia treatment there is no evidence of added benefit with a 10 mg twice-daily dose, but there is a clear increase in certain adverse reactions. In both bipolar I disorder and schizophrenia, the maximum dose should not exceed 10 mg two times a day. The safety of doses above 10 mg twice a day has not been evaluated in clinical studies. Side Effects The most common side effects observed in schizophrenic and bipolar disorders are somnolence, dizziness, EPS other than akathisia, and increased weight. In clinical trials, the mean weight gain after 52 weeks is 0.9 kg, and there were no clinically relevant differences in lipid profile and blood glucose after 52 weeks. In clinical trials, asenapine was found to increase the QTc interval in a range of 2 to 5 milliseconds compared to placebo. No patients treated with asenapine experienced QTc increases 60 milliseconds or greater from baseline measurements, nor did any experience a QTc of 500 milliseconds or more. Nevertheless, asenapine should be avoided in combination with other drugs known to prolong QTc interval, in patients with congenital prolongation of QT interval or a history of cardiac arrhythmias, and in circumstances that may increase the occurrence of torsades de pointes. Asenapine can elevate prolactin levels, and the elevation can persist during chronic administration. Galactorrhea, amenorrhea, gynecomastia, and impotence may occur. CLOZAPINE (CLOZARIL) Indications In addition to being the most effective drug treatment for patients who have failed to respond to standard therapies, clozapine has been shown to benefit patients with severe tardive dyskinesia. Clozapine suppresses these dyskinesias, but the abnormal movements return when clozapine is discontinued. This is true even though clozapine, on rare occasions, may cause tardive dyskinesia. Other clinical situations in which clozapine may be used include the treatment of psychotic patients who are intolerant of EPS caused by other agents, treatment-resistant mania, severe psychotic depression,

idiopathic Parkinson’s disease, Huntington’s disease, and suicidal patients with schizophrenia or schizoaffective disorder. Other treatment-resistant disorders that have demonstrated response to clozapine include pervasive developmental disorder, autism of childhood, and OCD (either alone or in combination with an SSRI). Used by itself, clozapine may very rarely induce obsessive-compulsive symptoms. Pharmacology Clozapine is a dibenzothiazepine. It is rapidly absorbed, with peak plasma levels reached in about 2 hours. Steady state is achieved in less than 1 week if twice daily dosing is used. The elimination half-life is about 12 hours. Clozapine has two major metabolites, one of which, N-dimethyl clozapine, may have some pharmacological activities.

Clozapine is an antagonist of 5-HT2A, D1, D3, D4, and α (especially α1) receptors. It has relatively low potency as a D2 receptor antagonist. Data from PET scanning show that whereas 10 mg of haloperidol produces 80 percent occupancy of striatal D2 receptors, clinically effective dosages of clozapine occupy only 40 to 50 percent of striatal D2 receptors. This difference in D2 receptor occupancy is probably why clozapine does not cause EPS. It has also been postulated that clozapine and other SDAs bind more loosely to the D2 receptor, and because of this “fast dissociation,” more normal dopamine neurotransmission is possible. Dosages Clozapine is available in 25 mg and 100 mg tablets. The initial dosage is usually 25 mg one or two times daily, although a conservative initial dosage is 12.5 mg twice daily. The dosage can then be increased gradually (25 mg a day every 2 or 3 days) to 300 mg a day in divided doses, usually two or three times a day. Dosages up to 900 mg a day can be used. Testing for blood concentrations of clozapine may be helpful in patients who fail to respond. Studies have found that plasma concentrations greater than 350 µg/mL are associated with a better likelihood of response. Drug Interactions Clozapine should not be used with any other drug that is associated with the development of agranulocytosis or bone marrow suppression. Such drugs include carbamazepine, phenytoin, propylthiouracil, sulfonamides, and captopril (Capoten). Lithium combined with clozapine may increase the risk of seizures, confusion, and movement disorders. Lithium should not be used in combination with clozapine by persons who have experienced an episode of neuroleptic malignant syndrome. Clomipramine (Anafranil) can increase the risk of seizure by lowering the seizure threshold and by increasing clozapine plasma concentrations. Risperidone, fluoxetine, paroxetine, and fluvoxamine increase serum concentrations of clozapine. Addition of paroxetine may precipitate clozapine-associated neutropenia.

