

Therapeutic Class Overview

Atypical Antipsychotics

INTRODUCTION

- Antipsychotic medications have been used for over 50 years to treat schizophrenia and a variety of other psychiatric disorders (*Miyamoto et al 2005*).
- Antipsychotic medications exert their effect in part by blocking D2 receptors. It is the blockade of these receptors in the mesolimbic pathway that is believed to contribute to desired antipsychotic effects, especially improvement of positive symptoms associated with schizophrenia (*Farah 2005*).
- Antipsychotics are divided into 2 distinct classes based on their affinity for D2 and other neuroreceptors: typical antipsychotics, also called first generation antipsychotics (FGAs), and atypical antipsychotics, also called second generation antipsychotics (SGAs) (*Miyamoto et al 2005*).
- Atypical antipsychotics do not have a uniform pharmacology or mechanism of action; these differences likely account for the different safety and tolerability profiles of these agents (*Clinical Pharmacology 2017*).
 - Clozapine is an antagonist at all dopamine receptors (D1-5), with lower affinity for D1 and D2 receptors and high affinity for D4 receptors. Aripiprazole acts as a partial agonist at the D2 receptor, functioning as an agonist when synaptic dopamine levels are low and as an antagonist when they are high. Brexpiprazole and cariprazine are partial agonists at D-2 and 5-HT1A receptors and antagonists at 5-HT2A receptors. The remaining atypical antipsychotics share the similarity of D2 and 5-HT2A antagonism, but differ in activity at other central nervous system (CNS) receptor classes.
- There are a number of atypical antipsychotic formulations available as both branded and generic products. Food and Drug Administration (FDA)-approved indications for the atypical antipsychotics include irritability associated with autistic disorder, bipolar disorder, Tourette's disorder, major depressive disorder (MDD), schizophrenia, and schizoaffective disorder:
- Autism
 - Autism spectrum disorders (ASD) are neurodevelopmental disorders characterized by impairment in socialization, communication, and behavior (*Weissman and Bridgemohan 2017*).
 - ASD are more common in males than females and estimates of prevalence vary based on populations studied.
 - Data from the Autism and Developmental Disabilities Monitoring Network in the United States report a prevalence of 14.6 per 1000 children at age 8 in 2012 (*Morbidity and Mortality Weekly Report [MMWR] 2016*).
 - The pathogenesis of ASD is not completely understood but is believed to have a genetic component which alters brain development (*Augustyn 2017*).
 - Overall treatment goals include maximization of functioning, improvement in quality of life, and helping the patient achieve and maintain independence.
 - Specific treatment goals include improving social, communication, and adaptation skills, improving academic functioning, and decreasing nonfunctional behaviors.
 - Treatments include educational and behavioral therapies and pharmacologic interventions to treat targeted symptoms including aggression, impulsivity, hyperactivity, anxiety, sleep disturbances, and depression (*Weissman and Bridgemohan 2017*).
- Bipolar disorder
 - Bipolar disorder is characterized by discrete mood instability. The lifetime prevalence of bipolar disorder is reported to be approximately 1%, although the true prevalence is uncertain (*Stovall 2017[a]*).
 - Genetics, in addition to environmental factors, appears to play an important role in the pathogenesis of bipolar disorder.
 - Drugs commonly used to treat acute mania or hypomanias include lithium, anticonvulsants, and antipsychotics. Benzodiazepines may be helpful when adjunctive treatment is needed for insomnia, agitation, or anxiety (*Stovall 2017[b]*).
- Major depressive disorder (MDD)
 - MDD manifests with symptoms of depressed mood, loss of interest or pleasure in almost all activities, altered sleep, change in appetite or weight, poor energy and/or concentration, thoughts of worthlessness, and potentially thoughts of death or suicide (*Gelenberg et al 2010*).

- For the diagnosis of MDD, patients must have ≥ 5 symptoms that have been present during the same 2-week period or represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. The goal of treatment is full remission (*Diagnostic and Statistical Manual of Mental Disorders [DSM] V 2013*).
- Based on data from 2006 to 2008, approximately 9% of US adults meet the criteria for current depression, including 3.4% who have MDD. Women are more likely to experience major depression in their lifetime as compared to men (11.7 vs 5.6%), and major depression is most prevalent in patients aged 45 to 64 years old (*CDC 2013, MMWR 2010*).
- Schizophrenia
 - Schizophrenia is a disorder involving chronic or recurrent psychosis and is associated with significant functional impairment. Schizophrenia is believed to be caused by an increase in the cerebral activity of dopamine in the mesolimbic and/or mesocortical regions of the brain (*Lehman et al 2004*).
 - The disease includes positive symptoms such as hallucinations, delusions, and disorganized speech, as well as negative symptoms including flat affect, cognitive impairment, and impairment in executive functioning (*DSM V 2013, Lehman et al 2004*).
 - For the diagnosis of schizophrenia, patients must have ≥ 2 symptoms that have been present for a significant portion of time during a 1-month period and continuous signs of the disturbance persist for at least 6 months. Symptoms must include 1 of the following: delusions, hallucinations, and disorganized speech, but may also include grossly disorganized or catatonic behavior, and negative symptoms (*DSM V 2013*).
 - The prevalence of schizophrenia is approximately 0.3 to 0.66%, and the lifetime incidence is 10.2 to 22 per 100,000 person-years (*McGrath et al 2008, van Os et al 2009*).
- Tourette's disorder
 - Tourette's disorder ranges greatly in terms of symptom severity and is often associated with comorbidities (*Murphy et al 2013*).
 - Tourette's disorder is characterized by persistent and repetitive motor and/or vocal tics, and onset is typically observed in childhood. For diagnosis, tics need to be present for at least 1 year. The pathophysiology of chronic tic disorders is not known but believed to be due to motor issues at both cortical and subcortical levels that are not properly modulated at the cortico-striatal-thalamo-cortical circuits.
 - Other comorbidities often observed with Tourette's disorder include attention-deficit hyperactivity disorder (ADHD) and obsessive compulsive disorder (OCD).
 - The prevalence of chronic tic disorders has been estimated as 0.5 to 3%, with approximately 7% of school age children having had tics in the previous year.
- The agents included in this review are listed in Table 1 by brand name. Since there are multiple branded agents that contain the same generic component, the remaining tables in the review are organized by generic name. This review is restricted to the atypical antipsychotic agents and their respective FDA-approved indications.
 - Aripiprazole lauroxil is the prodrug of aripiprazole, and paliperidone is the active metabolite of risperidone.

Table 1. Medications included within class review

Drug	Generic
Single Entity Agents	
Abilify (aripiprazole)	✓ *
Abilify Discmelt (aripiprazole)	✓ *
Clozaril (clozapine)	✓
Fanapt (iloperidone)	-†
Fazacllo (clozapine)	✓
Geodon (ziprasidone hydrochloride [HCl])	✓
Geodon (ziprasidone mesylate)	-
Invega (paliperidone extended-release [ER])	✓

Drug	Generic
Latuda (lurasidone)	-
Rexulti (brexpiprazole)	-
Risperdal (risperidone)	✓
Risperdal M-Tab (risperidone)	✓
Saphris (asenapine)	-
Seroquel (quetiapine)	✓
Seroquel XR (quetiapine ER)	✓
Versacloz (clozapine)	-
Vraylar (cariprazine)	-
Zyprexa (olanzapine)	✓
Zyprexa Zydis (olanzapine)	✓
Long-Acting Injectable Products	
Abilify Maintena (aripiprazole ER)	-
Aristada (aripiprazole lauroxil ER)	-
Invega Sustenna (paliperidone palmitate)	-
Invega Trinza (paliperidone palmitate)	-
Risperdal Consta (risperidone microspheres)	-
Zyprexa Relprevv (olanzapine pamoate)	-
Combination Products	
Symbyax (olanzapine/fluoxetine)	✓

*Brand Abilify oral solution and orally disintegrating tablets have been discontinued; generic products are available.

†Vanda filed a patent infringement lawsuit against Inventia for Fanapt generic products. In December 2016, Vanda and Inventia entered into a confidential stipulation regarding any potential launch date of the generic products (*ME staff press release, 2016*).

(*Drugs @FDA 2017, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2017*)

INDICATIONS

- The following summarizes all FDA-approved indications:
 - **Autism:** Aripiprazole and risperidone are the only agents indicated for the treatment of irritability associated with autistic disorder in pediatric patients (aged 6 to 17 years, and 5 to 17 years, respectively).
 - **Bipolar disorder:** All oral agents in class are indicated for use in bipolar disorder, except clozapine, iloperidone, paliperidone, and brexpiprazole. Risperidone long-acting injection is the only long-acting injectable indicated for the treatment of bipolar disorder.
 - Aripiprazole, olanzapine/fluoxetine, risperidone, quetiapine, and asenapine are approved for use in pediatric patients ≥ 10 years of age with bipolar disorder. Olanzapine is approved for use in patients ≥ 13 years of age with bipolar disorder.
 - **Depression:** Aripiprazole, brexpiprazole, and quetiapine ER are indicated as adjunctive treatment for MDD in patients already taking an antidepressant. Olanzapine/fluoxetine is indicated for treatment resistant depression.
 - **Schizophrenia:** All agents in class are indicated for use in schizophrenia with the exception of the combination agent, Symbyax (olanzapine/fluoxetine). Clozapine and paliperidone products, excluding Invega Trinza, are indicated for the treatment of schizoaffective disorder. Clozapine is the only agent in class FDA-approved for treatment-resistant schizophrenia.
 - Aripiprazole, lurasidone, olanzapine, quetiapine, and risperidone are approved for use in patients ≥ 13 years of age and paliperidone oral products are approved for patients ≥ 12 years of age with schizophrenia.

Data as of June 29, 2017 AVD/KAL

Page 3 of 33

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.



- Tourette's Disorder: Aripiprazole is the only agent indicated for the treatment of Tourette's disorder in pediatric patients, aged 6 to 18 years.
- Prescribing considerations: The labeling for iloperidone and ziprasidone state that when deciding among the alternative treatments, the prescriber should consider that these drugs are associated with prolongation of the QTc interval. In addition, patients must be titrated to an effective dose of iloperidone; thus control of symptoms may be delayed during the first 1 to 2 weeks of treatment compared to other antipsychotics that do not require similar titration.
- Table 2 highlights FDA-approved indications at a high level.



Table 2. Food and Drug Administration approved indications

Agent	Autism	Bipolar disorder: manic/mixed	Bipolar disorder: depressive	Depression – treatment-resistant	MDD: adjunct	Schizoaffective disorder	Schizophrenia	Schizophrenia: treatment-resistant	Tourette's Disorder
Single Entity Products									
aripiprazole	✓ *	✓ *	-	-	✓	-	✓ *	-	✓ *
asenapine	-	✓ *	-	-	-	-	✓	-	-
brexiprazole	-	-	-	-	✓	-	✓	-	-
cariprazine	-	✓	-	-	-	-	✓	-	-
clozapine	-	-	-	-	-	✓	-	✓	-
iloperidone	-	-	-	-	-	-	✓	-	-
lurasidone	-	-	✓	-	-	-	✓ *	-	-
olanzapine	-	✓ *	-	-	-	-	✓ ** #	-	-
paliperidone	-	-	-	-	-	✓	✓ *	-	-
quetiapine	-	✓ *	✓	-	✓ †	-	✓ *	-	-
risperidone	✓ *	✓ *	-	-	-	-	✓ *	-	-
ziprasidone HCl	-	✓	-	-	-	-	✓	-	-
ziprasidone mesylate	-	-	-	-	-	-	✓ §	-	-
Long-Acting Injectable Products									
aripiprazole ER	-	-	-	-	-	-	✓	-	-
aripiprazole lauroxil ER	-	-	-	-	-	-	✓	-	-
paliperidone palmitate (Invega Trinza Sustenna)	-	-	-	-	-	✓	✓	-	-
paliperidone palmitate (Invega Trinza)	-	-	-	-	-	-	✓	-	-
risperidone microspheres	-	✓	-	-	-	-	✓	-	-
olanzapine pamoate	-	-	-	-	-	-	✓ ‡	-	-
Combination Products									
olanzapine/fluoxetine	-	-	✓ *	✓	-	-	-	-	-

*FDA-approved indications for pediatric patients; †ER formulation; ‡ Patients must be observed by a health care professional for 3 hours post-dose administration; § intramuscular (IM) injection indicated for acute agitation associated with schizophrenia; #IM injection indicated for acute agitation associated with schizophrenia and bipolar mania.

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.



(Prescribing information: *Abilify 2017, Abilify Maintena 2017, Aristada 2017, Clozaril 2017, Fanapt 2017, Fazaclo 2017, Invega 2017, Invega Sustenna 2017, Invega Trinza 2017, Latuda 2017, Rexulti 2017, Risperdal 2017, Risperdal Consta 2017, Saphris 2017, Seroquel 2017, Seroquel XR 2017, Symbiyax 2017, Versacloz 2017, Vraylar 2017, Zyprexa 2017, Zyprexa Relprew 2017*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

CLINICAL EFFICACY SUMMARY

- The goal of this review is to evaluate key published literature regarding atypical antipsychotics for FDA-approved indications in children, adolescents, and adults. Numerous studies evaluating the efficacy of antipsychotic medications have been conducted. In clinical practice, the role of the atypical antipsychotics has been clearly established for the treatment of bipolar disorder and schizophrenia. In general, clinical consensus guidelines do not differentiate one agent from another, supporting the concept that all patients will require an individualized approach to treatment selection, taking into account the agent's safety profile and patient's individual risk factors.
- Key clinical studies evaluating the roles of atypical antipsychotic agents in the treatment of FDA-approved indications are included in the review. However, in recognition of the vast number of published studies of older atypical antipsychotics in adults, only a selection of randomized controlled studies (RCTs), systematic reviews (SR), and meta-analyses (MAs) are included in this review.

CHILDREN/ADOLESCENTS

The Agency for Healthcare Research and Quality (AHRQ) conducted an SR evaluating the safety and efficacy of antipsychotics in children and adolescents. The review included 135 studies of atypical antipsychotics (aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone), conducted in patients 24 years of age or younger, and used for various psychiatric conditions including schizophrenia and related disorders, autism spectrum disorders, bipolar disorder, and tic disorder, among others. Overall, indications associated with moderate strength evidence for the use of atypical antipsychotics included schizophrenia and related psychoses, bipolar disorder, autism spectrum disorders, and ADHD. The risk of weight gain was highest for olanzapine, clozapine, and lurasidone. It was found that atypical antipsychotics probably increase short-term risk for high triglyceride levels, extrapyramidal symptoms, sedation, and somnolence vs placebo (Pillay *et al* 2017).

Autism Spectrum Disorder

- For the treatment of irritability associated with autistic disorder, risperidone has been approved in pediatric patients aged 5 to 17 years and aripiprazole has been approved in patients aged 6 to 17 years. Very few RCTs have been conducted evaluating safety and efficacy, and only 1 low-quality study has been conducted evaluating comparative effectiveness. The primary outcome measure in trials was the change from baseline to endpoint in the Aberrant Behavior Checklist-Irritability subscale of the ABC (ABC-I), which measured symptoms of irritability in autistic disorder. One risperidone trial measured the Clinical Global Impression-Change (CGI-C) scores as a co-primary outcome measure.
- The safety and efficacy of aripiprazole was evaluated in 2 placebo-controlled (PC), 8-week trials. Over 75% of these subjects were under 13 years of age. In one of these trials, children and adolescents with autistic disorder (N = 98) received daily doses of placebo or aripiprazole 2 to 15 mg/day. The mean daily dose of aripiprazole at the end of 8-week period was 8.6 mg/day. Aripiprazole significantly improved ABC-I subscale scores, including emotional and behavioral symptoms of irritability, aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods (Owen *et al* 2009). In the second of these trials in children and adolescents with autistic disorder (N = 218), 3 fixed doses of aripiprazole (5, 10, or 15 mg/day) were compared to placebo. ABC-I subscale scores were significantly decreased by 12.4 points with 5 mg/day, 13.2 with 10 mg/day, and 14.4 with 15 mg/day compared with 8.4 for placebo. Clinical Global Impressions (CGI)-Improvement scores were significantly improved: 2.6 points for 5 mg/day, 2.5 for 10 mg/day, and 2.5 for 15 mg/day compared with 3.3 for placebo. At the higher doses, ABC stereotypy, hyperactivity, CGI-S (Severity of Illness) scores, and other secondary measures were also improved (Marcus *et al* 2009).
- In one MA of 3 trials evaluating pediatric patients (N = 316) treated with aripiprazole, results demonstrated a greater increase in weight vs placebo (weight gain, 1.13 kg; 95% confidence interval [CI], 0.71 to 1.54; $p < 0.00001$), and had a higher relative risk (RR) for sedation (RR, 4.28; 95% CI, 1.58 to 11.6; $p = 0.004$) and tremor (RR, 10.26; 95% CI, 1.37 to 76.63; $p = 0.02$) (Hirsch *et al* 2016).
- The safety and efficacy of risperidone was evaluated in two 8-week and one 6-week, PC pivotal trials (McCracken *et al* 2002, Shea *et al* 2004). Approximately 90% of these subjects were under 12 years of age. In the two 8-week trials, the efficacy and safety of risperidone were measured in patients aged 5 to 16 years (N = 101) in weight-based, twice-daily doses of 0.5 to 3.5 mg/day (the RUPP trial) and in patients aged 5 to 12 years (N = 79) who received 0.02 to 0.06 mg/kg/day given once or twice daily (McCracken *et al* 2002, Shea *et al* 2004). The 6-week trial measured efficacy and safety in patients using lower than FDA-approved recommended dosing, and outcomes did not demonstrate efficacy

(Risperdal prescribing information 2017). In the RUPP trial, risperidone-treated patients exhibited a 56.9% reduction in the mean ABC-I score from baseline, compared to a 14.1% reduction observed in the placebo group ($p < 0.001$) (McCracken *et al* 2002). Risperidone was generally well tolerated, and most adverse events were mild and transient. Due to the uncertainty of a clear benefit with regard to the core symptoms of autism, the authors recommend that risperidone be reserved for the treatment of moderate-to-severe behavioral problems accompanying autism. In the second 8-week trial, risperidone patients demonstrated a 64% improvement in ABC-I subscale vs 31% improvement with placebo, which was a significant positive finding for hyperactivity (Shea *et al* 2004). Somnolence was the most frequently reported adverse event (72.5% vs 7.7%), and risperidone-treated subjects experienced statistically greater increases in weight (2.7kg vs 1 kg), pulse rate, and systolic blood pressure.

