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 (Miyamato et al, 2005).
- Antipsychotic medications exert their effect in part by blocking D_2 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 D_2 and other neuroreceptors: typical antipsychotics, also called first generation antipsychotics, and atypical antipsychotics, also called second generation antipsychotics (SGAs) (Miyamato et al, 2005).
- 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 autism, bipolar disorder, Tourette's disorder, major depressive disorder (MDD), schizophrenia, and schizoaffective disorder. FDA-approved atypical agents include (Drugs@FDA, 2017):
  - Generic agents – aripiprazole, clozapine, iloperidone, olanzapine, paliperidone, quetiapine immediate- and extended-release, risperidone, ziprasidone, and olanzapine/fluoxetine
  - Branded agents –GEODON® (short-acting injection only), LATUDA®, REXULTI®, SAPHRIS®, VERSACLOZ® (oral suspension), and VRAYLAR™
  - Long-acting injections – ABILIFY MAINTENA®, ARISTADA™ , INVEGA SUSTENNA®, INVEGA TRINZA®, RISPERDAL CONSTA®, and ZYPREXA RELPREVV®
- Autism
  - Autism spectrum disorders (ASD) are neurodevelopmental disorders characterized by impairment in socialization, communication, and behavior (Weissman and Bridgemohan, 2016).
  - 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 1,000 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, 2016).
  - 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, 2016).
- 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, 2016[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, 2016[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 D_2 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 one-month period and continuous signs of the disturbance persist for at least 6 months. Symptoms must include one 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 one 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.

Table 1. Medications Included Within Class Review

Drug	Formulation	Manufacturer	FDA Approval Date	Generic
Single Entity Agents				
ABILIFY® (aripiprazole)	tab; sol	Otsuka (brand); various (generic)	11/15/2002 (tab) 12/12/2004 (sol)	✔
ABILIFY® DISCMELT™ (aripiprazole)	ODT	various (generic)	06/07/2006	✔
CLOZARIL® (clozapine)	tab	Heritage (brand); various (generic)	09/26/1989	✔
FANAPT® (iloperidone)	tab; titrate pack	Vanda and Inventia (brand)	05/06/2009	-*
FAZACLO® (clozapine)	ODT	Jazz (brand); various (generic)	02/09/2004	✔
GEODON® (ziprasidone hydrochloride)	cap	Pfizer (brand); various (generic)	02/05/2001	✔
GEODON® (ziprasidone mesylate)	inj (short-acting)	Pfizer	06/21/2002	-

Drug	Formulation	Manufacturer	FDA Approval Date	Generic
INVEGA® (paliperidone)	tab	Janssen (brand); various (generic)	12/19/2006	✔
LATUDA® (lurasidone)	tab	Sunovion	10/28/2010	-
REXULTI® (brexpiprazole)	tab	Otsuka	07/10/2015	-
RISPERDAL® (risperidone)	tab; sol	Janssen (brand); various (generic)	12/29/1993	✔
RISPERDAL® M-TAB® (risperidone)	ODT	Janssen (brand); various (generic)	04/02/2003	✔
SAPHRIS® (asenapine)	SL tab	Forest Pharma	08/13/2009	-
SEROQUEL® (quetiapine)	tab	AstraZeneca (brand); various (generic)	09/26/1997	✔
SEROQUEL XR® (quetiapine extended-release)	tab	AstraZeneca	05/17/2007	✔
VERSACLOZ® (clozapine)	susp	Jazz	02/06/2013	-
VRAYLAR™ (cariprazine)	cap; titrate pack	Allergan	09/17/2015	-
ZYPREXA® (olanzapine)	tab; inj (short-acting)	Eli Lilly (brand); various (generic)	09/30/1996 (tab) 03/29/2004 (inj)	✔
ZYPREXA ZYDIS® (olanzapine)	ODT	Eli Lilly (brand); various (generic)	04/06/2000	✔
Long-Acting Injectable Products				
ABILIFY MAINTENA® (aripiprazole extended-release)	inj	Otsuka	02/28/2013	-
ARISTADA™ (aripiprazole lauroxil extended-release)	inj	Alkermes	10/5/2015	-
INVEGA SUSTENNA® (paliperidone palmitate)	inj	Janssen	07/31/2009	-
INVEGA TRINZA® (paliperidone palmitate)	inj	Janssen	05/18/2015	-
RISPERDAL CONSTA® (risperidone microspheres)	inj	Janssen	10/29/2003	-
ZYPREXA RELPREVV® (olanzapine pamoate)	inj	Eli Lilly	12/11/2009	-
Combination Products				
SYMBYAX® Olanzapine/ fluoxetine	cap	Eli Lilly (brand); various (generic)	12/24/2003	✔