Side Effects The most common drug-related adverse effects are sedation, dizziness, syncope, tachycardia, hypotension, electrocardiography (ECG) changes, nausea, and vomiting. Other common adverse effects include fatigue, weight gain, various GI symptoms (most commonly constipation), anticholinergic effects, and subjective muscle weakness. Sialorrhea, or hypersalivation, is a side effect that begins early in treatment and is most evident at night. Patients report that their pillows are drenched with saliva. This side effect is most likely the result of impairment of swallowing. Although there are reports that clonidine or amitriptyline may help reduce hypersalivation, the most practical solution is to put a towel over the pillow. The risk of seizures is about 4 percent in patients taking dosages greater than 600 mg a day. Leukopenia, granulocytopenia, agranulocytosis, and fever occur in about 1 percent of patients. During the first year of treatment, there is a 0.73 percent risk of clozapine-induced agranulocytosis. The risk during the second year is 0.07 percent. For neutropenia, the risk is 2.32 percent and 0.69 percent, respectively, during the first and second years of treatment. The only contraindications to the use of clozapine are a white blood cell (WBC) count below 3,500 cells per mm3; a previous bone marrow disorder; a history of agranulocytosis during clozapine treatment; or the use of another drug that is known to suppress the bone marrow, such as carbamazepine (Tegretol). During the first 6 months of treatment, weekly WBC counts are indicated to monitor the patient for the development of agranulocytosis. If the WBC count remains normal, the frequency of testing can be decreased to every 2 weeks. Although monitoring is expensive, early indication of agranulocytosis can prevent a fatal outcome. Clozapine should be discontinued if the WBC count is below 3,000 cells per mm3 or the granulocyte count is below 1,500 per mm3. In addition, a hematological consultation should be obtained, and obtaining bone marrow sample should be considered. Persons with agranulocytosis should not be re-exposed to the drug. To avoid situations in which a physician

or a patient fails to comply with the required blood tests, clozapine cannot be dispensed without proof of monitoring. Patients exhibiting symptoms of chest pain, shortness of breath, fever, or tachypnea should be immediately evaluated for myocarditis or cardiomyopathy, an infrequent but serious adverse effect ending in death. Serial CPK-MB (creatine phosphokinase with myocardial band fractions), troponin levels, and EKG studies are recommended, with immediate discontinuation of clozapine. ILOPERIDONE (FANAPT) Indications Iloperidone (Fanapt) is indicated for the acute treatment of schizophrenia in adults. The safety and efficacy of iloperidone in children and adolescents has not been established.

Pharmacology Iloperidone is not a derivative of another antipsychotic agent. It has complex multiple antagonist effects on several neurotransmitter systems. Iloperidone has a strong affinity for dopamine D3 receptors, followed by decreasing affinities of α2c-noradrenergic, 5HT1a, D2a, and 5-HT6 receptors. Iloperidone has a low affinity for histaminergic receptors. As with other antipsychotics, the clinical significance of this receptor binding affinity is unknown. Iloperidone has a peak concentration of 2 to 4 hours and a half-life that is dependent on hepatic isoenzyme metabolism. It is metabolized primarily through CYP2D6 and CYP3A4, and the dosage should be reduced by half when administered concomitantly with strong inhibitors of these two isoenzymes. The half-life is 18 to 26 hours in CYP2D6 extensive metabolizers and is 31 to 37 hours in CYP2D6 poor metabolizers. Of note, approximately 7 to 10 percent of whites and 3 to 8 percent of African Americans lack the capacity to metabolize CYP2D6 substrates; hence, dosing should be determined with this caveat in mind. Iloperidone should be used with caution in persons with severe hepatic impairment. Side Effects Iloperidone prolongs the QT interval and may be associated with arrhythmia and sudden death. Iloperidone prolongs the QTc interval by 9 milliseconds at dosages of 12 mg twice daily. Concurrent use with other agents that prolong the QTc interval may result in additive effects on the QTc interval. The concurrent use of iloperidone with agents that prolong the QTc interval may result in potentially life-threatening cardiac arrhythmias, including torsades de pointes. Concurrent administration of other drugs that are known to prolong the QTc interval should be avoided. Cardiovascular disease, hypokalemia, hypomagnesemia, bradycardia, congenital prolongation of the QT interval, and concurrent use of inhibitors of CYP3A4 or CYP2D6, which metabolize iloperidone, may increase the risk of QT prolongation. The most common adverse effects reported are dizziness, dry mouth, fatigue, sedation, tachycardia, and orthostatic hypotension (depending on dosing and titration). Despite being a strong D2 antagonist, the rates of EPS and akathisia are similar to those of placebo. The mean weight gain in short-term and long-term trials is 2.1 kg. Due to its relatively limited use, there is no accurate understanding of iloperidone’s effects on weight and lipids. Some patients exhibit elevated prolactin levels. Three cases of priapism have been reported in the premarketing phase. Dosing Iloperidone must be titrated slowly to avoid orthostatic hypotension. It is available in a titration pack, and the effective dose (12 mg) should be reached in approximately 4 days based on a twice-a-day dosing schedule. It is usually started on day 1 at 1 mg twice