- In an extension of the RUPP trial, 63 responders received open-label (OL) risperidone for another 16 weeks. Risperidone dose adjustments were allowed up to a maximum total daily dose of 3.5 mg/day. At the end of the 4-month extension, an intention-to-treat analysis revealed a minor, but clinically insignificant increase in ABC-I score. There was also a significant time effect on the ABC-I scale at the end of the 4-month extension phase ($p = 0.02$) (McDougle *et al* 2005).
- Additional trials have been conducted measuring effects of risperidone; however, most trials included less than 50 patients per trial. The outcomes of these trials are more sensitive to variability within the trials due to the small effect size (Aman *et al* 2008, Capone *et al* 2008, Gagliano *et al* 2004, Gencer *et al* 2008, Luby *et al* 2006, Miral *et al* 2008, Nagaraj *et al* 2006).
- One head-to-head, prospective, 8-week trial was conducted comparing the effects of aripiprazole ≤ 10 mg/day (mean dose, 5.5 mg/day) to risperidone ≤ 3 mg/day (mean dose, 1.12 mg/day) in patients ($N = 59$) aged 4 to 18 years of age. Approximately 65% of patients were diagnosed with autism, and additional diagnoses included Asperger syndrome, pervasive developmental disorder, and disruptive behavior disorder. Study authors stated double-blind (DB) techniques were not enforced for all patients. At the end of the trial, the mean baseline ABC-I subscale was not statistically different ($p = 0.06$), but numerically favored risperidone. No differences were detected between groups for each adverse event or in the rate of discontinuations due to adverse events. Study authors concluded the safety and efficacy of both agents were comparable (Ghanizadeh *et al* 2014).

Bipolar Disorder

Manic/Mixed Episodes

- Aripiprazole, olanzapine, olanzapine/fluoxetine, risperidone, quetiapine and asenapine have FDA-approved indications for the treatment of pediatric patients diagnosed with bipolar disorder. All agents are approved for ages ≥ 10 years, except olanzapine which is approved in patients aged ≥ 13 years. In pediatric patients with bipolar disorder, evidence is extremely limited.
- In an AHRQ SR of 135 trials evaluating typical and atypical antipsychotics, a total of 19 trials measured efficacy and safety in adolescents with bipolar disorder. Compared with placebo, atypical antipsychotics decrease mania, decrease depression symptoms slightly, and improve symptom severity and global functioning to a small extent. In addition, they probably increase response and remission rates vs placebo for manic/mixed phases (Pillay *et al* 2017).
- In a 21-day, DB, PC trial, 403 patients aged 10 to 17 years with bipolar I disorder were randomized to placebo, asenapine 2.5 mg, 5 mg, or 10 mg twice daily. The primary endpoint, change from baseline in YMRS score, demonstrated a statistically significant and dose-dependent mean difference in YMRS scores at 21 days for all asenapine groups vs placebo (2.5 mg, -3.2; $p = 0.0008$ vs 5 mg, -5.3; $p < 0.001$ vs 10 mg, -6.2; $p < 0.001$). Weight gain was higher across the asenapine groups, with 8 to 12% of patients experiencing $\geq 7\%$ weight gain vs 1.1% of patients in the placebo group ($p < 0.05$). Fasting glucose, insulin and cholesterol changes were also numerically higher in the asenapine groups vs placebo ($p =$ not reported). Overall, asenapine was well tolerated and showed efficacy in the treatment of this pediatric population, although the duration of the study period was brief (Findling *et al* 2015).

Depressive Episodes

- Clinical trials measuring the safety and efficacy of atypical antipsychotics in depressive episodes in pediatric patients diagnosed with bipolar disorder are limited. Two trials examined efficacy of quetiapine in this population. In a small trial, a total of 32 patients aged 12 to 18 years were randomized to quetiapine 300 to 600 mg/day or placebo and followed over a period of 8 weeks. The primary endpoint was change in the Children's Depression Rating Scale, Revised Version (CDRS-R) score, in which both quetiapine and placebo groups exhibited statistically significant reductions in the CDRS-R scores from baseline ($p < 0.001$), with no difference between groups (19 vs 20; $p = 0.89$). All other efficacy measures

were not statistically different from placebo (*DelBello et al 2009*). A similar 8-week trial enrolled 193 patients aged 10 to 17 years with acute bipolar depression. Patients were randomized to placebo or quetiapine XR 150 to 300 mg/day. The primary endpoint was change in CDRS-R score from baseline, with mean CDRS-R scores decreasing from baseline in both placebo (-29.6) and treatment (-27.3) groups. The difference between groups was not statistically significant (95% CI, -6.22 to 1.65; $p = 0.25$). Triglyceride levels were elevated in 9.3% of the quetiapine XR group vs 1.4% of the placebo group. Mean weight gain was 1.3 kg in the quetiapine XR group vs 0.6 kg in the placebo group ($p =$ not reported) (*Findling et al 2014*).

- In a DB, PC trial, 291 patients aged 10 to 17 with bipolar I disorder and depressive episodes were randomized 2:1 to olanzapine/fluoxetine or placebo for 8 weeks. Doses of olanzapine/fluoxetine were titrated to 12/50 mg daily over 2 weeks. The olanzapine/fluoxetine group had a 5-point greater mean decrease in CDRS-R score from baseline vs placebo (-28.4 vs -23.4; $p = 0.003$). A total of 78.2% olanzapine/fluoxetine patients achieved response (defined as $\geq 50\%$ reduction of CDRS-R score from baseline and a Young Mania Rating Scale (YMRS) item 1 score ≤ 2) vs 59.2% of placebo group patients ($p = 0.003$). Weight gain was more common in the olanzapine/fluoxetine group vs placebo (4.4 vs 0.5 kg; $p < 0.001$), as well as increase in fasting total cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides (all $p < 0.001$). Mean prolactin increase was higher in the olanzapine/fluoxetine group vs placebo ($p < 0.001$) and increase in heart rate was also statistically significantly higher in the treatment group ($p = 0.013$). This trial demonstrated efficacy in pediatric patients, but also demonstrated serious adverse effects (*Detke et al 2015*).

Schizophrenia and/or Schizoaffective Disorder

- In pediatric patients diagnosed with schizophrenia, FDA-approved treatments include aripiprazole, lurasidone, olanzapine, quetiapine and risperidone for use in patients ≥ 13 years of age and paliperidone oral products in patients aged ≥ 12 years. Many trials include a small sample size of patients, or are not well-designed. However, efficacy has been demonstrated and results are similar to adult trials.
- An SR and network MA of 12 RCTs (N = 2158) evaluated 8 antipsychotics (aripiprazole, asenapine, paliperidone, risperidone, quetiapine, olanzapine, molindone, and ziprasidone) for treatment of children and adolescents with schizophrenia-spectrum disorders. Network MA found that change in Positive and Negative Syndrome Scale (PANSS) total, positive, and negative symptoms did not differ significantly between agents except for ziprasidone, which was inferior on PANSS total symptoms vs molindone, olanzapine, paliperidone, quetiapine, and risperidone, and inferior on PANSS negative symptoms vs molindone, olanzapine, and risperidone. All antipsychotics were superior to placebo on PANSS total symptom change except asenapine and ziprasidone. All antipsychotics, except ziprasidone, were superior to placebo on PANSS positive symptom change; additionally, all antipsychotics, except paliperidone, quetiapine, and ziprasidone, were superior to placebo on PANSS negative symptom change. Weight gain was primarily associated with olanzapine, while prolactin was increased with risperidone, paliperidone, and olanzapine (*Pagsberg et al 2017*).
- In an AHRQ SR of 135 trials evaluating typical and atypical antipsychotics, a total of 39 studies evaluated efficacy and safety in adolescents with schizophrenia. Compared with placebo, atypical antipsychotics as a class probably increase response rates; decrease slightly (not clinically significant for many patients) negative and positive symptoms; and improve slightly global impressions of improvement, severity, and functioning. Six studies comparing risperidone vs olanzapine found little or no difference in their effects for negative and positive symptoms, response rates, and global impressions of severity (*Pillay et al 2017*).
- A Cochrane review compared atypical antipsychotic medications to placebo, typical antipsychotics, or another atypical antipsychotic in adolescents with psychosis. Compared to typical antipsychotics, there were no significant differences in Brief Psychiatric Rating Scale (BPRS) scores in an analysis of 5 trials with 236 patients. There was no evidence to suggest the superiority of atypical antipsychotics over typical antipsychotics; however, fewer adolescents dropped out due to adverse effects when administered an atypical antipsychotic (RR, 0.65; 95% CI, 0.36 to 1.15). Minimal evidence was available comparing one atypical antipsychotic to another. In terms of the number of patients who did not respond (defined as $\leq 30\%$ reduction in BPRS score), results significantly favored clozapine, but increases in salivation, sweating, and higher glucose levels were observed vs olanzapine in 1 trial with 39 patients. Treatment with olanzapine, risperidone and clozapine was associated with weight gain. Aripiprazole was not associated with increased prolactin or dyslipidemia. Low-dose risperidone significantly decreased improvement in PANSS total score but also reduced the rate of extrapyramidal symptoms (EPS) vs standard-dose risperidone in 1 trial with 255 patients. Overall, efficacy between atypical and typical antipsychotics may be similar; however, safety benefits may favor treatment with atypical antipsychotics (*Kumar et al 2013*).

- A 6-week, randomized, PC trial evaluating the efficacy of lurasidone in acutely symptomatic adolescents with schizophrenia found that the least squares (LS) mean change in PANSS total score from baseline to week 6 was greater for the lurasidone 40 mg/day group (-18.6; $p < 0.001$; effect size = 0.51) and the lurasidone 80 mg/day group (-18.3; $p < 0.001$; effect size = 0.48) vs the placebo group (-10.5). The LS mean change from baseline to week 6 in CGI-S score was significantly greater for the lurasidone 40 mg/day group (-1.0; $p < 0.001$; effect size = 0.49) and the lurasidone 80 mg/day group (-0.9; $p = 0.0015$; effect size = 0.45) compared with the placebo group (-0.5). The most common adverse events in the lurasidone groups were nausea, anxiety, akathisia, somnolence, and vomiting (*Goldman et al 2017*).

Tourette's Disorder

- Aripiprazole is the only agent indicated for the treatment of Tourette's disorder. Efficacy and safety is based on low quality evidence in one fixed dose and one flexible dose trial. There is minimal evidence of safety and efficacy in this population.
- In one published, DB, PC, 10-week trial, aripiprazole significantly reduced total tic score (Yale Global Tic Severity Scale [YGTSS-TTS]; -15 vs -9.6) and phonic tic score (YGTSS-PTS; -7.4 vs -4.2), but not motor tic score, compared with placebo in patients aged 6 to 18 years with Tourette's disorder. The response rate (score of 1 or 2 on the Tourette's syndrome CGI-Improvement scale) was 66% vs 45%, respectively (*Yoo et al 2013*).
- In another similarly designed, unpublished, 8-week trial in patients aged 7 to 17 years who received weight-based aripiprazole, significant improvements compared with placebo were seen on YGTSS-TTS with a change of -13.4 and -16.9 points with low- and high-dose aripiprazole compared to -7.1 in placebo (*Abilify prescribing information 2017*).
- Aripiprazole was associated with increased body weight compared to placebo (range, 0.4 to 1.5 kg). Additional adverse reactions (incidence $\geq 5\%$ and at least twice that for placebo) were sedation, somnolence, nausea, headache, nasopharyngitis, fatigue, and increased appetite (*Abilify prescribing information 2017*). In one safety trial, aripiprazole had a safer cardiovascular profile vs pimozide, and was associated with a lower frequency of QT prolongation (*Guliano et al 2011*).

ADULTS

- The AHRQ conducted an SR of literature on the safety and efficacy of antipsychotics in adults comparing typical and atypical antipsychotics. The review included studies of atypical antipsychotics (aripiprazole, asenapine, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone), conducted in patients 18 to 64 years of age, and used for the following FDA-approved indications: bipolar disorder, schizophrenia, and schizophrenia-related psychoses. The most frequent comparisons involved haloperidol, with 43 studies comparing haloperidol with risperidone and 37 studies comparing haloperidol with olanzapine. Nevertheless, the number of studies available for each comparison and outcome was often limited. Overall, indications associated with moderate to low strength evidence for the use of atypical antipsychotics included schizophrenia and schizophrenia-related psychoses. Bipolar disorder was associated with low strength of evidence. Few differences of clinical importance for outcomes of effectiveness were found. Patient-important outcomes were rarely assessed. Data were sparse for the 4 key adverse events deemed to be most clinically important. In terms of efficacy, few differences were found between typical and atypical antipsychotic agents, specifically when compared to haloperidol and clinical significance (defined as $\geq 20\%$ difference between interventions) was rarely found. The evidence regarding safety, particularly those adverse events of most interest (ie, diabetes, tardive dyskinesia, metabolic syndrome, and mortality) were insufficient to draw firm conclusions about the risks among treatment groups. No differences were found in mortality for chlorpromazine vs clozapine and haloperidol vs aripiprazole, or in metabolic syndrome for haloperidol vs olanzapine. The most frequently reported adverse events with significant differences were EPS; in most cases, the atypical antipsychotic had fewer EPS than haloperidol (*Abou-Setta et al 2012*).

Bipolar Disorder

Manic/Mixed Episodes

- All oral atypical antipsychotic agents in class are indicated for use in bipolar disorder, except clozapine, iloperidone, paliperidone, and brexpiprazole. The following summarizes direct comparative evidence and recent MAs and SRs.
- In a 2012 AHRQ SR of 125 trials evaluating typical and atypical antipsychotics, a total of 12 measured efficacy and safety in adults with bipolar disorder. Compared to haloperidol, there was no difference in YMRS score for manic episodes for aripiprazole, olanzapine, and risperidone, and no difference in Montgomery-Asberg Depression Rating Scale (MADRS) score for aripiprazole in a total of 9 trials. In one trial of 350 patients, haloperidol was favored in terms of YMRS score over ziprasidone. Haloperidol produced lower relapse rates than aripiprazole in one trial with 347 patients

and provided better response rates than ziprasidone in one trial of 350 patients. The most frequently reported adverse effects with significant differences were in the category of EPS and most often involved haloperidol. Haloperidol appears to be an equally effective treatment compared with the atypical antipsychotics; however, it is associated with more incidences of EPS compared to other agents (*Abou-Setta et al 2012*).

- An SR and MA of 15 RCTs and 1 observational study was conducted to evaluate the efficacy of maintenance treatment in bipolar disorder using atypical antipsychotics, either as monotherapy or as adjunctive therapy. As adjunctive therapy to lithium or valproate, MAs showed that treatment with aripiprazole (RR, 0.65; 95% CI, 0.50 to 0.85), quetiapine (RR, 0.38; 95% CI, 0.32 to 0.46), or ziprasidone (RR, 0.62; 95% CI, 0.40 to 0.96) reduced the overall risk of relapses in patients that had responded during the stabilization phase. Quetiapine was the only drug that reduced both manic and depressive episodes. Due to high risk of bias and low levels of evidence, no conclusions could be drawn for olanzapine or risperidone. For monotherapy, quetiapine was shown to be better than lithium/valproate for both manic and depressive relapses; no reliable conclusions could be made for olanzapine due to the low quality of evidence. Monotherapy with olanzapine, quetiapine, and risperidone were shown to be superior vs placebo in reducing the overall risk of relapses; no reliable conclusions could be made for aripiprazole due to the low quality of evidence (*Lindström et al 2017*).
- One SR of 9 RCTs (N = 1289) compared the effectiveness of atypical antipsychotics to placebo, either as monotherapy or as adjunctive treatment with a mood stabilizer. Atypical antipsychotics, either alone or in combination with mood stabilizers, had superior efficacy in treating manic symptoms of mixed episodes compared to placebo in short term trials lasting 3 to 6 weeks ($p < 0.00001$). Atypical antipsychotics also had superior efficacy in treating depressive symptoms of mixed episodes ($p < 0.001$) (*Muralidharan et al 2013*).
- The efficacy and safety of asenapine in the treatment of manic or mixed bipolar I disorder were evaluated in 5 PC, and active-controlled (olanzapine) studies in adult patients, with or without psychotic features (*McIntyre et al 2009[a]*, *McIntyre et al 2010[a]*, *McIntyre et al 2009[b]*, *McIntyre et al 2010[b]*, *Szegedi et al 2011*). In a pooled analysis of patients experiencing bipolar mania, asenapine and olanzapine were comparable in terms of reduction from baseline in YMRS scores at week 52 of therapy (*McIntyre et al 2010[b]*). An MA of various anti-manic therapy options found that asenapine was associated with a statistically significant improvement in YMRS scores from baseline compared to placebo (mean difference [MD], -0.3; 95% CI, -0.53 to -0.07), though it was less effective compared to olanzapine (0.22; 95% CI, 0.08 to 0.37) (*Cipriani et al 2011*). The most commonly reported adverse events reported with asenapine included sedation, dizziness, somnolence and weight gain. Of note, it was calculated that for every 9 patients treated with olanzapine over asenapine, one would experience clinically significant weight gain with olanzapine (19 vs 31%) (*McIntyre et al 2009[b]*).
- The approval of the newest FDA-approved agent, cariprazine, was based on the efficacy and safety from 3 flexible dose, DB, PC, 3-week trials (*Calabrese et al 2015*, *Durgam et al 2015[a]*, *Sachs et al 2014*). A total of 1047 adult patients with acute manic or mixed episodes were administered placebo or cariprazine 3 to 12 mg per day based on tolerability. Across trials, the mean daily dose was 8.8 mg per day and the mean final dose was 10.4 mg per day (*FDA/CBER summary review 2015*). All doses were superior to placebo in reducing YMRS and CGI-S scores and a significant reduction in YMRS was observed as early as 4 days in some studies and persisted until week 3. The proportion of YMRS remitters was significantly higher in the cariprazine group than placebo (difference range, 15 to 19%) (*Calabrese et al 2015*, *Durgam et al 2015[a]*, *Sachs et al 2014*). Of note, doses higher than 6 mg had similar efficacy, but adverse events were less tolerable. Due to the long half-life and pharmacokinetics of the active metabolite, DDCAR, the steady state was not achieved in trials (*FDA/CBER summary review 2015*). It is anticipated that late-onset of adverse reactions would be observed if assessed for a longer period. In bipolar studies, 4% of patients with normal hemoglobin A1c developed elevated levels ($\geq 6.5\%$). According to pooled analysis (n = 1940 cariprazine-treated patients) within the FDA summary review, the most frequently observed adverse events include akathisia (14.2%), EPS (20.8%), constipation (7.6%), and nausea/vomiting (6 to 8%). The proportion of patients with weight increase $\geq 7\%$ from baseline ranged from 1 to 3% across cariprazine doses.
- The efficacy and safety of risperidone 1 to 6 mg/day compared to olanzapine 5 to 20 mg/day were evaluated in a 3-week, DB, RCT in patients hospitalized for bipolar I disorder, manic or mixed episode, without psychotic features. Olanzapine and risperidone mean doses were 14.7 mg/day and 3.9 mg/day, respectively. There was no difference between groups in many outcome measures in remission or response in YMRS, 21-item Hamilton Rating Scale for Depression (HAM-D-21), or MADRS scales. More patients given olanzapine completed the trial compared with patients given risperidone (78.7% vs 67%, respectively). In total, 62.1% of patients in the olanzapine group and 59.5% of patients in the risperidone group were categorized as responders (defined as $\geq 50\%$ reduction in the YMRS score at endpoint).