Abbrv: cap = capsule; inj = injection; ODT = oral disintegrating tablet; SL = sublingual; sol = solution; susp = suspension; tab = tablet; titrate pak = titration pack

*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. Currently, Inventia is only manufacturing the Fanapt titration pack (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 REXULTI. RISPERDAL CONSTA is the only long-acting injectable indicated for the treatment of bipolar disorder.
    - Aripiprazole, olanzapine/fluoxetine, risperidone, quetiapine, and SAPHRIS 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, REXULTI, and SEROQUEL XR 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.
  - 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, 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.
  - Tourette's Disorder: Aripiprazole is the only agent indicated for the treatment of Tourette's disorder in pediatric patients, aged 6 to 18 years.
- Table 2 highlights FDA-approved indications at a high level. Please refer to Tables 4 and 5 for a detailed explanation of indications by agent, age, formulation, and use as an adjunct or monotherapy.

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
Oral Products									
aripiprazole	✔ *	✔ *	-	-	✔	-	✔ *	-	✔ *
asenapine	-	✔ *	-	-	-	-	✔	-	-
brexpiprazole	-	-	-	-	✔	-	✔	-	-
cariprazine	-	✔	-	-	-	-	✔	-	-
clozapine	-	-	-	-	-	✔	✔	✔	-
iloperidone	-	-	-	-	-	-	✔	-	-
lurasidone	-	-	✔	-	-	-	✔	-	-
olanzapine	-	✔ *	-	-	✔ †	-	✔ *	-	-
olanzapine/ fluoxetine	-	-	✔ *	✔	-	-	-	-	-
paliperidone	-	-	-	-	-	✔	✔ *	-	-
quetiapine	-	✔ *	✔	-	✔ †	-	✔ *	-	-
risperidone	✔ *	✔ *	-	-	-	-	✔ *	-	-
ziprasidone	-	✔	-	-	-	-	✔	-	-
Long-Acting Injectable Products									
aripiprazole ER	-	-	-	-	-	-	✔	-	-
aripiprazole lauroxil ER	-	-	-	-	-	-	✔	-	-
paliperidone palmitate (SUSTENNA)	-	-	-	-	-	✔	✔	-	-
paliperidone palmitate (TRINZA)	-	-	-	-	-	-	✔	-	-
risperidone microspheres	-	✔	-	-	-	-	✔	-	-
olanzapine pamoate	-	-	-	-	-	-	✔ ‡	-	-

*FDA-approved indications for pediatric patients; †Extended-release formulation; ‡ Patients must be observed by a health care professional for 3 hours post-dose administration

(Prescribing information: ABILIFY, 2016; ABILIFY MAINTENA, 2016; ARISTADA, 2016; CLOZARIL, 2016; FANAPT, 2016; FAZACLO, 2015; GEODON, 2015; INVEGA, 2016; INVEGA SUSTENNA, 2016; INVEGA TRINZA, 2016; LATUDA, 2013; REXULTI, 2016; RISPERDAL, 2016; RISPERDAL CONSTA, 2016; SAPHRIS, 2017; SEROQUEL, 2013; SEROQUEL XR, 2016; SYMBYAX, 2016; VERSACLOZ, 2015; VRAYLAR, 2016; ZYPREXA, 2016; ZYPREXA RELPREVV, 2016)

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 a SR of literature on the safety and efficacy of antipsychotics in children and adolescents. The review included studies of atypical antipsychotics (aripiprazole, clozapine, olanzapine, quetiapine, risperidone, paliperidone, and ziprasidone), conducted in patients 24 years of age or younger, used for the following FDA-approved and off-label indications: pervasive developmental disorder, attention deficit hyperactivity disorder/disruptive behavior disorders, bipolar disorder, schizophrenia, psychosis, Tourette's syndrome, OCD, post-traumatic stress disorder, anorexia nervosa, and miscellaneous behavioral issues. Overall, indications associated with moderate strength evidence for the use of atypical antipsychotics included disruptive behavior disorder, bipolar disorder, schizophrenia, and Tourette's syndrome. No significant differences between the different atypical antipsychotics were noted in the identified head-to-head comparisons. The risks of weight gain (weight gain, 4.6 kg) and dyslipidemia were highest with olanzapine. Weight gain with ziprasidone was not significantly different from placebo. The other atypical antipsychotics were associated with intermediate weight gain. Risperidone was associated with the greatest incidence of prolactin-related adverse events (consistent with adult data). Extrapyramidal adverse events were significantly more common with risperidone and aripiprazole compared to placebo (Seida et al, 2012[a]; Seida et al, 2012[b]).