a day and increased daily on a twice-a-day schedule to reach 12 mg by day 4. The maximum recommended dose is 12 mg twice a day (24 mg a day), and it can be administered without regard to food. LURASIDONE HCL (LATUDA) Indications Lurasidone hydrochloride is an oral, once-daily atypical antipsychotic indicated for the treatment of patients with schizophrenia. To date there has not been extensive clinical experience with lurasidone. Side Effects The most commonly observed adverse reactions associated with the use of lurasidone are similar to those seen with other new-

generation antipsychotics. These include, but are not limited to somnolence, akathisia, nausea, parkinsonism, and agitation. Based on clinical trial data, lurasidone appears to cause less weight gain and metabolic changes than the two other most recently approved SDAs, asenapine and iloperidone. More extensive clinical experience with the drug is required to determine whether this is in fact the case. Drug Interactions When coadministration of lurasidone with a moderate CYP3A4 inhibitor such as diltiazem is considered, the dose should not exceed 40 mg per day. Lurasidone should not be used in combination with a strong CYP3A4 inhibitor (e.g., ketoconazole). Lurasidone also should not be used in combination with a strong CYP3A4 inducer (e.g., rifampin). Dosages Lurasidone is available as 20, 40, 80, and 120 mg tablets. Initial dose titration is not required. The recommended starting dose is 40 mg once daily, and the medication should be taken with food. It has been shown to be effective in a dose range of 40 to 120 mg per day. Although there is no proven added benefit with the 120 mg per day dose, there may be a dose-related increase in adverse reactions. Still, some patients may benefit from the maximum recommended dose of 160 mg per day. Dose adjustment is recommended in patients with renal impairment. The dose in moderate to severe renal impairment should not exceed 80 mg per day. The dose in severe hepatic impairment patients should not exceed 40 mg per day. CLINICAL GUIDELINES FOR SDAS All SDAs are appropriate for the management of an initial psychotic episode, but