Olanzapine-treated patients experienced significantly greater elevations in liver function enzymes and weight gain (2.5 kg vs 1.6 kg). Risperidone-treated patients experienced significantly more prolactin elevations and sexual dysfunction (Perlis et al 2006[a]).

Depressive Episodes

- PC trials measuring effects for the treatment of bipolar depression have demonstrated efficacy with lurasidone, quetiapine (immediate- and extended-release [ER]), and olanzapine/fluoxetine as monotherapy and adjunctive treatment (Calabrese et al 2005, Corya et al 2006, McElvoy et al 2010, Loebel et al 2014[a], Loebel et al 2014[b], Shelton et al 2005, Suppes et al 2010, Thase et al 2007, Young et al 2010).
- Treatment with olanzapine/fluoxetine was superior to monotherapy with olanzapine and lamotrigine in achieving greater improvements in MADRS and CGI-BP (bipolar version) (Tohen et al 2003, Brown et al 2009). Patients treated with olanzapine/fluoxetine had significantly greater rates of treatment response and remission compared to those receiving olanzapine monotherapy (Tohen et al 2003). It is not clear if quetiapine outperforms lithium in terms of treatment of bipolar depression, as various studies have produced different results (Chiesa et al 2012, Young et al 2010).
- MAs have found that combination treatment with olanzapine/fluoxetine may be the optimal treatment for bipolar depression compared to other treatment options. However, the overall evidence quality was considered low, trials had limited durations, and a high placebo effect was observed. Olanzapine, quetiapine, lurasidone, valproate, selective-serotonin reuptake inhibitors (SSRIs), lithium, and tricyclic antidepressants (TCAs) also appeared to be effective, but with varied acceptability (Ostacher 2017, Fornaro et al 2016, Silva et al 2013, Taylor et al 2014, Vieta et al 2010). No notable efficacy differences were identified between atypical antipsychotics, suggesting that lurasidone, quetiapine, and olanzapine/fluoxetine may be reasonable choices.

Major Depressive Disorder (MDD)

Key MDD Meta-Analyses

- A number of MAs and SRs have been conducted evaluating the safety and efficacy of atypical antipsychotics to augment treatment for MDD. Aripiprazole, brexpiprazole, and quetiapine ER are indicated for the treatment of MDD as adjunctive treatment; and olanzapine, in combination with fluoxetine, is indicated for the treatment of treatment-resistant depression. The most recent, well-designed MAs have been summarized for efficacy and safety evaluations.
- One MA, which followed Cochrane methodologies, evaluated 17 trials of short-term duration ranging from 4 to 12 weeks. The analysis compared adjunctive atypical antipsychotics treatment in combination with a SSRI/serotonin-norepinephrine reuptake inhibitor (SNRI) to SSRI or SNRI monotherapy in patients with refractory or treatment-resistant MDD. Results demonstrated that the augmentation of antidepressants with atypical antipsychotics (olanzapine, quetiapine, aripiprazole, and risperidone [Note: risperidone is not FDA-approved for this indication]) was more effective than antidepressant monotherapy in improving response and remission rates. However, adjunctive atypical antidepressant therapy was associated with a higher discontinuation rate due to adverse effects (9.1% vs 2.6%). The attributable risk for the discontinuation rate due to adverse effects was 0.07 (number needed to harm [NNH], 16; 95% CI, 12 to 20) (Wen et al 2014).
- Another MA evaluated 14 trials in patients with current MDD and an inadequate response to at least 1 course of antidepressant medication treatment. Compared to placebo, the atypical antipsychotics significantly improved remission rates: aripiprazole (odds ratio [OR], 2.01; 95% CI, 1.48 to 2.73), olanzapine/fluoxetine (OR, 1.42; 95% CI, 1.01 to 2), quetiapine (OR, 1.79; 95% CI, 1.33 to 2.42) and risperidone (OR, 2.37; 95% CI, 1.31 to 4.3). In terms of remission, all atypical antipsychotics were efficacious; however, olanzapine/fluoxetine had a higher number needed to treat (NNT) compared to other agents (NNT for olanzapine/fluoxetine, 19 vs NNT for aripiprazole, quetiapine, risperidone, 9). Treatment was associated with several adverse events, including akathisia (aripiprazole), sedation (quetiapine, olanzapine/fluoxetine and aripiprazole), abnormal metabolic laboratory results (quetiapine and olanzapine/fluoxetine), and weight gain (all 4 drugs, especially olanzapine/fluoxetine). However, little to no information was provided in detail regarding the adverse events (Spielmans et al 2013).

Adjunctive treatment for MDD

- Aripiprazole, brexpiprazole, and quetiapine ER are indicated for the treatment of MDD as adjunctive treatment. The following information describes the pivotal trials used for FDA-approval.
- The FDA-approval of aripiprazole for the adjunctive treatment of MDD was based on 2 PC, 6-week trials in adult patients (N = 381; N = 362) who had failed 1 to 3 courses of antidepressant therapy, including an inadequate response to 8

weeks of antidepressant treatment. Aripiprazole was superior to placebo in reducing the mean MADRS total scores and remission rates. The NNT to reduce remission rates (defined as MADRS total score ≤ 10 and $\geq 50\%$ reduction in MADRS) was 10 (Berman *et al* 2007, Marcus *et al* 2008). Increased incidences of akathisia were seen across trials with one trial reporting a NNH of 4 (Marcus *et al* 2008). One pooled analysis of 3 similarly designed trials (N = 409) measured the effects of aripiprazole in older vs younger patients. Results demonstrated adjunctive aripiprazole was effective in improving depressive symptoms in older patients, 50 to 67 years and akathisia was the most commonly reported adverse event in both the older (17.1%) and younger (26%) patient groups (Steffens *et al* 2011). Other trials have demonstrated similar results (Kamijima *et al* 2013, Papakostas *et al* 2005). In a 12-week, randomized, DB, PC trial evaluating the safety and efficacy of aripiprazole for adjunctive MDD treatment in patients over the age of 60 (N = 181), a higher percentage of patients achieved remission (defined as a MADRS score of ≤ 10) in the aripiprazole group as compared to placebo (44% vs 29%; $p = 0.03$; NNT 6.6). Similar to other studies, akathisia was the most common side effect in the aripiprazole group (26% vs 12%), and Parkinsonism was also more often reported (17% vs 2%) (Lenze *et al* 2015).

- The safety and efficacy of brexpiprazole was evaluated in 2 DB, PC, pivotal, 6-week trials in adult patients as an adjunct to antidepressant therapy for MDD. In the pivotal studies, brexpiprazole 2 mg daily doses significantly reduced the mean MADRS score, the primary endpoint, compared with placebo (Study 1 [N = 353], -8.4 points with brexpiprazole 2 mg vs -5.2 points with placebo) (Thase *et al* 2015[a]). In an FDA analysis, the brexpiprazole 1 mg and 3 mg dose did not reduce the mean MADRS score; however, an FDA analysis found evidence of efficacy based on phase 2 data, and per protocol and intention-to-treat analyses of Study 2 (Thase *et al* 2015[b], FDA briefing document 2015). The most common adverse reactions in MDD trials were akathisia (NNH, 15), increased weight (NNH, 20) and somnolence (NNH, 22); and in schizophrenia trials were increased weight (NNH, 48) and tremor (NNH, 51) (Correll *et al* 2015, Kane *et al* 2015[a], Thase *et al* 2015[b]). An SR and MA of 4 DB, randomized, PC trials evaluating the efficacy and safety of brexpiprazole for adjunctive treatment of MDD found that it was superior to placebo for MADRS (MD, -1.76; 95% CI, -2.45 to -1.07; $p < 0.00001$) and the HAM-D-17 (MD, -1.21; 95% CI, -1.71 to -0.72; $p < 0.00001$). The RRs for response and remission were 1.57 (95% CI, 1.29 to 1.91) and 1.55 (95% CI, 1.22 to 1.96), respectively (Yoon *et al* 2017).
- The FDA-approval of quetiapine fumarate ER as an adjunct to antidepressant therapy for the treatment of MDD was based on two 6-week, PC, fixed dose trials (N = 939) in doses of 150 mg or 300 mg/day. A pooled analysis of the 2 RCTs demonstrated that quetiapine fumarate 300 mg/day (58.3%; $p < 0.01$; NNT, 9) dose significantly improved the MADRS response (defined as $\geq 50\%$ decrease in MADRS total score), but the quetiapine fumarate 150 mg/day (53.7%; $p = 0.06$) did not compared to placebo (46.2%). However, MADRS remission was significantly improved for both the quetiapine fumarate 300 mg/day (36.5%; $p < 0.001$; NNT, 8) and 150 mg/day dose (35.6%; $p < 0.01$; NNT, 9) vs placebo (24.1%). The most common adverse events leading to discontinuation were somnolence and sedation. For the quetiapine fumarate 300 mg/day, 150 mg/day, and placebo treatment, the mean weight gain was 1.3, 0.9, and 0.2 kg, and the incidence of EPS was 6.4, 3.8, and 4.2%, respectively (Bauer *et al* 2010).

Treatment-resistant depression

- Olanzapine, combined with fluoxetine, is the only agent in class indicated for treatment-resistant depression. Approval of olanzapine/fluoxetine for the acute treatment of treatment-resistant depression was based on 3 clinical trials of 8- (2 trials) and 12-week duration. Treatment with olanzapine/fluoxetine was generally more effective than monotherapy with either olanzapine or fluoxetine in improving MADRS scores; however, results in trials have been mixed (Corya *et al* 2006, Shelton *et al* 2005, Thase *et al* 2007). In one 12-week, DB trial, olanzapine/fluoxetine was compared to olanzapine, fluoxetine, or venlafaxine monotherapy. Olanzapine/fluoxetine demonstrated a statistical MADRS advantage over all monotherapy agents after week 1 which was maintained up to week 6; however, this effect was only sustainable over olanzapine monotherapy at week 12 (Corya *et al* 2006). Other trial data demonstrated that olanzapine/fluoxetine was not significantly different compared to other antidepressants such as nortriptyline and fluoxetine monotherapy in improving MADRS scores (Corya *et al* 2006, Shelton *et al* 2005).
- Treatment with olanzapine/fluoxetine has consistently demonstrated increases in the incidence ($\geq 10\%$) of weight gain, increased appetite, somnolence, and dry mouth. Additional adverse events have varied in trials. Compared to fluoxetine and olanzapine monotherapy, the most common adverse events for olanzapine/fluoxetine (incidence $\geq 10\%$) included peripheral edema and hypersomnia, which were significantly higher than that of fluoxetine monotherapy ($p < 0.001$) (Thase *et al* 2007). Compared to olanzapine, fluoxetine or venlafaxine monotherapy, the most common adverse events for olanzapine/fluoxetine (incidence $\geq 10\%$) included dizziness, asthenia, peripheral edema, and headache. More patients in the combination therapy group discontinued due to weight gain (Corya *et al* 2006). Compared to fluoxetine,

olanzapine, and nortriptyline monotherapy, the most common adverse events for olanzapine/fluoxetine combination therapy (incidence $\geq 10\%$) were asthenia, headache, anxiety, tremor, nervousness, insomnia, and nausea (*Shelton et al 2005*).

Schizophrenia and/or Schizoaffective Disorder

- All oral atypical antipsychotic agents in class are indicated for use in schizophrenia with the exception of combination agent olanzapine/fluoxetine. Clozapine is the only agent indicated for treatment-resistant schizophrenia. Clozapine and paliperidone products, excluding Invega Trinza, are indicated for the treatment of schizoaffective disorder. The following summarizes recent MAs and SRs, landmark trials in schizophrenia, and study evidence related to newer atypical antipsychotic agents (ie, aripiprazole, brexpiprazole, loperidone, and lurasidone) that do not have extensive trial evidence.
- Based on a 2012 AHRQ SR of 125 trials evaluating typical and atypical antipsychotics, a total of 113 measured efficacy and safety in adults with schizophrenia or schizophrenia-related psychoses. Compared to haloperidol, there was no difference in PANSS (and/or Scale for the Assessment of Positive Symptoms [SAPS]) score for positive symptoms for aripiprazole, clozapine, olanzapine, quetiapine, and risperidone. Outcomes measuring negative symptoms demonstrated a significant difference in PANSS scores favoring aripiprazole for 1701 patients in 3 trials, risperidone for 4043 patients in 20 trials, and olanzapine-treatment for 3742 patients in 14 trials. When compared with haloperidol, risperidone yielded lower relapse rates for 1405 patients in 6 trials and olanzapine provided better response rates for 4099 patients in 14 trials and remission rates for 582 patients in 3 trials. The most common adverse effects with significant differences were in the category of EPS and most often involved haloperidol. Haloperidol appears to be equally effective to treatment with the atypical antipsychotics in terms of positive symptoms; however, for negative symptom scores aripiprazole, risperidone, and olanzapine may be better options for treatment. Olanzapine and risperidone may be better options when remission/relapse rates are considered (*Abou-Setta et al 2012*).
- One large, recent Bayesian MA of 212 RCTs compared 15 antipsychotic medications for efficacy and safety outcomes in patients with schizophrenia or related disorders in short term trials. The primary endpoint was efficacy measured by mean overall change in symptoms after 6 weeks and all antipsychotics were significantly more effective than placebo. Clozapine had the greatest mean difference in the change in symptom scores and was significantly superior to all other antipsychotics, including olanzapine and risperidone which have demonstrated some efficacy in treatment-resistant patients. After clozapine, olanzapine, and risperidone were significantly more effective than the other antipsychotics apart from paliperidone. Overall, effect sizes were small and there were some inconsistencies between results, but the authors did not consider that this was substantial enough to change the results. Safety assessment for the FDA-approve agents indicated that EPS was lowest for clozapine and highest for haloperidol; sedation was lowest for risperidone and highest for clozapine; weight gain was lowest for haloperidol and highest for olanzapine; prolactin increase was lowest for aripiprazole and highest for paliperidone; and QT prolongation was lowest for lurasidone and highest for ziprasidone. The authors concluded that the properties of antipsychotic drugs differed greatly among agents and that treatment should be fit to individual patients' needs. As the MA had many limitations, including substantial differences between studies, and uncertainties surround indirect comparisons, generalizability of the findings and authors' conclusions are limited. This is similar to many large atypical antipsychotic MAs (*Leucht et al 2013*).
- One Cochrane SR evaluated aripiprazole vs other atypical antipsychotics for the treatment of schizophrenia. Differences in efficacy between aripiprazole and other atypical antipsychotics (olanzapine, risperidone, and ziprasidone) demonstrated no advantage in terms of overall global state (defined as MD in CGI-S score) or mental state (defined as MD total change in PANSS score). When compared with any one of several new generation antipsychotic drugs in one RCT (N = 523), the aripiprazole group showed improvement in energy, mood, negative symptoms, somnolence, and weight gain. More nausea was seen in patients given aripiprazole (N = 2881; RR, 3.13; 95% CI, 2.12 to 4.61). Weight gain with aripiprazole-treatment was less common (N = 330; RR, 0.35; 95% CI, 0.19 to 0.64). Attrition ranged from 30% to 40% (no differences between groups). Due to the high attrition rates validity is limited, thereby making it difficult to make strong conclusions. There is limited data on the safety and efficacy of aripiprazole. Based on current available evidence, efficacy of aripiprazole appears to be similar and there may be benefits in terms of weight gain, but there appears to be an increased incidence of nausea compared to other agents (*Khanna et al 2014*).
- One Cochrane SR evaluated quetiapine compared to other atypical antipsychotics for the treatment of schizophrenia. Efficacy and safety were evaluated in 5971 patients across 35 RCTs. For the primary efficacy endpoint, PANSS total score, the comparator drugs may be more effective than quetiapine, but the clinical meaning of these data is unclear. There were no significant differences in efficacy between quetiapine and clozapine, but quetiapine was associated with

fewer adverse events. Quetiapine demonstrated fewer movement disorders compared to risperidone (RR, 0.5; 95% CI, 0.36 to 0.69), olanzapine (RR, 0.51; 95% CI, 0.32 to 0.81), and paliperidone (RR, 0.64; 95% CI, 0.45 to 0.91). There are limited studies; however, data provide evidence that quetiapine-treated patients may need to be hospitalized more frequently than those taking risperidone or olanzapine. Quetiapine may be slightly less effective than risperidone and olanzapine in reducing symptoms, and it may cause less weight gain and fewer side effects and associated problems (such as heart problems and diabetes) than olanzapine and paliperidone, but more than risperidone and ziprasidone (Asmal *et al* 2013).