Autism Spectrum Disorder

- For the treatment of irritability associated with autistic disorder in patients, 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 one 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, 2014). 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 (2.7 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 SAPHRIS (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.
- Based on a 2012 AHRQ SR of 81 trials evaluating typical and atypical antipsychotics, a total of 11 trials measured efficacy and safety in adolescents with bipolar disorder. Compared to placebo, aripiprazole, olanzapine, ziprasidone, quetiapine and risperidone were associated with greater improvements in response rates in analysis of 7 trials with 1,006 patients (RR, 1.76; 95% CI, 1.46 to 2.13); number needed to treat [NNT], 3 to 7). Increased remission rates were observed with atypical antipsychotic use in 6 trials with 976 patients (RR, 2.4; 95% CI, 1.5 to 3.83; NNT, 2 to 12); however, significant heterogeneity was noted across trials. Comparing olanzapine to risperidone, olanzapine was associated with significantly smaller improvement in Young Mania Rating Scale (YMRS) score and a non-significant lower response rate (RR, 0.72; 95% CI, 0.5 to 1.03) in analysis of 2 trials with 92 patients. Risperidone significantly improved YMRS score vs ziprasidone in 1 trial with 84 patients. Overall, atypical antipsychotics may improve remission rates compared to placebo in adolescents with bipolar disorder (Seida et al, 2012[a]; Seida et al, 2012[b]).
- 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 (2.5mg, -3.2; P = 0.0008 vs 5mg, -5.3; P < 0.001 vs 10mg, -6.2; P < 0.001). Weight gain was higher across the asenapine groups, with 8 to 12% of patients experiencing ≥ 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 12/50mg 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 ≥ 50% reduction of CDRS-R score from baseline and a 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, 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, 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.
- Based on a 2012 AHRQ SR of 81 trials evaluating typical and atypical antipsychotics, a total of 23 randomized trials and 2 cohort studies measured efficacy and safety in adolescents with schizophrenia. Clozapine, olanzapine, and risperidone were associated with greater improvements compared to haloperidol in Brief Psychiatric Rating Scale (BPRS) score in analysis of 3 trials with 71 patients. Risperidone significantly improved Positive and Negative Syndrome Scale (PANSS) score in 1 trial with 8 patients. There was no significant difference in PANSS score comparing olanzapine vs haloperidol in 1 trial with 19 patients. Overall, clozapine, olanzapine, and risperidone may be more effective than haloperidol in adolescents with schizophrenia (Seida et al, 2012[a]; Seida et al, 2012[b]).
- 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 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 ≤ 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).

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, 2015).
- Aripiprazole was associated with increased body weight compared to placebo (range, 0.4 to 1.5 kg). Additional adverse reactions (incidence ≥ 5% and at least twice that for placebo) were sedation, somnolence, nausea, headache, nasopharyngitis, fatigue, and increased appetite (ABILIFY prescribing information, 2015). In one safety trial, aripiprazole had a safer cardiovascular profile vs pimozide, and was associated with a lower frequency of QT prolongation (Gulisano et al, 2011).

ADULTS

- The AHRQ conducted a SR of literature on the safety and efficacy of antipsychotics in adults comparing first- (typical antipsychotics) and second-generation (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 ≥ 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 REXULTI (brexpiprazole). The following summarizes direct comparative evidence and recent MAs and SRs.
- Based on a 2012 AHRQ SR of 125 trials evaluating typical and atypical antipsychotics, a total of 11 measured efficacy and safety in adults with bipolar disorder. Compared to haloperidol, there was no difference in YMRS score for manic episodes when compared to aripiprazole, olanzapine, and risperidone, and difference in Montgomery-Asberg Depression Rating Scale (MADRS) score compared to 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).
- One SR of 9 RCTs (N = 1,289) 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]). A meta-analysis 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 1,047 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 (≥ 6.5%). According to pooled analysis (n = 1,940 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 ≥ 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 ≥ 50% reduction in the YMRS score at endpoint). Olanzapine-treated patients experienced significantly greater elevations in liver function enzymes and weight gain (2.5 vs 1.6 kg). Risperidone-treated patients experienced significantly more prolactin elevations and sexual dysfunction (Perlis et al, 2006[a]).