clozapine is reserved for persons who are refractory to all other antipsychotic drugs. If a person does not respond to the first SDA, other SDAs should be tried. The choice of drug should be based on the patient’s clinical status and history of response to medication. Recent studies have challenged the notion that SDAs require 4 to 6 weeks to reach full effectiveness, and it may take up to 8 weeks for the full clinical effects of an SDA to become apparent. The newer meta-analyses suggest that the apparent benefits may be seen as early as 2 to 3 weeks, and early response or failure is an indicator of subsequent response or failure. Nevertheless, it is acceptable practice to augment an SDA with a high-potency DRA or benzodiazepine in the first few weeks of use. Lorazepam (Ativan) 1 to 2 mg orally or IM can be used as needed for acute agitation. Once effective, dosages can be lowered as tolerated. Clinical improvement may take 6 months of treatment with SDAs in some particularly treatment-refractory persons. Use of all SDAs must be initiated at low dosages and gradually tapered upward to therapeutic dosages. The gradual increase in dosage is necessitated by the potential development of adverse effects. If a person stops taking an SDA for more than 36 hours, drug use should be resumed at the initial titration schedule. After the decision to terminate olanzapine or clozapine use, dosages should be tapered whenever possible to avoid cholinergic rebound symptoms such as diaphoresis, flushing, diarrhea, and hyperactivity. After a clinician has determined that a trial of an SDA is warranted for a particular person, the risks and benefits of SDA treatment must be explained to the person and the family. In the case of clozapine, an informed consent procedure should be documented in the person’s chart. The patient’s history should include information about blood disorders, epilepsy, cardiovascular disease, hepatic and renal diseases, and drug abuse. The presence of a hepatic or renal disease necessitates using low starting dosages of the drug. The physical examination should include supine and standing blood pressure measurements to screen for orthostatic hypotension. The laboratory examination should include an ECG and several complete blood counts with WBC counts, which can then be averaged; and liver and renal function tests. Periodic monitoring of blood glucose, lipids, and body weight is recommended. Although the transition from a DRA to an SDA may be made abruptly, it is wiser to taper off the DRA slowly while titrating up the SDA. Clozapine and olanzapine both have anticholinergic effects, and the transition from one to the

other can usually be accomplished with little risk of cholinergic rebound. The transition from risperidone to olanzapine is best accomplished by tapering the risperidone off over 3 weeks while simultaneously beginning olanzapine at 10 mg a day. Risperidone, quetiapine, and ziprasidone lack anticholinergic effects, and the abrupt transition from a DRA, olanzapine, or clozapine to one of these agents may cause cholinergic rebound, which consists of excessive salivation, nausea, vomiting, and diarrhea. The risk of cholinergic rebound can be mitigated by initially augmenting risperidone, quetiapine, or ziprasidone with an anticholinergic drug, which is then tapered off slowly. Any initiation and termination of SDA use should be accomplished gradually. It is wise to overlap administration of the new drug with the old drug. Of interest,

some people have a more robust clinical response while taking the two agents during the transition and then regressing on monotherapy with the newer drug. Little is known about the effectiveness and safety of a strategy of combining one SDA with another SDA or with a DRA. Persons receiving regular injections of depot formulations of a DRA who are to switch to SDA use are given the first dose of the SDA on the day the next injection is due. Persons who developed agranulocytosis while taking clozapine can safely switch to olanzapine use, although initiation of olanzapine use in the midst of clozapine-induced agranulocytosis can prolong the time of recovery from the usual 3 to 4 days up to 11 to 12 days. It is prudent to wait for resolution of agranulocytosis before initiating olanzapine use. Emergence or recurrence of agranulocytosis has not been reported with olanzapine, even in persons who developed it while taking clozapine. SDA use by pregnant women has not been studied, but consideration should be given to the potential of risperidone to raise prolactin concentrations, sometimes up to three to four times the upper limit of the normal range. Because the drugs can be excreted in breast milk, they should not be taken by nursing mothers. The dosages for selected SDAs are given in Table 29.29-1. Table 29.29-1 Comparison of Usual Dosinga for Some Available Second-generation Antipsychotics in Schizophrenia

REFERENCES Davidson M, Emsley R, Kramer M, Ford L, Pan G, Lim P, Eerdekens M. Efficacy, safety and early response of paliperidone extended-release tablets (paliperidone ER): Results of a 6-week, randomized, placebo-controlled study. Schizophr Res. 2007;93(1–3):117. Frieling H, Hillemacher T, Ziegenbein M, Neundorfer B, Bleich S. Treating dopamimetic psychosis in Parkinson’s disease: structured review and meta-analysis. Eur Neuropsychopharmacol. 2007;17(3):165. Isom AM, Gudelsky GA, Benoit SC, Richtand NM. Antipsychotic medications, glutamate, and cell death: A hidden, but common medication side effect? Med Hypotheses. 2013;80(3):252–258.