- The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) was a large, multi-center study initiated by the National Institute of Mental Health to examine the effectiveness of SGAs compared to FGAs in patients with chronic schizophrenia. It was intended to include patients treated in typical clinical settings and to reflect typical clinical practice in which individuals with schizophrenia may require multiple medication trials before finding one that is adequately both efficacious and tolerable. The study design allowed for patients who discontinued one study antipsychotic drug to enter subsequent phases of the study to receive additional antipsychotic medications (Lieberman *et al* 2005, Stroupe *et al* 2006, Stroupe *et al* 2009). Among the unexpected outcomes was the finding that, with the exception of clozapine, the SGAs did not separate out robustly from the FGAs with respect to overall efficacy and times to treatment discontinuation. However, because of relatively high discontinuation rates across all treatment arms, potential biases regarding optimal dosing of individual drugs, and clear differences in treatment-emergent side effect profiles, the implications of CATIE are subject to interpretation which may preclude definitive guidance in developing pharmacotherapy guidelines for patients with schizophrenia as a whole.
- The efficacy of asenapine in the treatment of schizophrenia in adults was evaluated in 4 published, randomized, DB, PC, and active-controlled (haloperidol, risperidone, and olanzapine) trials, ranging in duration from 6 weeks to 1 year (Kane *et al* 2011, Kane *et al* 2010[a], Potkin *et al* 2007, Schoemaker *et al*, 2010). Asenapine was associated with statistically significant improvement in PANSS scores from baseline compared to placebo, starting from week 2 of therapy. CGI-I and CGI-S scores were also significantly improved with asenapine therapy compared to placebo. Moreover, an extension study demonstrated a reduced risk of relapse associated with continuation of asenapine therapy (Kane *et al* 2011). However, a direct-comparison study suggests that asenapine is less effective than olanzapine in terms of changes from baseline in PANSS and CGI-S scores. Furthermore, study discontinuation due to inadequate efficacy was noted in only 14% of patients receiving olanzapine compared to 25% of patients in the asenapine group. Mean weight gain was 0.9 kg with asenapine and 4.2 kg with olanzapine (Shoemaker *et al* 2010). In another study, while 17% of patients receiving risperidone experienced a weight gain of at least 7% from baseline, 9% of patients in the asenapine group were noted to exhibit clinically significant weight gain (Potkin *et al* 2007).
- The safety and efficacy of brexpiprazole was evaluated in 2 DB, PC, 6-week trials in adults with schizophrenia. In the pivotal studies, brexpiprazole 2 mg and 4 mg daily doses significantly reduced the PANSS score (-20.73 and -19.65 vs -12.01 points with placebo), the primary endpoint, compared with placebo; however, in the BEACON trial, only the brexpiprazole 4 mg dose significantly reduced the PANSS score (-20 vs -13.53 points with placebo) (Correll *et al* 2015; Kane *et al* 2015[a]). The most common adverse reactions in MDD trials were akathisia (NNH, 15), increased weight (NNH, 20) and somnolence (NNH, 22); in schizophrenia trials, the most common adverse effects were increased weight (NNH, 48) and tremor (NNH, 51) (Correll *et al* 2015, Kane *et al* 2015[a], Thase *et al* 2015[b]). The safety and efficacy of brexpiprazole for maintenance therapy of schizophrenia was evaluated in a randomized, DB, MC, PC trial. It enrolled 524 patients with an acute exacerbation of psychotic symptoms to be stabilized on brexpiprazole 1 to 4 mg daily. Patients who achieved stabilization (criteria including PANSS total score \leq 70, CGI-S score \leq 4 [moderately ill], no current suicidal behavior, or violent or aggressive behavior) for 12 weeks then entered a 52-week maintenance phase where they were randomized to their stabilization dose of brexpiprazole (N = 97) or placebo (N = 105). The co-primary endpoints were time to exacerbation of psychotic symptoms or impending relapse, defined as worsening of CGI-I and PANSS scores, hospitalization due to worsening of psychotic symptoms, suicidal behavior, or violent/aggressive behavior. In the maintenance phase, 13.5% of patients in the brexpiprazole group experienced impending relapse vs 38.5% of placebo patients ($p < 0.0001$) and time to impending relapse was statistically significantly lower (Hazard ratio [HR], 0.34; $p = 0.0008$). However, based on results of an interim analysis, the trial was terminated early. Only a small number of patients were exposed to brexpiprazole for the prescribed 52 weeks and, therefore, conclusions cannot be drawn for long-term use (Fleischhacker *et al* 2016).
- The efficacy and safety of cariprazine in schizophrenia were demonstrated in 3 DB, randomized, PC, 6-week trials (Durgam *et al* 2014, Durgam *et al* 2015[b], Kane *et al* 2015[b]). A total of 1792 adult patients with acute exacerbation of schizophrenia were administered placebo or cariprazine 1.5 to 9 mg per day. Two trials were fixed-dose studies and

included active comparators, risperidone 4 mg and aripiprazole 10 mg, to assess sensitivity; one study was a flexible dose study with no active comparator. In the flexible dose study, the mean daily dose ranged from 5 to 8 mg per day (*Kane et al 2015[b]*). All doses were superior to placebo in reducing PANSS and CGI-S scores and a significant PANSS reduction was observed as soon as 7 days for the higher doses and 2 to 3 weeks for the lower doses (*FDA/CBER summary review 2015*). Of note, higher doses do result in quicker control of symptoms; however, if high doses continue resulting in accumulation of the active metabolite DDCAR it is not clear how this may influence safety results. Delayed incidences of akathisia occurred. According to pooled analysis (n = 1317 cariprazine-treated patients) within the FDA clinical summary, the most common adverse events reported in schizophrenia trials were EPS (28.5%) and akathisia (11.2%) (*FDA/CBER summary review 2015*). The akathisia observed at cariprazine doses ≤ 6 mg is comparable to those observed with aripiprazole, but accumulation of the DDCAR metabolite may result in later-onset effects. In schizophrenia studies, 4% of patients with normal hemoglobin A1c developed elevated levels ($\geq 6.5\%$). The proportion of patients with weight increase $\geq 7\%$ from baseline ranged from 8 to 17% across cariprazine doses. In an OL 48-week extension (N = 97) of a 6-week trial, safety and tolerability were found to be maintained. The most common adverse events were akathisia (14%), insomnia (14%), and weight gain (11.8%) (*Durgam et al 2014, Durgam et al 2017*). Another study evaluated cariprazine for maintenance therapy for schizophrenia relapse in 765 patients. A flexible-dose, OL, 8-week, run in phase was followed by a 12-week, fixed-dose, stabilization phase. Patients completing the OL phase (N = 264) entered a DB phase and received cariprazine (3 to 9 mg/day), or placebo for up to 72 weeks. During the DB phase, 24.8% of the cariprazine group experienced relapse vs 47.5% of the placebo group (HR, 0.45; 95%CI, 0.28 to 0.73). Time to relapse was statistically significantly longer for the cariprazine group vs placebo (25th percentile time to relapse, 224 vs 92 days, respectively; $p < 0.001$). The long-term safety profile of cariprazine was found to be consistent with findings from previous trials (*Durgam et al 2016*).

- Iloperidone has been studied as monotherapy for the treatment of adults with an acute or subacute exacerbation of schizophrenia. Three 6-week, randomized, DB, placebo- and active comparator (risperidone and haloperidol)-controlled studies found iloperidone to be significantly more effective than placebo (*Potkin et al 2008*). Another 4-week, placebo- and active comparator- (ziprasidone) controlled study found a significant improvement in PANSS scores with iloperidone therapy compared to placebo (*Cutler et al 2008*). Two MAs of these 4 studies corroborated earlier data, finding iloperidone more effective than placebo in terms of improvement from baseline in various subscales of the PANSS scale and BPRS scores (*Citrome et al 2011, Citrome et al 2012*). The long-term efficacy and safety of iloperidone in the treatment of schizophrenia was evaluated in an MA that pooled the follow-up data (up to 52 weeks) from 3 prospective RCTs. The MA found the long-term efficacy of iloperidone, assessed via the time to relapse endpoint, to be comparable to haloperidol ($p = 0.85$), with a more favorable long-term safety profile (*Kane et al 2008*). Moreover, another MA designed to evaluate the short-term safety of iloperidone found the following dose-related adverse effects: dry mouth, dizziness, somnolence and dyspepsia. EPS was noted in association with iloperidone but was more common with haloperidol and risperidone therapies. Iloperidone was also associated with QTc prolongation and weight gain (1.5 to 2.1 kg) (*Weiden et al 2008*). The efficacy of iloperidone for relapse-prevention during maintenance phase of schizophrenia treatment was evaluated in a DB, PC, randomized withdrawal study. Patients were not blinded and were stabilized for 24 weeks. If clinically stable for 12 weeks, they were then randomized to iloperidone (8 to 24 mg/day) (N = 153) or placebo (N = 150) for 26 weeks. The primary endpoints were time to relapse and proportion of patients experiencing relapse (defined as hospitalization due to worsening schizophrenia, worsening of PANSS and CGI-I scores, suicidal or aggressive behavior, or treatment escalation [ie, dose increases or additional medications]). The trial was stopped early due to superior iloperidone relapse prevention. Time to relapse was statistically significantly longer with iloperidone vs placebo (140 vs 95 days, respectively; $p < 0.0001$). The relapse rate for placebo was 64% vs 17.9% for iloperidone ($p < 0.0001$). The safety was comparable to other trial results, with dizziness, insomnia, headache, dry mouth, and somnolence being the most common adverse events. Weight gain $\geq 7\%$ occurred in 25.2% of iloperidone-treated patients in the relapse-prevention phase. Mean change in QTcF from baseline was 4.9 ms in the iloperidone group (vs 1 ms in placebo) during the relapse-prevention phase. Rates of EPS (2.5% in stabilization phase/1.3% in relapse-prevention phase) and akathisia (3.7% and 1%, respectively) were consistently low in iloperidone-treated patients as well (*Weiden et al 2016*).
- Lurasidone was investigated for the treatment of adult patients with acute and chronic symptoms of schizophrenia in 2 PC, 6-week studies and two 21-day studies directly comparing the safety and efficacy of lurasidone 120 mg once daily with ziprasidone 80 mg twice daily. In PC studies, lurasidone dosed 40, 80, or 120 mg once daily was associated with significant improvements from baseline in PANSS and the BPRS scores, compared to placebo (*Meltzer et al 2011, Nakamura et al 2009*). The 2 direct-comparison studies demonstrated comparable improvements in the lurasidone and ziprasidone groups in terms of the reduction in total PANSS, PANSS positive symptom, PANSS general symptom, CGI-

S scores, and several cognition scales. Likewise, the 2 groups were comparable in terms of rates of discontinuation for any reason and discontinuation due to adverse events (*Harvey et al 2011, Potkin et al 2011*). Of note, lurasidone was more effective in improving negative symptom PANSS scores compared to ziprasidone ($p = 0.046$). Both therapies were associated with a small weight loss from baseline and neither therapy was associated with a clinically significant electrocardiogram abnormality. Extrapyramidal adverse events were noted in 3.3% of patients in the ziprasidone group and in 3.3% of patients receiving lurasidone (*Potkin et al 2011*). The efficacy of lurasidone in maintenance treatment was evaluated in a DB, PC, RCT. Patients ($N = 676$) with schizophrenia experiencing an acute exacerbation entered into an OL stabilization phase for 12 to 24 weeks. Patients achieving stabilization for 12 weeks ($N = 285$) were randomized into a 28-week, DB phase to receive lurasidone (40 to 80 mg/day), or placebo. The probability of relapse at the 28-week point was 42.2% vs 51.2% in the lurasidone and placebo groups, respectively ($NNT = 12$). Lurasidone statistically significantly delayed the time to relapse vs placebo ($p = 0.039$). In patients receiving lurasidone in both the OL and DB phases, the most common adverse events were akathisia (16.7%), insomnia (12.5%), and headache (11.8%) (*Tandon et al 2016*).

Long-Acting Injectable Atypical Antipsychotics:

Bipolar Disorder

- Risperidone long-acting injection is the only long-acting injection FDA-approved for bipolar I disorder as monotherapy or in combination with lithium or valproate for maintenance therapy. Compared to placebo, risperidone long-acting injection has demonstrated superior efficacy in acute and non-acute patients with similar safety effects to that of oral risperidone (*Mcfadden et al 2009, Quiroz et al 2010, Vieta et al 2012, Yatham et al 2007*).
- For maintenance therapy, risperidone long-acting injection monotherapy has demonstrated inconsistent results regarding the endpoint of delayed time to recurrence of any mood episode compared to placebo (*Quiroz et al 2010, Vieta et al 2012*). When risperidone long-acting injection was used in combination with mood stabilizers (eg, lithium and valproate), antidepressants, or anxiolytics, the time to relapse was significantly longer with fewer proportions of patients relapsing compared to placebo (*Mcfadden et al 2009*). An exploratory post hoc analysis showed that the time to recurrence of any mood episode was also significantly longer with oral olanzapine compared with risperidone long-acting injection ($p = 0.001$) (*Vieta et al 2012*). The adverse effect profile of long-acting injection therapy is not fully understood; however, EPS, weight gain, hyperprolactinemia, and cardiovascular events were observed in risperidone long-acting injection therapy trials (*Mcfadden et al 2009, Quiroz et al 2010, Vieta et al 2012, Yatham et al 2007*).

Schizophrenia

- All 6 long-acting injectable atypical antipsychotics are FDA-approved for the treatment of schizophrenia in adults. These agents include Abilify Maintena (aripiprazole ER), Aristada (aripiprazole lauroxil), Zyprexa Relprevv (olanzapine pamoate), Invega Sustenna (paliperidone palmitate once-a-month injection), Invega Trinza (paliperidone palmitate once-every-3-months injection), and Risperdal Consta (risperidone microspheres). Invega Sustenna is the only agent FDA-approved for the treatment of schizoaffective disorder as monotherapy and as an adjunct to mood stabilizers or antidepressants.
- A number of MAs and SRs have been conducted evaluating long-acting injection atypical antipsychotics compared to oral antipsychotics for the treatment of schizophrenia. Comparative effectiveness data between long-acting injectable atypical antipsychotics are lacking and there is insufficient evidence to draw firm conclusions. The most recent, well-designed MAs have been summarized for efficacy and safety evaluations.
- One MA of atypical antipsychotics included 13 RCTs measuring the efficacy and safety of long-acting injection atypical antipsychotics vs oral antipsychotics or placebo in patients with schizophrenia. Long-acting injectable atypical antipsychotics were not associated with a significant decrease in the PANSS total score from baseline from oral antipsychotics ($p = 0.33$); therefore, both formulations had similar efficacy. No additional significant differences were noted. The long-acting injectable atypical antipsychotics were associated with a higher incidence of EPS compared to placebo ($p < 0.001$) and oral antipsychotics ($p = 0.048$) (*Fusar-Poli et al 2013*).
- One SR and MA of long-acting antipsychotic injectable agents (including typical and atypical agents) measured the safety and efficacy of treatment compared to oral antipsychotics in 21 RCTs (11 trials measured atypical antipsychotic agents). Patients with schizophrenia, schizophreniform, or schizoaffective disorder were evaluated in longer duration trials of greater than or equal to 6 months. Long-acting injectable antipsychotics were similar to oral antipsychotics for relapse prevention in outpatient studies lasting ≥ 1 year (RR, 0.93; 95% CI, 0.71 to 1.07; $p = 0.03$). Among individual long-acting injectable antipsychotics, only fluphenazine was superior to oral antipsychotics in drug efficacy ($p = 0.02$).

and in preventing hospitalization ($p = 0.04$). There was no difference between each individual long-acting injectable antipsychotic and pooled long-acting injectable antipsychotics compared to oral antipsychotics regarding discontinuation due to adverse events ($p = 0.65$) (*Kishimoto et al 2013*).

- One MA compared outcomes for once-monthly long acting injections of paliperidone palmitate and risperidone across 7 RCTs. Paliperidone palmitate was less likely to show no improvement in global state (defined as reduction in PANSS scores) vs placebo (RR, 0.79; 95% CI, 0.74 to 0.85). When comparing both active treatments, one trial favored paliperidone palmitate and one trial favored risperidone long-acting injection; therefore, conclusions could not be made. In terms of safety, paliperidone palmitate and risperidone long-acting injection were similar. Compared to placebo, paliperidone palmitate led to significant elevations in serum prolactin, regardless of patient gender (*Nussbaum et al 2012*).
- One SR of 41 trials measuring safety concluded that long-acting injectable atypical antipsychotics are associated with similar adverse effects to that of oral formulations, and no clinically significant trends can be conclusively drawn. Data suggested that olanzapine pamoate was associated with dose-dependent weight gain, lipid and glucose metabolism issues, and may increase prolactin levels even at low doses. Post-injection syndrome, due to accidental intravascular injection of olanzapine pamoate, was characterized by delirium and/or excessive sedation (incidence, 1.2%). The risperidone long-acting injection may increase the risk of QT prolongation, although the clinical significance is unknown. Hyperprolactinemia, EPS, cardiovascular events (ie, tachycardia and orthostatic hypotension), and weight gain are known side effects of risperidone long-acting injection and paliperidone palmitate. The most common adverse event associated with paliperidone palmitate was worsening of psychotic symptoms (incidence, 3.5% to 16%) (*Gentile et al 2013*).
- Two additional long-acting injectable agents were approved in 2015, Aristada (aripiprazole lauroxil) and Invega Trinza (paliperidone palmitate once-every-3-months injection).
 - The safety and efficacy of aripiprazole lauroxil in adult patients with schizophrenia was established in one PC, DB, RCT of 622 patients over a period of 12 weeks. Oral aripiprazole was administered concomitantly for the first 3 weeks of treatment. The PANSS total score was significantly decreased at day 85 by 10.9 with monthly intramuscular (IM) injections of aripiprazole lauroxil 441 mg and by 11.9 with 882 mg IM monthly compared with placebo ($p < 0.001$ for both). PANSS was significantly improved as early as day 8 and maintained throughout the study. In terms of safety, more than double the proportion of patients taking aripiprazole lauroxil experienced akathisia (441 mg, 11.6%; 882 mg, 11.5%) compared to placebo (4.3%). The majority of the akathisia (75%) was experienced before the second injection within the first 3 weeks. Additional treatment-emergent adverse effects (incidence $\geq 2\%$) included insomnia, headache, and anxiety (*Meltzer et al 2015*).
 - The FDA-approval of Invega Trinza, the 3-month IM paliperidone palmitate injection, was based on one PC, OL/DB trial of 305 patients with schizophrenia experiencing acute symptoms. Prior to administration of paliperidone palmitate once every 3 months injection, patients were administered flexible oral doses for 17 weeks, and then administered the paliperidone palmitate once monthly injection for 12 weeks. If stable, patients were then administered the once every 3 month injection. Paliperidone palmitate once every 3 months injection significantly lengthened the median time to first relapse vs placebo. The mean change in PANSS total scores showed greater improvement in the paliperidone group compared to placebo ($p < 0.001$). Due to the low percentage of relapse in treated patients (7.4%), the median time was not estimated; however, in the placebo group, 23% experienced relapse, with a median time of 274 days. The trial was stopped early due to demonstration of efficacy. Those adverse events noted more frequently in the group receiving paliperidone palmitate vs the placebo group included headache (9 vs 4%), weight increased (9% vs 3%), nasopharyngitis (6% vs 1%), and akathisia (4% vs 1%) (*Berwaerts et al 2015*).

CLINICAL GUIDELINES

- The use of these agents for the treatment of schizophrenia is recognized by national and international guidelines as a mainstay in therapy. Guidelines vary by indication and the following outlines use in children, adolescents, and adults:
Adults
 - Bipolar disorders – Guidelines recommend the use of drugs such as lithium, anticonvulsants and/or antipsychotics for the treatment of bipolar disorders (*Hirschfeld et al 2002, Hirschfeld et al 2005, VA/DoD 2010*).
 - Drugs likely to be beneficial for bipolar mania include lithium, anticonvulsants (eg, valproate, carbamazepine), and atypical antipsychotics. Lithium or valproate may be combined with an atypical antipsychotic.
 - Treatment options for bipolar depression include lithium, lamotrigine, and certain atypical antipsychotics (eg, quetiapine, olanzapine in combination with fluoxetine, and lurasidone).

- MDD – In general, guidelines state that no particular antidepressant agent is superior to another in efficacy or time to response. Choice can be guided by matching patient's symptoms to side effect profile, presence of medical and psychiatric comorbidity, and prior response (*VA/DoD 2016; Gelenberg et al 2010*).
 - For the majority of patients, an SSRI, SNRI, bupropion or mirtazapine is optimal for first-line treatment. Atypical antipsychotics may be useful to augment antidepressant therapy (*Gelenberg et al 2010*).
- Schizophrenia – Guidelines recommend that agents should be chosen based on clinical circumstances and side effects. Clozapine has the greatest efficacy on persistent hostility, aggressive behavior, suicidal behavior, and should be considered in patients with suicidal ideation; recent evidence has also demonstrated there may be lower rates of overall mortality with clozapine use. Clozapine should be used to treat persistent psychotic symptoms or treatment-resistant patients. A minimum of 6 weeks is needed for an adequate trial to establish efficacy. If a patient is non-adherent to treatment or has chronic relapse, a long-acting injectable antipsychotic agent may be considered (*Dixon et al 2009; Lehman et al 2004; VA Pharmacy Benefits Management Services 2012*).

Children and Adolescents

- Use of atypical antipsychotics - According to guidelines from the American Academy of Child and Adolescent Psychiatry (AACAP), prior to the initiation of antipsychotic therapy, patients should undergo a thorough diagnostic assessment and evaluation for comorbid medical conditions and concomitant medications. Furthermore, a multidisciplinary plan that includes education and psychotherapy should be established. The prescriber should also have a thorough discussion about the risks and benefits of psychotropic treatment (*Findling et al 2011*).
- Autism Spectrum Disorders (ASD) – AACAP guidelines state that pharmacotherapy may be considered in children with ASD when there is a specific target symptom or comorbid condition. Risperidone and aripiprazole are FDA-approved for irritability associated with autism; other drugs that have been studied include: clonidine, olanzapine, valproic acid, lamotrigine, levetiracetam, clomipramine, amantadine, pentoxifylline (in combination with risperidone), and naltrexone (*Volkmar et al 2014*).
- Bipolar disorder – According to AACAP guidelines for treatment of children and adolescents with bipolar disorder, pharmacotherapy is the primary treatment for bipolar mania. Standard therapy includes lithium, valproate, and/or atypical antipsychotic agents, with other adjunctive medications used as indicated (*McClellan et al 2007*).
- Schizophrenia – According to AACAP guidelines, antipsychotics are a primary treatment for schizophrenia spectrum disorders in children and adolescents. The choice of agent is typically based on factors such as FDA-approval status, side effect profile, patient and family preference, and cost (*McClellan et al 2013*).
- Tourette's disorder – According to AACAP guidelines for the treatment of children and adolescents with tic disorders, pharmacotherapy should be considered for moderate to severe tics causing severe impairment in quality of life, or when psychiatric comorbidities are present that can also be targeted. Most clinicians use atypical antipsychotics before first-generation agents and some prefer α -agonists over antipsychotic medications due to the adverse effect profile. Commonly used drugs include risperidone, aripiprazole, and clonidine (*Murphy et al 2013*).

SAFETY SUMMARY

- Ziprasidone is contraindicated in patients with recent acute myocardial infarction (MI), uncompensated heart failure (HF), and history of QT prolongation, or is taking drugs that have demonstrated QT prolongation. Lurasidone is contraindicated for concomitant use with strong CYP3A4 inducers and/or inhibitors. Lastly, asenapine is contraindicated in patients with severe hepatic impairment.
- All atypical antipsychotic agents have a boxed warning for increased mortality in elderly patients with dementia-related psychosis. Those agents (ie, aripiprazole, lurasidone, brexpiprazole, quetiapine, quetiapine ER, and olanzapine/fluoxetine) indicated for depressive episodes carry a boxed warning for an increased risk of suicidal thoughts and behaviors. Zyprexa Relprevv has a boxed warning for incidences of post-injection delirium and/or sedation syndrome. Lastly, clozapine-containing agents (ie, Clozaril, Fazaclo, and Versacloz) have a boxed warning for severe neutropenia, orthostatic hypotension, bradycardia, syncope, seizures, myocarditis, and cardiomyopathy.
- The atypical antipsychotics have warnings relating to risks of neuroleptic malignant syndrome, tardive dyskinesia, metabolic changes, falls, orthostatic hypotension, leukopenia/neutropenia/agranulocytosis, seizures, cognitive and motor impairment, body temperature dysregulation, suicide, and dysphagia. Additional warnings for various agents include:
 - Aripiprazole: Pathological gambling and other compulsive behaviors
 - Clozapine-containing products: Hepatotoxicity, QT prolongation, pulmonary embolism, fever, and anticholinergic toxicity
 - Iloperidone: QT prolongation, hyperprolactinemia, and priapism

- Ziprasidone: QT prolongation, severe cutaneous reactions (eg, Drug Reaction with Eosinophilia and Systemic Symptoms [DRESS] and Stevens-Johnson syndrome), hyperprolactinemia, and priapism
- Paliperidone: QT prolongation, hyperprolactinemia, priapism, and potential for gastrointestinal obstruction (due to non-deformable tablet)
- Lurasidone: Hyperprolactinemia
- Risperidone: Priapism and hyperprolactinemia
- Asenapine: QT prolongation, hyperprolactinemia, and hypersensitivity reactions
- Quetiapine: QT prolongation, cataracts, hypothyroidism, and hyperprolactinemia
- Olanzapine: DRESS and hyperprolactinemia
- Clozapine-containing products and Zyprexa Relprevv are a part of the Risk Evaluation and Mitigation Strategies (REMS) program. Registry, training, and counseling is required as part of both programs (*REMS@FDA 2017*). Clozapine products also require certain laboratory levels prior to prescribing. Zyprexa Relprevv requires patients to be observed in clinic for 3 hours after administration. In December 2016, the FDA announced that the full clozapine REMS program would not be implemented in 2016 due to technical and logistical challenges. The date of full launch is unknown (*FDA safety communication [clozapine] 2016*).
 - In September 2015, the FDA made modifications to the clozapine REMS program. The absolute neutrophil count (ANC) requirements were modified to a lower ANC level. Benign ethnic neutropenia (BEN) patients were also included as now eligible for clozapine-treatment (*FDA safety communication [clozapine] 2015*).
- Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at an increased risk of extrapyramidal and/or withdrawal symptoms. Neonates exposed to fluoxetine, a component of Symbyax, late in the third trimester have developed complications arising immediately upon delivery requiring prolonged hospitalization, respiratory support, and tube feeding. These drugs should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In general, a decision should be made whether to discontinue nursing or to discontinue the antipsychotic drug, taking into account the importance of the drug to the mother. It is recommended that women do not breastfeed during treatment with iloperidone, olanzapine, and ziprasidone.
- Many factors are taken into consideration when prescribing an atypical antipsychotic, including co-morbid conditions and safety risks. Common adverse events observed within the class include EPS, sedation, increased prolactin levels, autonomic effects, metabolic effects, and cardiac risks including the risk of ventricular arrhythmias (QT prolongation). Table 3 outlines the relative adverse event trends observed between the various atypical antipsychotic agents:



Table 3. Relative adverse event risk observed in trials for atypical antipsychotic agents

Adverse Event	Aripiprazole	Asenapine	Brexipiprazole	Cariprazine	Clozapine*	Iloperidone	Lurasidone	Olanzapine	Paliperidone	Quetiapine	Risperidone	Ziprasidone
	Low	Moderate	Low	Low	High	Low	Moderate	Moderate	Low	Moderate	Low	Low
Sedation – sleepiness	Low	Moderate	Low	Low	High	Low	Moderate	Moderate	Low	Moderate	Low	Low
Diabetes	Low	Moderate	Low	Low	Very high	Moderate	Negligible to low	High	High	High	High	Negligible to low
EPS – akathisia (motor restlessness), parkinsonism (tremor, rigidity, and slow movements), dystonia (continuous muscle spasms or contractions), and tardive dyskinesia (jerky movements).	Low	Moderate	Low	Moderate	Negligible to low	Negligible to low	Moderate	Low	High	Negligible to low	High	Low
Anticholinergic – blurred vision, constipation, dry mouth, drowsiness, memory impairment, etc.	Negligible	Negligible	Negligible to low	Negligible to low	High	Low	Negligible	Moderate	Negligible	Moderate	Low	Negligible
Orthostasis – low blood pressure resulting in dizziness when standing up.	Negligible	Low	Negligible to low	Negligible to low	High	High	Low	Low	Moderate	Moderate	Low	Low
Weight Gain	Low	Moderate	Low	Low	Very high	Moderate	Negligible to low	High	High	High	High	Negligible to low
Prolactin – high levels linked to gynecomastia, sexual dysfunction, menstrual disruption, acne, amenorrhea, hirsutism, osteoporosis, increased risk of hip fracture, etc.	Negligible	Moderate	Negligible to low	Negligible to low	Negligible to low	Negligible to low	Negligible to low	Low	High	Negligible to low	High	Low
QT prolongation	Negligible to low	Low	Negligible to low	Negligible to low	Low	Moderate	Negligible to low	Low	Low	Low	Low	Moderate
Hypercholesterolemia	Negligible	Negligible	Low	Negligible to low	Very high	Moderate	Negligible to low	Very high	Low	High	Low	Negligible to low

Abbvr: EPS = extrapyramidal side effects

Note: Information is based on indirect comparisons and expert assessments; however, more head-to-head trials are warranted to substantiate observations

*Granulocytopenia or agranulocytosis has been reported in 1%. Clozapine associated with excess risk of myocarditis and venous thromboembolism (VTE), including fatal pulmonary embolism (PE).

(Jibson et al 2017)

DOSING AND ADMINISTRATION
Table 4. Dosing and administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Abilify (aripiprazole)	Tablets, orally disintegrating tablets, oral solution	Oral	Daily	Dose adjustments are recommended in known CYP2D6 poor metabolizers, or with concomitant CYP2D6 inhibitors, and/or CYP3A4 inhibitors/inducers.
Abilify Maintena (aripiprazole ER)	Injection	IM	Monthly	Must be administered by a healthcare professional. Dose adjustments are recommended in known CYP2D6 poor metabolizers, or with concomitant CYP2D6 inhibitors, and/or CYP3A4 inhibitors/inducers.
Aristada (aripiprazole lauroxil)			Monthly (441 mg, 662 mg, or 882 mg) or every 6 weeks (882 mg) or every 2 months (1064 mg)	Aripiprazole-naïve patients should establish tolerability with oral formulations prior to initiating long-acting injections.
Saphris (asenapine)	Sublingual tablets	Oral	Twice daily	Sublingual tablets should be placed under the tongue and left to dissolve completely; they should not be swallowed. Eating and drinking should be avoided for 10 minutes after administration.
Rexulti (brexpiprazole)	Tablets	Oral	Daily	Dose adjustments are recommended in known CYP2D6 poor metabolizers, concomitant moderate to strong CYP2D6 and/or CYP3A4 inhibitors, and/or CYP3A4 inducers. Dosage adjustments are recommended for hepatic and renal impairment.
Vraylar (cariprazine)	Capsules	Oral	Daily	Dose adjustments are recommended with concomitant CYP3A4 inhibitors. Concomitant use is not recommended with CYP3A4 inducers. Use of the drug is not recommended in severe hepatic or renal impairment since it has not been studied in these populations.
Clozaril (clozapine)	Tablets	Oral	Daily up to divided doses daily	Prior to initiating, a baseline ANC must be $\geq 1500/\text{mCL}$ ($\geq 1000/\text{mCL}$ for patients with BEN). To continue treatment, ANC must be monitored regularly.
Fazaclo (clozapine)	Orally disintegrating tablets			Dose adjustments are recommended in patients with renal/hepatic impairment,

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Versacloz (clozapine)	Suspension			CYP2D6 poor metabolizers, taking concomitant CYP2D6, CYP1A2, CYP3A4 inhibitors and/or CYP3A4, CYP1A2 inducers.
Fanapt (iloperidone)	Tablets	Oral	Twice daily	Dose adjustments are recommended in patients with hepatic impairment, CYP2D6 poor metabolizers, taking concomitant CYP2D6 and/or CYP3A4 inhibitors.
Latuda (lurasidone)	Tablets	Oral	Daily	Dose adjustment recommended with concomitant use with a moderate CYP3A4 inhibitor and renal/hepatic impairment. Should be administered with food (\geq 350 calories).
Zyprexa (olanzapine)	Tablets	Oral	Daily	
Zyprexa Zydis (olanzapine)	Orally disintegrating tablets			
Zyprexa (olanzapine)	Injection	IM	As needed; max. 3 doses 2 to 4 hrs apart	
Zyprexa Relprevv (olanzapine)	Injection	IM	Every 2 weeks (initial: 210 mg or 300 mg; maintenance: 150mg, 210 mg, or 300 mg) or every 4 weeks (initial: 405 mg; maintenance: 300 mg or 405 mg)	This product is available only through a restricted distribution program and must be administered by a healthcare professional; patient observation is required for at least 3 hours after injection due to the potential for Post-Injection Delirium/Sedation Syndrome. Tolerability with oral olanzapine must be established prior to initiating therapy with this long-acting injection.
Symbyax (olanzapine/fluoxetine)	Capsules	Oral	Daily	
Invega (paliperidone ER)	Tablets	Oral	Daily	Tablets should be swallowed whole and should not be chewed, divided, or crushed.
Invega Sustenna (paliperidone ER)	Injection	IM	Monthly	Must be administered by a healthcare professional. Dosage adjustment for renal impairment. For patients naïve to oral paliperidone or oral or injectable risperidone, tolerability with oral paliperidone or oral risperidone must be established prior to initiating therapy with this long-acting injection.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Invega Trinza (paliperidone ER)	Injection	IM	Every 3 months	Must be administered by a healthcare professional. Prior to initiation, patients must have been adequately treated with Invega Sustenna for at least 4 months. Dosage adjustment for renal impairment.
Seroquel (quetiapine)	Tablets	Oral	Daily to twice daily	Dosage adjustment for hepatic impairment, geriatric use, and with concomitant CYP3A4 inhibitors and/or inducers.
Seroquel XR (quetiapine ER)	Tablets	Oral	Daily	Tablets should be swallowed whole and not split, chewed, or crushed. Dosage adjustment for hepatic impairment, geriatric use, and with concomitant CYP3A4 inhibitors and/or inducers
Risperdal (risperidone)	Tablets, oral solution	Oral	Daily to twice daily	Dosage adjustment for renal/hepatic impairment.
Risperdal M-Tabs (risperidone)	Orally disintegrating tablets			
Risperdal Consta (risperidone)	Injection	IM	Every 2 weeks	Must be administered by a healthcare professional. Tolerability to oral risperidone must be established prior to initiating therapy with this long-acting injection.
Geodon (ziprasidone)	Capsules	Oral	Twice daily	IM ziprasidone should be administered with caution to patients with impaired renal function as the cyclodextrin excipient is cleared by renal filtration.
	Injection	IM	As needed; 10 mg every 2 hrs or 20 mg every 4 hrs up to a maximum of 40 mg/day	

See the current prescribing information for full details

CONCLUSION

- The antipsychotics are divided into 2 distinct classes: typical antipsychotics, also called first generation antipsychotics, and atypical antipsychotics, also called second generation antipsychotics (*Miyamoto et al 2005*).
- There are a number of atypical antipsychotics formulations available as both branded and generic products. These agents are available in various dosage forms including capsules, tablets, injections, oral solutions, sublingual tablets, and orally disintegrating tablets.
- FDA-approved indications for the atypical antipsychotics include irritability associated with autistic disorder, bipolar disorder, Tourette's disorder, major depressive disorder, schizophrenia, and schizoaffective disorder. The indications vary by diagnosis, age, or by use as mono- or adjunctive-therapy. All agents in class are indicated for use in schizophrenia with the exception of combination agent Symbyax (olanzapine/fluoxetine). Clozapine and paliperidone products, excluding Invega Trinza, are indicated for the treatment of schizoaffective disorder, and clozapine is the only

agent in class FDA-approved for treatment-resistant schizophrenia. Aripiprazole, lurasidone, olanzapine, quetiapine and risperidone are approved for use in patients ≥ 13 years of age and paliperidone oral products are approved for patients ≥ 12 years of age with schizophrenia. All oral agents in class are indicated for use in bipolar disorder, except clozapine, iloperidone, paliperidone, and brexpiprazole. Risperidone long-acting injection is the only long-acting injectable indicated for the treatment of bipolar disorder. Aripiprazole, olanzapine/fluoxetine, risperidone, quetiapine, and asenapine are approved for use in pediatric patients ≥ 10 years of age with bipolar disorder. Olanzapine is approved for use in patients ≥ 13 years of age with bipolar disorder. Aripiprazole and risperidone are the only agents indicated for the treatment of irritability associated with autistic disorder in pediatric patients (aged 6 to 17 years, and 5 to 17 years, respectively). Aripiprazole is the only agent indicated for the treatment of Tourette's disorder in pediatric patients, aged ≥ 6 years. Aripiprazole, brexpiprazole, and quetiapine ER are indicated as adjunctive treatment for major depressive disorder in patients already taking an antidepressant. Olanzapine, when prescribed in combination with fluoxetine, is indicated for treatment-resistant depression.