Kahn RS, Fleischhacker WW, Boter H, Davidson M, Vergouwe Y, Keet IP, Gheorghe MD, Rybakowski JK, Galderisi S, Libiger J, Hummer M, Dollfus S, Lopez-Ibor JJ, Hranov LG, Gaebel W, Peuskens J, Lindefors N, Riecher-Rossler A, Grobbee DE. Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: An open randomised clinical trial. Lancet. 2008;371(9618):1085. Kane JM, Meltzer HY, Carson WH Jr, McQuade RD, Marcus RN. Aripiprazole for treatment-resistant schizophrenia: Results of a multicenter, randomized, double-blind, comparison study versus perphenazine. J Clin Psychiatry. 2007;68(2):213. Kane J, Canas F, Kramer M, Ford L, Gassmann-Mayer C, Lim P, Eerdekens M. Treatment of schizophrenia with paliperidone extended-release tablets: A 6-week placebo-controlled trial. Schizophr Res. 2007;90(1–3):147. Keefe RS, Bilder RM, Davis SM. Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE Trial. Arch Gen Psychiatry. 2007;64(6):633. Kumra S, Kranzler H, Gerbino-Rosen G, Kester HM, De Thomas C, Kafantaris V, Correll CU, Kane JM. Clozapine and “highdose” olanzapine in refractory early-onset schizophrenia: A 12-week randomized and double-

blind comparison. Biol Psychiatry. 2008;63(5):524. Kumra S, Oberstar JV, Sikich L, Findling RL, McClellan JM. Efficacy and tolerability of second-generation antipsychotics in children and adolescents with schizophrenia. Schizophr Bull. 2008;34(1):60. Leucht S, Komossa K, Rummel-Kluge C, Corves C, Hunger H, Schmid F, Lobos CA, Schwartz S, Davis JM. A meta-analysis of head-to-head comparisons of second-generation antipsychotics in the treatment of schizophrenia. Am J Psychiatry. 2009;166(2):152. Mamo D, Graff A, Mizrahi R, Shammi CM, Romeyer F. Differential effects of aripiprazole on D(2), 5-HT(2), and 5-HT(1A) receptor occupancy in patients with schizophrenia: A triple tracer PET study. Am J Psychiatry. 2007;164(9):1411. Marder SR, Hurford IM, van Kammen DP. Second-generation antipsychotics. In: Sadock BJ, Sadock VA, Ruiz P, eds. Kaplan & Sadock's Comprehensive Textbook of Psychiatry. 9th ed. Vol. 2. Philadelphia: Lippincott Williams & Wilkins; 2009:3206. McEvoy JP, Lieberman JA, Perkins DO, Hamer RM, Gu H. Efficacy and tolerability of olanzapine, quetiapine, and risperidone in the treatment of early psychosis: A randomized, double-blind 52-week comparison. Am J Psychiatry. 2007;164(7):1050. McEvoy JP, Lieberman JA, Stroup TS. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. Am J Psychiatry. 2006;163(4):600. Novick D, Haro JM, Suarez D, Vieta E, Naber D. Recovery in the outpatient setting: 36-month results from the Schizophrenia Outpatients Health Outcomes (SOHO) study. Schizophr Res. 2009;108(1–3):223. Owen RT. Inhaled loxapine: A new treatment for agitation in schizophrenia or bipolar disorder. Drugs Today. 2013;49(3):195–201. Patil ST, Zhang L, Martenyi F, Lowe SL, Jackson KA. Activation of mGlu2/3 receptors as a new approach to treat schizophrenia: A randomized phase 2 clinical trial. Nat Med. 2007;13(9):1102. Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Atypical antipsychotic drugs and the risk of sudden cardiac death. N Engl J Med. 2009;360(3):225. Sikich L, Frazier JA, McClellan J, Findling RL, Vitiello B, Ritz L, Ambler D, Puglia M, Maloney AE, Michael E, De Jong S, Slifka K, Noyes N, Hlastala S, Pierson L, McNamara NK, Delporto-Bedoya D, Anderson R, Hamer RM, Lieberman JA. Double-blind comparison of first- and second-generation antipsychotics in early-onset schizophrenia and schizoaffective disorder: findings from the treatment of early-onset schizophrenia spectrum disorders (TEOSS) study. Am J Psychiatry. 2008;165(11):1420. Stroup TS, Lieberman JA, McEvoy JP. Results of phase 3 of the CATIE schizophrenia trial. Schizophr Res. 2009;107(1):1.

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