- Comparative effectiveness data are most available for the treatment of schizophrenia and schizophrenia-like psychosis in adults; however, outcomes are often inconsistent. Study evidence demonstrates that there are no consistent differences in the efficacy between the atypical antipsychotics in acute or short-term trials, although clozapine has often been touted as significantly more effective for patients with treatment-resistant schizophrenia compared to all other atypical antipsychotics (*Leucht et al 2013, Lieberman et al 2005, Stroupe et al 2006, Stroupe et al 2009*). In general, clozapine is often followed by olanzapine and risperidone in terms of improved efficacy (*Lehman et al 2004, Leucht et al 2013*). There is also very little evidence evaluating the long-acting injection agents and newer agents brexpiprazole, cariprazine, iloperidone, and lurasidone. Challenges associated with comparative effectiveness reviews are mainly due to high attrition rates, internal validity study concerns, and small sample sizes within trials.
- Each atypical antipsychotic has a distinctive chemical structure, mechanism of action, and neuropharmacologic and adverse event profile. It should be noted that paliperidone is an active metabolite of risperidone and therefore carries some similarity in chemical structure and pharmacologic effects with the parent drug. Plasma levels of cariprazine and its metabolite accumulate over time; adverse reactions may not appear until after several weeks of drug administration.
- Safety profiles vary between agents and are often an important component of treatment selection. The long-acting injection antipsychotics are often prescribed for patients who demonstrate adherence issues with oral formulations. Common adverse events observed within the class include EPS, increased prolactin levels, autonomic effects, metabolic effects, and cardiac risks including risk of ventricular arrhythmias (QT prolongation). When compared to the typical antipsychotics, the atypical antipsychotics are associated with a lower risk of EPS and tardive dyskinesia, making them a generally better-tolerated treatment option (*Abou-Setta et al 2012, Lehman et al 2004, VA Pharmacy Benefits Management Services 2012, Clinical Pharmacology 2017*). However, certain atypical antipsychotic agents appear to have varying levels of risk according to the side effect profile (*Jibson et al 2017; Micromedex 2017*). The following factors may be considered when selecting certain agents in patients:
 - Metabolic syndrome – Metabolic effects influencing weight gain, glycemic effects, and lipid profiles have been reported to fluctuate with all atypical antipsychotics. Clozapine and olanzapine have been associated with the highest risks; aripiprazole, lurasidone, and ziprasidone have been associated with lower risks. Despite the stratified risks, routine monitoring of metabolic measures is recommended for patients on all antipsychotics.
 - EPS or tardive dyskinesia – Atypical antipsychotics have a lower risk of these side effects compared to typical antipsychotic agents. Tardive dyskinesia risks have been reported to be similar to the prevalence of EPS. Risperidone has been associated with a higher risk of EPS (up to 25% in adults); clozapine and quetiapine carry the lowest risk.
 - Anticholinergic effects – Anticholinergic side effects include dry mouth, constipation, blurred vision, and urinary retention. Clozapine has the strongest affinity for muscarinic receptors among the agents in class; therefore, anticholinergic side effects are reported most often. This is followed by olanzapine and quetiapine.
 - QT prolongation – QT prolongation has been reported with a number of atypical antipsychotic agents, but to a lesser degree than other classes of medications. Iloperidone and ziprasidone have been reported to prolong the QT interval (average increase in QTc of 9 to 10 msec) most often, and should be avoided in high risk patients. Those less likely to cause cardiac arrhythmias include aripiprazole, lurasidone, and cariprazine; however, very few studies have been conducted with lurasidone and cariprazine.
 - Myocarditis and cardiomyopathy – Clozapine has been associated with fatal cases, often within the first few months of treatment.
 - Orthostatic hypotension and tachycardia – Changes in heart rate and blood pressure are most frequently observed with clozapine (9% to 25%) and iloperidone (3% to 12%). In pediatric patients, quetiapine has been associated with increased systolic/diastolic pressure in 15% to 41% of patients, but in adults orthostatic hypotension and tachycardia

have been reported in up to 7% of patients. Tachycardia has been reported in up to 16% of paliperidone-treated adult patients. Hypotension has been reported less frequently with aripiprazole, asenapine, brexpiprazole, cariprazine, and lurasidone. However, fewer studies have been conducted with the newer agents.

- Seizure – All atypical antipsychotics carry a risk for seizures; however, this appears to be associated with lowering the seizure threshold vs new-onset seizures. Incidences of seizure are most often reported with clozapine (3% to 5%), and to a lesser degree risperidone (0.3%).
- Prolactin levels and sexual side effects – Elevations of prolactin have been most associated with risperidone and paliperidone. This is particularly concerning in pediatric patients as it is associated with changes in estrogen and testosterone levels and may result in gynecomastia and menstrual disturbances. In pediatric patients administered risperidone, hyperprolactinemia has been reported in 49% to 87% of patients versus adults in which incidences range from 1% to 4% depending on formulation (IM or oral routes). Abnormal prolactin levels have also been associated with sexual dysfunction, infertility and galactorrhea. Of the atypical antipsychotics that are well studied, prolactin abnormalities are less frequently reported with olanzapine and ziprasidone. For patients in which sexual dysfunction is a concern, a number of MAs have referred to aripiprazole as the drug of choice (*Serretti et al 2011*).
- Sedation – Clozapine is most associated with sedation (46%), followed by olanzapine (20% to 52%) and quetiapine (18% to 57%). In class, aripiprazole is unique as insomnia was reported in $\geq 10\%$ of adult patients, but somnolence/fatigue and insomnia were reported in $\geq 10\%$ of pediatric patients.
- Agranulocytosis – Agranulocytosis, leukopenia, and neutropenia are associated with use of clozapine. Within the first few months of treatment, this is particularly evident in patients with pre-existing low blood counts or those who had prior drug-induced blood dyscrasias.
- Hypersensitivity – Olanzapine and ziprasidone have a specific warning for a fatal drug reaction with eosinophilia and systemic symptoms or DRESS. Asenapine has a warning for hypersensitivity reactions.
- Newly FDA-approved agent, cariprazine, has demonstrated safe and effective use in doses ≤ 6 mg/day for the treatment of bipolar disorder or schizophrenia in short-term adult trials (*Calabrese et al 2015, Durgam et al 2015[a], Durgam et al 2014, Durgam et al 2015[b], FDA/CBER summary review 2015, Kane et al 2015[b], Sachs et al 2014*). The most common adverse events with treatment are EPS and akathisia. The clinical implications of the long half-life have not been well characterized and some experts have cited safety concerns associated with the accumulating active metabolite. One 72-week (N = 264) and one 48-week (N = 97) extension trial in patients with schizophrenia have demonstrated comparable results to short-term trials of 6 weeks. Patients who are able to persist on treatment maintained efficacy and tolerability at cariprazine doses of 1.5 mg to 9 mg daily during maintenance therapy (*Durgam et al 2016, Durgam et al 2017*).
- For the treatment of Tourette's disorder, aripiprazole has demonstrated safe and effective use compared to placebo in trials of 8 to 10 weeks in pediatric patients aged ≥ 6 years. Adverse events most frequently observed included sedation-like effects, nausea, headache, nasopharyngitis, and increased appetite (*Abilify prescribing information 2017, Gulisano et al 2011, Yoo et al 2013*).
- For the treatment of irritability associated with autism, one small, low quality study (N = 59) compared the effects of aripiprazole and risperidone in patients aged 4 to 18 years over a period of 8 weeks, although FDA-approval stipulates therapy should be initiated for ages 5 to 6 years. No differences were detected in terms of safety or efficacy; however, the ABC-I scores numerically favored risperidone ($p = 0.06$) (*Ghanizadeh et al 2014*). Both agents have demonstrated safe and effective use in placebo controlled trials (*Marcus et al 2009, McCracken et al 2002, Owen et al 2009, Shea et al 2004, McDougle et al 2005*). Based on current data, both agents appear to have similar efficacy and safety.
- For the treatment of MDD, aripiprazole, brexpiprazole, and quetiapine ER have demonstrated effectiveness when combined with adjunctive treatment, generally in trials with a 6-week duration and combined with an SSRI or SNRI. Olanzapine/fluoxetine (Symbyax) has also demonstrated effectiveness in treatment-resistant depression. Most studies have been PC trials. Brexpiprazole is the newest agent to be FDA approved; results from RCTs and an MA demonstrate efficacy vs placebo, and the safety profile appears to be similar to aripiprazole (*Thase et al 2015[a], Thase et al 2015[b], Yoon et al 2017*). One MA found all agents were more effective than antidepressant monotherapy in improving response and remission rates, although adjunctive atypical antidepressant therapy was associated with a higher discontinuation rate due to adverse effects (*Wen et al 2014*). Another MA concluded aripiprazole and quetiapine may have an advantage in reducing remission (NNT, 9) compared to olanzapine/fluoxetine (NNT, 19) (*Spielmann et al 2013*). More well-designed, head-to-head trials are needed to validate conclusions. Treatment was associated with several medication-specific adverse events, including akathisia (aripiprazole), sedation (quetiapine, olanzapine/fluoxetine, and

aripiprazole), abnormal metabolic laboratory results (quetiapine and olanzapine/fluoxetine), and weight gain (all drugs, especially olanzapine/fluoxetine).

- For the treatment of bipolar disorder, a number of atypical antipsychotics have demonstrated effective use for managing symptoms associated with manic or mixed episodes; however, only a few agents have demonstrated efficacy for depressive episodes. In adolescents and children, aripiprazole, olanzapine, olanzapine/fluoxetine, risperidone, quetiapine, and asenapine are FDA-approved for manic or mixed episodes, although only quetiapine and olanzapine/fluoxetine have been studied for depressive episodes. **An AHRQ SR found that atypical antipsychotics decrease mania, decrease depression symptoms slightly, and improve symptom severity and global functioning to a small extent vs placebo. In addition, they probably increase response and remission rates vs placebo for manic/mixed phases (Pillay et al 2017).** For depressive episodes, evidence is less clear, but point to efficacy with the FDA approved agents (Findling et al 2014, Detke et al 2015). Support for use of atypical antipsychotics in adult patients with bipolar disorder have been demonstrated in several MAs (Abou-Setta et al 2012, Muralidharan et al 2013, Lindström et al 2017). Risperdal Consta is the only long-acting injection agent in class that has demonstrated safe and effective use (McFadden et al 2009, Quiroz et al 2010, Vieta et al 2012, Yatham et al 2007). Although only lurasidone, quetiapine (immediate- and extended-release), and olanzapine/fluoxetine have demonstrated efficacy for depressive episodes, MAs have concluded that olanzapine/fluoxetine may be the optimal treatment compared to other treatment options for depressive episodes (Fornaro et al 2016, Silva et al 2013, Taylor et al 2014, Vieta et al 2010).
- For the treatment of schizophrenia, MAs evaluating the roles of available atypical antipsychotics in the treatment of schizophrenia suggest that all agents are significantly more effective than placebo. Most analyses and studies have demonstrated that with the exception of clozapine, the atypical antipsychotics do not separate out robustly from the typical antipsychotics with respect to overall efficacy and times to treatment discontinuation. The trends for respective efficacy suggest that clozapine, olanzapine, and risperidone may be more effective agents based on relapse and remission rates compared to typical antipsychotics or placebo; however, many atypical antipsychotics haven't been studied to the same extent as these agents. In general, due to high attrition rates in trials, validity is limited, thereby making it difficult to make strong conclusions (Abou-Setta et al 2012, Asenjo Lobos et al 2010, Asmal et al 2013, Cipriani et al 2011, Citrome et al 2009, Durgam et al 2014, Durgam et al 2015[b], Glick et al 2011, Jones et al 2010, Kane et al 2015[b], Khanna et al 2014, Klemp et al 2011, Komossa et al 2009[a], Komossa et al 2010[a], Komossa et al 2009[b], Komossa et al 2010[b], Komossa et al 2011, Kumar et al 2013, Leucht et al 2009[a], Leucht et al 2009[b], Leucht et al 2013, Lieberman et al 2005, Pagsberg et al 2017, Perlis et al 2006[b], Pillay et al 2017, Riedel et al 2010, Stroupe et al 2006, Stroupe et al 2009, Tarr et al 2011, Vieta et al 2010, Yildiz et al 2011).
- The use of these agents for the treatment of schizophrenia is recognized by national and international guidelines as a mainstay in therapy. Guidelines vary by indication and the following outlines use in children, adolescents, and adults:

Adults

- Bipolar disorders – Guidelines recommend the use of drugs such as lithium, anticonvulsants and/or antipsychotics for the treatment of bipolar disorders (Hirschfeld et al 2002, Hirschfeld et al 2005, VA/DoD 2010).
 - Drugs likely to be beneficial for bipolar mania include lithium, anticonvulsants (eg, valproate, carbamazepine), and atypical antipsychotics. Lithium or valproate may be combined with an atypical antipsychotic.
 - Treatment options for bipolar depression include lithium, lamotrigine, and certain atypical antipsychotics (eg, quetiapine, olanzapine in combination with fluoxetine, and lurasidone).
- MDD – In general, guidelines state that no particular antidepressant agent is superior to another in efficacy or time to response. Choice can be guided by matching patient's symptoms to side effect profile, presence of medical and psychiatric comorbidity, and prior response (VA/DoD 2016, Gelenberg et al 2010).
 - For the majority of patients, an SSRI, SNRI, bupropion or mirtazapine is optimal for first-line treatment. Atypical antipsychotics may be useful to augment antidepressant therapy (Gelenberg et al 2010).
- Schizophrenia – Guidelines recommend that agents should be chosen based on clinical circumstances and side effects. Clozapine has the greatest efficacy on persistent hostility, aggressive behavior, suicidal behavior, and should be considered in patients with suicidal ideation; recent evidence has also demonstrated there may be lower rates of overall mortality with clozapine use. Clozapine should be used to treat persistent psychotic symptoms or treatment-resistant patients. A minimum of 6 weeks is needed for an adequate trial to establish efficacy. If a patient is non-adherent to treatment or has chronic relapse, a long-acting injectable antipsychotic agent may be considered (Dixon et al 2009, Lehman et al 2004, VA Pharmacy Benefits Management Services 2012).

Children and Adolescents

- Use of atypical antipsychotics - According to guidelines from the American Academy of Child and Adolescent Psychiatry (AACAP), prior to the initiation of antipsychotic therapy, patients should undergo a thorough diagnostic

assessment and evaluation for comorbid medical conditions and concomitant medications. Furthermore, a multidisciplinary plan that includes education and psychotherapy should be established. The prescriber should also have a thorough discussion about the risks and benefits of psychotropic treatment (*Findling et al 2011*).

- Autism Spectrum Disorders (ASD) – AACAP guidelines state that pharmacotherapy may be considered in children with ASD when there is a specific target symptom or comorbid condition. Risperidone and aripiprazole are FDA-approved for irritability associated with autism; other drugs that have been studied include: clonidine, olanzapine, valproic acid, lamotrigine, levetiracetam, clomipramine, amantadine, pentoxifylline (in combination with risperidone), and naltrexone (*Volkmar et al 2014*).
- Bipolar disorder – According to AACAP guidelines for treatment of children and adolescents with bipolar disorder, pharmacotherapy is the primary treatment for bipolar mania. Standard therapy includes lithium, valproate, and/or atypical antipsychotic agents, with other adjunctive medications used as indicated (*McClellan et al 2007*).
- Schizophrenia – According to AACAP guidelines, antipsychotics are a primary treatment for schizophrenia spectrum disorders in children and adolescents. The choice of agent is typically based on factors such as FDA-approval status, side effect profile, patient and family preference, and cost (*McClellan et al 2013*).
- Tourette's disorder – According to AACAP guidelines for the treatment of children and adolescents with tic disorders, pharmacotherapy should be considered for moderate to severe tics causing severe impairment in quality of life, or when psychiatric comorbidities are present that can also be targeted. Most clinicians use atypical antipsychotics before first-generation agents and some prefer α -agonists over antipsychotic medications due to the adverse effect profile. Commonly used drugs include risperidone, aripiprazole, and clonidine (*Murphy et al 2013*).
- Pharmacologic therapy treatment is highly individualized and dependent on a number of patient characteristics and response to treatment. In certain patient groups, such as pediatric patients, liquid formulations are useful for better dose-control, so clinicians may titrate and taper doses in those that may have sensitive responses to treatment. Agents with different chemical structures have different clinical responses and adverse events; therefore, access to the atypical antipsychotic medication class is important in order to tailor therapies to individual patients.

REFERENCES

- Abilify [package insert]. Princeton, NJ: Otsuka America Pharmaceutical, Inc.; February 2017.
- Abilify Maintena [package insert]. Princeton, NJ: Otsuka America Pharmaceutical, Inc; February 2017.
- Abou-Setta AM, Mousavi SS, Spooner C, et al. First-generation and second-generation antipsychotics in adults: Comparative Effectiveness Review. [Monograph on the internet]. Agency for Healthcare Research and Quality (AHRQ). Rockville, MD. 2012 Aug. No. 63. <http://www.ncbi.nlm.nih.gov/books/NBK42934/>. Accessed June 29, 2017.
- Aman MG, Hollway JA, McDougle CJ, et al. Cognitive effects of risperidone in children with autism and irritable behavior. *J Child Adolesc Psychopharmacol*. 2008;18(3):227-236.
- American Psychiatric Association. Diagnostic and Statistical manual of Mental Disorders, 5th edition (DSM V). Washington, DC: In Section II, Depressive Disorders and Schizophrenia Spectrum and Other Psychotic Disorders. May 2013.
- Aristada [package insert]. Waltham, MA: Alkermes, Inc.; June 2017.
- Asenjo Lobos C, Komossa K, Rummel-Kluge C, et al. Clozapine vs other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev*. 2010;(11):CD006633.
- Asmal A, Flegar SJ, Wang J, et al. Quetiapine versus other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev*. 2013;11:CD006625.
- Augustyn, M. Autism spectrum disorder: terminology, epidemiology, and pathogenesis. UpToDate Web site. 2017. www.uptodate.com/. Accessed June 29, 2017.
- Bauer M, El-Khalili N, Datto C, et al. A pooled analysis of two randomized, placebo-controlled studies of extended release quetiapine fumarate adjunctive to antidepressant therapy in patients with major depressive disorder. *Journal of Affective Disorders*. 2010;127:19-30.
- Berman RM, Marcus RN, Swanink R, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*. 2007;68(6):843-853.
- Berwaerts J, Liu Y, Gopal S, et al. Efficacy and safety of the 3-month formulation of paliperidone palmitate vs placebo for relapse prevention of schizophrenia. *JAMA Psychiatry*. 2015;72(8):830-839.
- Biederman J, McDonnell MA, Wozniak J, et al. Aripiprazole in the treatment of pediatric bipolar disorder: a systematic chart review. *CNS Spectrums*. 2005;10(2):141-148.
- Brown E, Dunner DL, McElroy SL, et al. Olanzapine/fluoxetine combination vs lamotrigine in the 6-month treatment of bipolar depression. *Int J Neuropsychopharmacol*. 2009;12:773-782.
- Calabrese JR, Keck PE, Starace A, et al. Efficacy and safety of low- and high-dose cariprazine in acute and mixed mania associated with bipolar I disorder: a double-blind, placebo-controlled study. *J Clin Psychiatry*. 2015; 76(3):284-292.
- Capone GT, Goyal P, Grados M, et al. Risperidone use in children with Down syndrome, severe intellectual disability, and comorbid autistic spectrum disorders: a naturalistic study. *J Dev Behav Pediatr*. 2008;29:106-116.
- Centers for Disease Control and Prevention (CDC). Burden of Mental Illness. October 4, 2013. <https://www.cdc.gov/mentalhealth/basics/burden.htm>. Accessed June 29, 2017.

- Chiesa A, Chierzi F, De Ronchi D, et al. Quetiapine for bipolar depression: a systematic review and meta-analysis. *Int Clin Psychopharmacol*. 2012;27(2):76-90.
- Cipriani A, Barbui C, Salanti G, et al. Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. *Lancet*. 2011;378(9799):1306-1315.
- Citrome L, Meng X, Hochfeld M. Efficacy of iloperidone in schizophrenia: a PANSS five-factor analysis. *Schizophrenia Research*. 2011;131:75-81.
- Citrome L, Meng X, Hochfeld M. Efficacy of iloperidone in the short-term treatment of schizophrenia: a post hoc analysis of pooled patient data from four phase III, placebo- and active-controlled trials. *Hum Psychopharmacol Clin Exp*. 2012;27:24-32.
- Citrome L. Asenapine for schizophrenia and bipolar disorder: a review of the efficacy and safety profile for this newly approved sublingually absorbed second-generation antipsychotic. *Int J Clin Pract*. 2009;63(12):1762-1784.
- Clinical Pharmacology Web site. 2017. <http://www.clinicalpharmacology-ip.com>. Accessed June 29, 2017.
- Clozaril [package insert]. Rosemont, PA: HLS Therapeutics; February 2017.
- Correll CU, Manu P, Olshanskiy V, et al. Cardiovascular risk of second-generation antipsychotic medications during first-time use in children and adolescents. *JAMA*. 2009;302(16):1765-1773.
- Correll CU, Skuban A, Ouyang J, et al. Efficacy and safety of brexpiprazole for the treatment of acute schizophrenia: A 6-week randomized, double-blind, placebo-controlled trial. *Am J Psychiatry*. 2015;172(9):870-880.
- Corya SA, Williamson D, Sanger TM, et al. A randomized, double-blind comparison of olanzapine/fluoxetine combination, olanzapine, fluoxetine, and venlafaxine in treatment-resistant depression. *Depress Anxiety*. 2006;23:364-372.
- Cutler AJ, Kalali AH, Weiden PJ, et al. Four-week, double-blind, placebo- and ziprasidone-controlled trial of iloperidone in patients with acute exacerbations of schizophrenia. *J Clin Psychopharmacol*. 2008;28:S20-28.
- DelBello MP, Chang K, Welge JA, et al. A double-blind, placebo-controlled pilot study of quetiapine for depressed adolescents with bipolar disorder. *Bipolar Disorders*. 2009;11:483-93.
- Detke HC, DelBello, MP, Landry J, et al. Olanzapine/fluoxetine combination in children and adolescents with bipolar I depression: a randomized, double-blind, placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2015;54(3):217-224.
- Dixon L, Perkins D, Calmes C; for the American Psychiatric Association. Guideline Watch (September 2009): Practice guideline for the treatment of patients with schizophrenia. American Psychiatric Association. 2009. http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/schizophrenia-watch.pdf. Accessed June 29, 2017.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. 2017. <http://www.accessdata.fda.gov/scripts/cder/daf>. Accessed June 29, 2017.
- Durgam S, Cutler AJ, Lu K, et al. Cariprazine in acute exacerbation of schizophrenia: A fixed-dose, phase 3, randomized, double-blind, placebo- and active-controlled trial. *J Clin Psychiatry*. 2015 [a]; 76(12):e1574-1582.
- Durgam S, Earley W, Li R, et al. Long-term cariprazine treatment for the prevention of relapse in patients with schizophrenia: a randomized, double-blind, placebo-controlled trial. *Schizophr Res*. 2016;176(2-3):264-271.
- Durgam S, Greenberg WM, Li D, et al. Safety and tolerability of cariprazine in the long-term treatment of schizophrenia: results from a 48-week, single-arm, open-label extension study. *Psychopharmacology*. 2017;234(2):199-209.
- Durgam S, Starace A, Li D, et al. An evaluation of the safety and efficacy of cariprazine in patients with acute exacerbation of schizophrenia: A phase II, randomized clinical trial. *Schizophr Res*. 2014;152(2-3):450-457.
- Durgam S, Starace A, Migliore R, et al. The efficacy and tolerability of cariprazine in acute mania associated with bipolar I disorder: A phase II trial. *Bipolar Disord*. 2015[b];17(1):63-75.
- Fanapt [package insert]. Washington, D.C.: Vanda Pharmaceuticals Inc.; February 2017.
- Farah A. Atypicality of atypical antipsychotics. *Prim Care Companion J Clin Psychiatry*. 2005;7:268-274.
- Fazaclo [package insert]. Palo Alto, CA: Jazz Pharmaceuticals; February 2017.
- FDA and Center for Drug Evaluation and Research (CDER). Summary Review: Vraylar (cariprazine). Food and Drug Administration Web site. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/204370Orig1Orig2s000SumR.pdf. September 17, 2015. Accessed June 29, 2017.
- FDA Drug Safety Communication: FDA modifies monitoring for neutropenia associated with schizophrenia medicine clozapine; approves new shared REMS program for all clozapine medicines. Food and Drug Administration Web site. <http://www.fda.gov/drugs/drugsafety/ucm461853.htm>. September 15, 2015. Accessed June 29, 2017.
- FDA Drug Safety Communication: FDA working with manufacturers to resolve challenges with the Clozapine REMS program. Food and Drug Administration Web site. <http://www.fda.gov/drugs/drugsafety/ucm467560.htm>. December 16, 2016. Accessed June 29, 2017.
- Findling RL, Drury SS, Jensen PS, et al; for the American Academy of Children and Adolescent Psychiatry (AACAP). Practice Parameter for the Use of Atypical Antipsychotic Medications in Children and Adolescents. Approved by the AACAP Council on August 2, 2011. https://www.aacap.org/App_Themes/AACAP/docs/practice_parameters/Atypical_Antipsychotic_Medications_Web.pdf. Accessed June 29, 2017.
- Findling RL, Landbloom RL, Szegei A, et al. Asenapine for the acute treatment of pediatric manic or mixed episode of bipolar I disorder. *J Am Acad Child Adolesc Psychiatry*. 2015;54(12):1032-1041.
- Findling RL, Pathak S, Earley W, et al. Efficacy and safety of extended-release quetiapine fumarate in youth with bipolar depression: an 8 week, double-blind, placebo-controlled trial. *J Child Adolesc Psychopharmacol*. 2014;24(6):325-335.
- Fleischhacker WW, Hobart M, Ouyang J, et al. Efficacy and safety of brexpiprazole (OPC-34712) as maintenance treatment in adults with schizophrenia: a randomized, double-blind, placebo-controlled study. *Int J Neuropsychopharmacol*. 2016.pii:pyw076.
- Fornaro M, Stubbs B, De Barardis D, et al. Atypical antipsychotics in the treatment of acute bipolar depression with mixed features: a systematic review and exploratory meta-analysis of placebo-controlled clinical trials. *Int J Mol Sci*. 2016;17(2):241.
- Fusar-Poli P, Kempton MJ, Rosenheck RA. Efficacy and safety of second-generation long-acting injections in schizophrenia: A meta-analysis of randomized-controlled trials. *Int Clin Psychopharmacol*. 2013;28(2):57-66.
- Gagliano A, Germano E, Pustorino G, et al. Risperidone treatment of children with autistic disorder: effectiveness, tolerability, and pharmacokinetic implications. *J Child Adolesc Psychopharmacol*. 2004 Spring;14(1):39-47.

- Gelenberg AJ, Freeman MP, Markowitz JC, et al; for the American Psychiatric Association Work Group on Major Depressive Disorder. Practice guideline for the treatment of patients with major depressive disorder. Third edition. Arlington, VA; 2010. http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf. Accessed June 29, 2017.
- Gencer O, Emiroglu FNI, Miral S, et al. Comparison of long-term efficacy and safety of risperidone and haloperidol in children and adolescents with autistic disorder: an open-label maintenance study. *Eur Child Adolesc Psychiatry*. 2008;217-225.
- Gentile S. Adverse effects associated with second-generation antipsychotic long-acting injection treatment: a comprehensive systematic review. *Pharmacotherapy*. 2013;33(10):1087-1106.
- Geodon [package insert]. New York, NY: Pfizer Pharmaceuticals; February 2017.
- Ghanizadeh A, Sahraeizadeh A, Berk M. A head-to-head comparison of aripiprazole and risperidone for safety and treating autistic disorders, a randomized double blind clinical trial. *Child Psychiatry Hum Dev*. 2014;45(2):185-192.
- Glick ID, Correll CU, Altamura AC, et al. Mid-term and long-term efficacy and effectiveness of antipsychotic medications for schizophrenia: a data driven, personalized clinical approach. *J Clin Psychiatry*. 2011;72(12):1616-1627.
- Goldman R, Loebel A, Cucchiaro J, Deng L, Findling RL. Efficacy and safety of lurasidone in adolescents with schizophrenia: A 6-Week, randomized placebo-controlled study. *J Child Adolesc Psychopharmacol*. 2017 May 5. doi:10.1089/cap.2016.0189. [Epub ahead of print]
- Gulisano M, Cali PV, Cavanna AE, et al. Cardiovascular safety of aripiprazole and pimozide in young patients with Tourette syndrome. *Neurolo Sci*. 2011;32(6):1213-1217.
- Hamilton Depression Rating Scale. Food and Drug Administration Web site. 2007. [http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4273b1_04-DescriptionofMADRSHAMDDepressionR\(1\).pdf](http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4273b1_04-DescriptionofMADRSHAMDDepressionR(1).pdf). Accessed June 29, 2017.
- Harvey PD, Ogasa M, Cucchiaro, et al. Performance and interview-based assessments of cognitive change in a randomized, double-blind comparison of lurasidone vs ziprasidone vs ziprasidone. *Schizophrenia Research*. 2011;127:188-194.
- Hirsch LE, Pringsheim T. Aripiprazole for autism spectrum disorders (ASD). *Cochrane Database Syst Rev*. 2016;(6):CD009043.
- Hirschfeld RMA, Bowden CL, Gitlin MJ, et al. Practice guideline for the treatment of patients with bipolar disorder [monograph on the internet]. Arlington (VA): American Psychiatric Association; April 2002. <http://psychiatryonline.org/guidelines>. Accessed June 29, 2017.
- Hirschfeld RMA; for the American Psychiatric Association. Guideline Watch: Practice guideline for the treatment of patients with bipolar disorder, 2nd ed. Arlington (VA): American Psychiatric Association; November 2005. <http://psychiatryonline.org/guidelines>. Accessed June 29, 2017.
- Invega [package insert]. Titusville, NJ: Janssen Pharmaceuticals. February 2017.
- Invega Sustenna [package insert]. Titusville, NJ: Janssen Pharmaceuticals. Titusville, NJ; June 2017.
- Invega Trinza [package insert]. Titusville, NJ: Janssen Pharmaceuticals; February 2017.
- Jibson MD, Marder S, Herman R. Second-generation antipsychotic medications: Pharmacology, administration, and side effects. UpToDate Web site. 2017. www.uptodate.com/. Accessed June 29, 2017.
- Jones MP, Nicholl D, Trakas K, et al. Efficacy and tolerability of paliperidone ER and other oral atypical antipsychotics in schizophrenia. *Int J Clin Pharmacol Ther*. 2010;48(6):383-399.
- Kamijima K, Higuchi T, Ishigooka J, et al. Aripiprazole augmentation to antidepressant therapy in Japanese patients with major depressive disorder: a randomized, double-blind, placebo-controlled study (ADMIRE study). *J Affect Disord*. 2013;151(3):899-905.
- Kane JM, Cohen M, Zhao J, et al. Efficacy and safety of asenapine in a placebo- and haloperidol-controlled trial in patients with acute exacerbation of schizophrenia. *J Clin Psychopharmacol*. 2010[a];30:106-115.
- Kane JM, Detke HC, Naber D, et al. Olanzapine long-acting injection: a 24-week, randomized, double-blind trial of maintenance treatment in patients with schizophrenia. *Am J Psychiatry*. 2010[b];167:181-189.
- Kane JM, Lauriello J, Laska E, et al. Long-term efficacy and safety of iloperidone: results from three clinical trials for the treatment of schizophrenia. *J Clin Psychopharmacol*. 2008;28:S29-S35.
- Kane JM, Mackle M, Snow-Adami L, et al. A randomized placebo-controlled trial of asenapine for the prevention of relapse of schizophrenia after long-term treatment. *J Clin Psychiatry*. 2011;72(3):349-355.
- Kane JM, Skuban A, Ouyang J, et al. A multicenter, randomized, double-blind, controlled phase 3 trial of fixed-dose brexpiprazole for the treatment of adults with acute schizophrenia. *Schizophr Res*. 2015[a];164(1-3):127-135.
- Kane JM, Zukin S, Wang Y, et al. Efficacy and safety of cariprazine in acute exacerbation of schizophrenia: Results from an international, phase III clinical trial. *J Clin Psychopharmacol*. 2015[b]; 35(4):367-373.
- Khanna P, Suo T, Komossa K, et al. Aripiprazole versus other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev*. 2014;1:CD006569.
- Kishimoto T, Robenzadeh A, Leucht S, et al. Long-acting injectable vs oral antipsychotics for relapse prevention in schizophrenia: a meta-analysis of randomized trials. *Schizophr Bull*. 2014;40(1):192-213.
- Klomp M, Tvete IF, Skomedal T, et al. A review and Bayesian meta-analysis of clinical efficacy and adverse effects of four atypical neuroleptic drugs compared to haloperidol and placebo. *J Clin Psychopharmacol*. 2011;31:698-704.
- Komossa K, Depping AM, Gaudchau A, et al. Second-generation antipsychotics for major depressive disorder and dysthymia. *Cochrane Database of Systematic Reviews*. 2010[c]; (12): CD008121.
- Komossa K, Rummel-Kluge C, Hunger H, et al. Olanzapine vs other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev*. 2010 [a];(3):CD006654.
- Komossa K, Rummel-Kluge C, Hunger H, et al. Ziprasidone vs other atypical antipsychotics for schizophrenia. *Cochrane Database of Systematic Reviews*. 2009[b]; (4): CD006627.
- Komossa K, Rummel-Kluge C, Schmid F, et al. Quetiapine vs other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev*. 2010 [b];(1):CD006625.
- Komossa K, Rummel-Kluge C, Schmid F, et al. Risperidone vs other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev*. 2011;(1):CD006626.
- Komossa K, Rummel-Kluge, Schmid F, et al. Aripiprazole vs other atypical antipsychotics for schizophrenia. *Cochrane Database of Systematic Reviews*. 2009[a];4:CD006569.
- Kumar A, Datta S, Wright S, et al. Atypical antipsychotics for psychosis in adolescents. *Cochrane Database Syst Rev*. 2013 Oct 15;10:CD009582.

- Latuda [package insert]. Marlborough, MA: Sunovion Pharmaceuticals, Inc.; February 2017.
- Lehman AF, Lieberman JA, Dixon LB, et al; for the American Psychiatric Association Work Group on Schizophrenia. Practice guideline for the treatment of patients with schizophrenia. Second edition. Arlington, VA; 2004.
http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/schizophrenia.pdf. Accessed June 29, 2017.
- Lenze EJ, Mulsant BH, Blumberger DM, et al. Efficacy, safety, and tolerability of augmentation pharmacotherapy with aripiprazole for treatment-resistant depression in late life: a randomized, double-blind, placebo-controlled trial. *Lancet*. 2015;386:2404-2412.
- Leucht S, Cipraini A, Spinelli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet*. 2013; 382: 951-962.
- Leucht S, Corves C, Arbter D, et al. Second-generation vs first-generation drugs for schizophrenia: a meta-analysis. *Lancet*. 2009[a];373:31-41.
- Leucht S, Komossa K, Rummel-Kluge C, et al. A meta-analysis of head-to-head comparisons of second-generation antipsychotics in the treatment of schizophrenia. *Am J Psychiatry*. 2009[b];166:152-163.
- Lieberman JA, Stroup TS, McElvoy JP, et al. Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;353(12):1209-1223.
- Lindström L, Lindström E, Nilsson M, Höistad M. Maintenance therapy with second generation antipsychotics for bipolar disorder - A systematic review and meta-analysis. *J Affect Disord*. 2017 ;213:138-150.
- Loebel A, Cucchiario J, Silva R, et al. Lurasidone as adjunctive therapy with lithium or valproate for the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. *Am J Psychiatry*. 2014[a];171(2):169-177.
- Loebel A, Cucchiario J, Silva R, et al. Lurasidone monotherapy in the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. *Am J Psychiatry*. 2014[b];171(2):160-168.
- Luby J, Mrakotsky C, Stalets MM, et al. Risperidone in preschool children with autistic spectrum disorders: an investigation of safety and efficacy. *J Child Adolesc Psychopharmacol*. 2006;16(5):575-587.
- Marcus RN, McQuade RD, Carson WH, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol*. 2008;28(2):156-165
- Marcus RN, Owen R, Kamen L, et al. A placebo-controlled, fixed-dose study of aripiprazole in children and adolescents with irritability associated with autistic disorder. *J Am Acad Child Adolesc Psychiatry*. 2009;48(11):1110-1119.
- Marcus RN, Owen R, Manos G, et al. Safety and tolerability of aripiprazole for irritability in pediatric patients with autistic disorder: a 52-week, open-label, multicenter study. *J Clin Psychiatry*. 2011;72(9):1270-1276.
- Market Exclusive (ME) staff. Vanda Pharmaceuticals, Inc (NASDAQ:VNDA) Files An 8-K Other Events. [press release]. December 20, 2016. Available at: <https://marketexclusive.com/vanda-pharmaceuticals-inc-nasdaqvnda-files-an-8-k-other-events-2/49544/>. Accessed June 29, 2017.
- McClellan J, Kowatch R, Findling RL, et al; for the American Academy of Children and Adolescent Psychiatry (AACAP). Practice parameter for the assessment and treatment of children and adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry*. 2007;46(1):107-125.
- McClellan J, Stock S; for the American Academy of Children and Adolescent Psychiatry (AACAP) Committee on Quality Issues (CQI). Practice parameter for the assessment and treatment of children and adolescents with schizophrenia. *J Am Acad Child Adolesc Psychiatry*. 2013;52(9):976–990.
- McCracken JT, McGough J, Shah J, et al. Risperidone in children with autism and serious behavioral problems (RUPP). *N Engl J Med*. 2002;347:314-321.
- McDougle CJ, Scahill L, Aman MG, et al. Risperidone for the core symptom domains of autism: results from the study by the Autism Network of the Research Units on Pediatric Psychopharmacology. *Am J Psychiatry*. 2005;162:1142-1148.
- Mcfadden W, Alphs L, Haskins JT, et al. A randomized, double-blind, placebo-controlled study of maintenance treatment with adjunctive risperidone long-acting therapy in patients with bipolar I disorder who relapse frequently. *Bipolar Disorders*. 2009;11(8):827-839.
- McGrath J, Saha S, Chant D, et al. Schizophrenia: A concise overview of incidence, prevalence, and mortality. *Epidemiol Rev*. 2008;30:67-76.
- McIntyre RS, Cohen M, Zhao J, et al. A three-week, randomized, placebo-controlled trial of asenapine in the treatment of acute mania in bipolar mania and mixed states. *Bipolar Disorders*. 2009[a];11:673-686.
- McIntyre RS, Cohen M, Zhao J, et al. Asenapine for long-term treatment of bipolar disorder: a double-blind 40-week extension study. *Journal of Affective Disorders*. 2010[b];126:358-365.
- McIntyre RS, Cohen M, Zhao J, et al. Asenapine in the treatment of acute mania in bipolar I disorder: a randomized, double-blind, placebo-controlled trial. *Journal of Affective Disorders*. 2010[a];122:27-38.
- McIntyre RS, Cohen M, Zhao J, et al. Asenapine vs olanzapine in acute mania: a double-blind extension study. *Bipolar Disorders*. 2009[b];11:815-826.
- Meltzer HY, Cucchiario J, Silva R, et al. Lurasidone in the treatment of schizophrenia: a randomized, double-blind, placebo-and olanzapine-controlled study. *Am J Psychiatry*. 2011;168:957-967.
- Meltzer L, Risinger R, Nasrallah M, et al. A randomized, double-blind, placebo-controlled trial of aripiprazole lauroxil in acute exacerbation of schizophrenia. *J Clin Psychiatry*. 2015;76(8):1085-1090.
- Micromedex Solutions Web site. 2017. <http://www.micromedexsolutions.com/home/dispatch>. Accessed June 29, 2017.
- Miral S, Gencer O, Inal-Emiroglu FN, et al. Risperidone vs haloperidol in children and adolescents with AD: a randomized, double-blind trial. *Eur Child Adolesc Psychiatry*. 2008;17:1-8.
- Miyamoto S, Duncan GE, Marx CE, et al. Treatments for schizophrenia: a critical review of pharmacology and mechanisms of action of antipsychotic drugs. *Molecular Psychiatry*. 2005;10:79-104.
- Morbidity and Mortality Weekly Report (MMWR). Current Depression Among Adults – United States, 2006 and 2008. *MMWR Weekly*. 2010; 59(38):1229-1235.
- Morbidity and Mortality Weekly Report (MMWR). Prevalence and characteristics of autism spectrum disorder among children aged 8 years—Autism and Developmental Disabilities Monitoring Network, 11 sites, United States, 2012. *MMWR Weekly*. 2016 65(3);1-23.
- Muralidharan K, Ali M, Silveira LE, et al. Efficacy of second generation antipsychotics in treating acute mixed episodes in bipolar disorder: a meta-analysis of placebo-controlled trials. *J Affect Disord*. 2013;150(2):408-414.
- Murphy TK, Lewin AB, Storch EA, et al; for the American Academy of Children and Adolescent Psychiatry (AACAP). Practice parameter for the assessment and treatment of children and adolescents with tic disorders. *J Am Acad Child Adolesc Psychiatry*. 2013;52(12):1341–1359.

- Nagaraj R, Singhi P, Malhi P. Risperidone in children with autism: randomized, placebo-controlled, double-blind study. *J Child Neurol*. 2006;21(6):450-455.
- Nakamura M, Ogasa MS, Guarino J, et al. Lurasidone in the treatment of acute schizophrenia: a double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2009;70(6):829-836.
- Nussbaum A and Stroup T. Paliperidone palmitate for schizophrenia. *Cochrane Database Syst Rev*. 2012;6:CD008296.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. <https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>. Accessed June 29, 2017.
- Ostacher M, Ng-Mak D, Patel P, Ntais D, Schlueter M, Loebel A. Lurasidone compared to other atypical antipsychotic monotherapies for bipolar depression: A systematic review and network meta-analysis. *World J Biol Psychiatry*. 2017;1-11.
- Owen R, Sikich L, Marcus RN, et al. Aripiprazole in the treatment of irritability in children and adolescents with autistic disorder. *Pediatrics*. 2009;124:1533-1540.
- Pagsberg AK, Tarp S, Glinborg D, et al. Acute antipsychotic treatment of children and adolescents with schizophrenia-spectrum disorders: A systematic review and network meta-analysis. *J Am Acad Child Adolesc Psychiatry*. 2017;56(3):191-202.
- Papakostas GI, Petersen TJ, Kinrys G, et al. Aripiprazole augmentation of selective serotonin-reuptake inhibitors for treatment-resistant major depressive disorder. *J Clin Psychiatry*. 2005; 66(10):1326-1330.
- Perlis RH, Baker RW, Zarate CA, et al. Olanzapine vs risperidone in the treatment of manic or mixed states in bipolar I disorder: a randomized, double-blind trial. *J Clin Psychiatry*. 2006[a];67:1747-1753.
- Perlis RH, Welge JA, Vornik LA, et al. Atypical antipsychotics in the treatment of mania: a meta-analysis of randomized, placebo-controlled trials. *J Clin Psychiatry*. 2006[b];76:509-516.
- Pillay J, Boylan K, Carrey N, et al. First- and second-generation antipsychotics in children and young adults: Systematic review update. Comparative Effectiveness Review No. 184. AHRQ Publication No. 17-EHC001-EF. Rockville, MD: Agency for Healthcare Research and Quality; March 2017. www.effectivehealthcare.ahrq.gov/reports/final/cfm. doi: <https://doi.org/10.23970/AHRQEPCCER184>. Accessed June 29, 2017.
- Potkin SG, Cohen M, Panagides J. Efficacy and tolerability of asenapine in acute schizophrenia: a placebo- and risperidone-controlled trial. *J Clin Psychiatry*. 2007;68:1492-1500.
- Potkin SG, Litman RE, Torres R, et al. Efficacy of iloperidone in the treatment of schizophrenia: initial phase three studies. *J Clin Psychopharm*. 2008;28:S4-S11.
- Potkin SG, Ogasa M, Cucchiario J, et al. Double-blind comparison of the safety and efficacy of lurasidone and ziprasidone in clinically stable outpatients with schizophrenia or schizoaffective disorder. *Schizophrenia Research*. 2011;132:101-107.
- Quiroz JA, Yatham LN, Palumbo JM, et al. Risperidone long-acting injectable monotherapy in the maintenance treatment of bipolar I disorder. *Biol Psychiatry*. 2010;68(2):156-162.
- REMS@FDA . Food and Drug Administration Web site. 2017. <http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm>. Accessed June 29, 2017.
- Rexulti [package insert]. Rockville, MD: Otsuka Pharmaceuticals Co., Ltd; February 2017.
- Riedel M, Schennach-Wolff R, Dehning MS, et al. Neurocognition and its influencing factors in the treatment of schizophrenia-effects of aripiprazole, olanzapine, quetiapine and risperidone. *Hum Psychopharmacol Clin Exp*. 2010; 25:116-125.
- Risperdal [package insert]. Titusville, NJ: Janssen Pharmaceuticals; February 2017.
- Risperdal Consta [package insert]. Titusville, NJ: Janssen Pharmaceuticals; February 2017.
- Sachs GS, Greenberg WM, Starace A, et al. Cariprazine in the treatment of acute mania in bipolar I disorder: A double-blind, placebo-controlled, Phase III trial. *J Affect Disord*. 2015;174:296-302.
- Saphris [package insert]. St. Louis, MO: Forest Pharmaceuticals; February 2017.
- Schoemaker J, Naber D, Vrijland P, et al. Long-term assessment of asenapine vs olanzapine in patients with schizophrenia or schizoaffective disorder. *Pharmacopsychiatry*. 2010; 43:e1-e10.
- Seroquel [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; February 2017.
- Seroquel XR [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP. February 2017.
- Serretti A, Chiesa A. A meta-analysis of sexual dysfunction in psychiatric patients taking antipsychotics. *Int Clin Psychopharm*. 2011;26:130.
- Shea S, Turgay A, Carroll A, et al. Risperidone in the treatment of disruptive behavioral symptoms in children with autistic and other pervasive developmental disorders. *Pediatrics*. 2004;114:e634-e641.
- Shelton RC, Williamson DJ, Corya SA, et al. Olanzapine/ fluoxetine combination for treatment-resistant depression: a controlled study of SSRI and nortriptyline resistance. *J Clin Psychiatry*. 2005;66:1289-1297.
- Silva MT, Zimmermann IR, Galvao TF, et al. Olanzapine plus fluoxetine for bipolar disorder: a systematic review and meta-analysis. *J Affect Disord*. 2013;146(3):310-318.
- Spielmans GI, Berman MI, Linardatos E, et al. Adjunctive atypical antipsychotic treatment for major depressive disorder: a meta-analysis of depression, quality of life, and safety outcomes. *PLoS Med*. 2013;10(3):e1001403. doi: 10.1371/journal.pmed.1001403.
- Steffens DC, Nelson JC, Eudicone JM, et al: Efficacy and safety of adjunctive aripiprazole in major depressive disorder in older patients: a pooled subpopulation analysis. *Int J Geriatr Psychiatry*. 2011; 26(6):564-572.
- Stovall J. Bipolar disorder in adults: epidemiology and pathogenesis. UpToDate Web site. 2017[a]. www.uptodate.com/. Accessed June 29, 2017.
- Stovall J. Bipolar disorder in adults: Pharmacotherapy for acute mania and hypomania. UpToDate Web site. 2017[b]. www.uptodate.com/. Accessed June 29, 2017.
- Stroup TS, Lieberman JA, McEvoy JP, et al; for the CATIE Investigators. Results of phase three of the CATIE schizophrenia trial. *Schizophr Res*. 2009;107(1):1-12.
- Stroup TS, Lieberman JA, McEvoy JP, et al; for the CATIE Investigators. Effectiveness of olanzapine, quetiapine, risperidone, and ziprasidone in patients with chronic schizophrenia following discontinuation of a previous atypical antipsychotic. *Am J Psychiatry*. 2006;163(4):611-622.
- Symbyax [package insert]. Indianapolis, IN: Eli Lilly and Company; March 2017.
- Szegedi A, Zhao J, van Willigenburg A, et al. Effects of asenapine on depressive symptoms in patients with bipolar I disorder experiencing acute manic or mixed episodes: a post hoc analysis of two 3-week clinical trials. *BMC Psychiatry*. 2011;11:101.

- Tandon R, Cucchiaro J, Phillips D, et al. A double-blind, placebo-controlled, randomized withdrawal study of lurasidone for the maintenance of efficacy in patients with schizophrenia. *J Psychopharmacol*. 2016;30(1):69-77.
- Tarr GP, Glue P, Herbison P. Comparative efficacy and acceptability of mood stabilizer and second generation antipsychotic monotherapy for acute mania-a systematic review and meta-analysis. *Journal of Affective Disorders*. 2011;134:14-19.
- Taylor DM, Cornelius V, Smith L, Young AH. Comparative efficacy and acceptability of drug treatments for bipolar depression: a multiple-treatments meta-analysis. *Acta Psychiatr Scand*. 2014;130(6):452-469.
- Thase ME, Corya SA, Osuntokun O, et al. A randomized, double-blind comparison of olanzapine/fluoxetine combination, olanzapine, and fluoxetine in treatment-resistant major depressive disorder. *J Clin Psychiatry*. 2007;68:224-236.
- Thase ME, Youakim JM, Skuban A, et al. Adjunctive brexpiprazole 1 and 3 mg for patients with major depressive disorder following inadequate response to antidepressants: a phase 3, randomized, double-blind study. *J Clin Psychiatry*. 2015[b];76(9):1232-1240.
- Thase ME, Youakim JM, Skuban A, et al. Efficacy and safety of adjunctive brexpiprazole 2 mg in major depressive disorder. *J Clin Psychiatry*. 2015[a];76(9):1224-1231.
- Tohen M, Vieta E, Calabrese J, et al. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. *Arch Gen Psychiatry*. 2003;60(11):1079-1088.
- Van Os J, Kapur S. Schizophrenia. *Lancet*. 2009;374(9690):635-645.
- Versacloz [package insert]. Palo Alto, CA: Jazz Pharmaceuticals, Inc.; February 2017.
- Veterans Administration (VA) and Department of Defense (DoD) Clinical Practice Guideline for Management of Major Depressive Disorder. VA/DoD Web site. April 2016. <http://www.healthquality.va.gov/guidelines/MH/mdd/>. Accessed June 29, 2017.
- Veterans Administration (VA) Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives. Recommendations for antipsychotic selection in schizophrenia and schizoaffective disorders. June 2012. <http://www.pbm.va.gov/clinicalguidance/clinicalrecommendations.asp>. Accessed June 29, 2017.
- Veterans Administration (VA) Pharmacy Benefits Management Services; for the Management of Bipolar Disorder Working Group. VA/DoD clinical practice guideline for management of bipolar disorder in adults. Washington (DC): Department of Veterans Affairs, Department of Defense; 2010 May. 176 p. http://www.healthquality.va.gov/bipolar/bd_305_full.pdf. Accessed June 29, 2017.
- Vieta E, Locklear J, Gunther O, et al. Treatment options for bipolar depression: a systematic review of randomized, controlled trials. *J Clin Psychopharmacol*. 2010;30:579-590.
- Vieta E, Montgomery S, Sulaiman AH, et al. A randomized, double-blind, placebo-controlled trial to assess prevention of mood episodes with risperidone long-acting injectable in patients with bipolar I disorder. *Eur Neuropsychopharmacol*. 2012;22(11):825-835.
- Volkmar F, Siegel M, Woodbury-Smith M, et al; for the American Academy of Children and Adolescent Psychiatry (AACAP). Practice Parameter for the Assessment and Treatment of Children and Adolescents With Autism Spectrum Disorder. *J Am Acad Child Adolesc Psychiatry*. 2014;53(2):237-257.
- Vraylar [package insert]. Irvine, CA: Allergan USA, Inc.; February 2017.
- Weiden PJ, Cutler AJ, Polymeropoulos MH, Wolfgang CD. A pooled analysis of six-week acute-phase pivotal trials. *J Clin Psychopharmacol*. 2008;28:S12-S19.
- Weiden PJ, Manning R, Wolfgang CD, et al. A randomized trial of iloperidone for prevention of relapse in schizophrenia: the REPRIEVE study. *CNS Drugs*. 2016;30(8):735-747.
- Weissman L, Bridgemohan C. Autism spectrum disorders in children and adolescents: overview and management. UpToDate Web site. 2017. www.uptodate.com/. Accessed June 29, 2017.
- Wen XJ, Wang LM, Liu ZL, et al. Meta-analysis on the efficacy and tolerability of the augmentation of antidepressants with atypical antipsychotics in patients with major depressive disorder. *Braz J Med Res*. 2014;47(7):605-616.
- Yatham LN, Fallu A, Binder CE. A six-month randomized open-label comparison of continuation of oral atypical antipsychotic therapy or switch to long acting injectable risperidone in patients with bipolar disorder. *Acta Psychiatr Scand Suppl*. 2007;(434):50-56.
- Yildiz A, Vieta E, Leucht S, et al. Efficacy of antimanic treatments: meta-analysis of randomized, controlled trials. *Neuropsychopharmacology*. 2011;36:375-389.
- Yoo HK. A multicenter, randomized, double-blind, placebo-controlled study of aripiprazole in children and adolescents with Tourette's disorder. *J Clin Psychiatry*. 2013;74(8):e772-e780.
- Yoon S, Jeon SW, Ko YH, et al. Adjunctive brexpiprazole as a novel effective strategy for treating major depressive disorder: A systematic review and meta-analysis. *J Clin Psychopharmacol*. 2017;37(1):46-53.
- Young AH, McElroy SL, Bauer M, et al. A double-blind, placebo-controlled study of quetiapine and lithium monotherapy in adults in the acute phase of bipolar depression (EMBOLDEN I). *J Clin Psychiatry*. 2010;71(2):150-162.
- Zyprexa Relprevv [package insert]. Indianapolis, IN: Eli Lilly and Company; February 2017.
- Zyprexa Zydys [package insert]. Indianapolis, IN: Eli Lilly and Company; February 2017.
- Zyxprexa [package insert]. Indianapolis, IN: Eli Lilly and Company; February 2017.