Depressive Episodes

- Placebo-controlled 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 (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.

<u>Major Depressive Disorder (MDD)</u>

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, REXULTI (brexpiprazole), and SEROQUEL XR (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 meta-analysis, 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 meta-analysis evaluated 14 trials in patients with current MDD and an inadequate response to at least one 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 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, REXULTI, and SEROQUEL XR 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 ≥ 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). 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; 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).
- 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 ≥ 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 (≥ 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 ≥ 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 ≥ 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 ≥ 10%) were asthenia, headache, anxiety, tremor, nervousness, insomnia, and nausea (Shelton et al, 2005).

<u>Schizophrenia and/or Schizoaffective Disorder</u>

- All oral atypical antipsychotic 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. The following summarizes recent MAs and SRs, landmark trials in schizophrenia, and study evidence related to newer atypical antipsychotic agents (ie, asenapine, brexpiprazole, Iloperidone, 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 vs aripiprazole, clozapine, olanzapine, quetiapine, and risperidone. Outcomes measuring negative symptoms demonstrated a significant difference in PANSS scores favoring aripiprazole for 1,701 patients in 3 trials, risperidone for 4,043 patients in 20 trials, and olanzapine-treatment for 3,742 patients in 14 trials. When compared with haloperidol, risperidone yielded lower relapse rates for 1,405 patients in 6 trials and olanzapine provided better response rates for 4,099 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 meta-analysis 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 meta-analysis 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 = 2,881; 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 5,971 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 provides 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 one 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); 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). 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 ≤ 70, CGI-S score ≤ 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 was based on 3 DB, randomized, PC 6-week trials (Durgam et al, 2014; Durgam et al, 2015[b]; Kane et al, 2015[b]). A total of 1,792 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 = 1,317 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 (≥ 6.5%). The proportion of patients with weight increase ≥ 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, 2016[b]). 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[a].)
- 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 a meta-analysis that pooled the follow-up data (up to 52 weeks) from 3 prospective RCTs. The meta-analysis 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 meta-analysis 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 ≥ 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).

<u>Long-Acting Injectable Atypical Antipsychotics:</u>

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 meta-analysis 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 meta-analysis 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 meta-analysis 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 ≥ 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).

SAFETY SUMMARY

- All atypical antipsychotic agents have a boxed warning of increased mortality in elderly patients with dementia-related psychosis. Those agents (ie., ABILIFY, LATUDA, REXULTI, SEROQUEL, SEROQUEL XR, and SYMBYAX) indicated for depressive episodes carry a boxed warning of an increased risk of suicidal thoughts and behaviors. ZYPREXA RELPREVV has a boxed warning of incidences of post-injection delirium and/or sedation syndrome. Lastly, clozapine-containing agents (ie., CLOZARIL, FAZACLO, and VERSACLOZ) have boxed warnings of severe neutropenia, orthostatic hypotension, bradycardia, syncope, seizures, myocarditis, and cardiomyopathy.
- GEODON is contraindicated in patients with recent acute myocardial infarction (MI), history of QT prolongation or with drugs that prolong QT, and uncompensated heart failure (HF). LATUDA is contraindicated for concomitant use with strong CYP3A4 inducers and/or inhibitors. Lastly, SAPHRIS is contraindicated in patients with severe hepatic impairment.
- 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. 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).
- A vast number of Warnings and Precautions are assigned to the atypical antipsychotic agents. The following outlines the most recent FDA safety communications:
    - In May 2016, the FDA warned that impulse-control problems had been associated with the use of aripiprazole. Uncontrollable urges to gamble, binge eat, shop, and have sex were reported. New warnings were added to the drug labels and patient Medication Guides (FDA safety communication [aripiprazole], 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).
    - In March 2015, the FDA concluded their study after 2 unexplained deaths were reported as a result of high plasma drug concentrations after the appropriate doses of ZYPREXA RELPREVV were administered. Study results were inconclusive; therefore, the FDA did not make recommendations to change treatment (FDA safety communication [ZYPREXA RELPREVV], 2015).
    - In May 2016, the FDA warned that olanzapine can cause a Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). In December 2014, 6 patients reported incidences of DRESS with GEODON use. If DRESS is suspected, use should be discontinued immediately. As a result, DRESS was added as a Warning and Precaution to both products (FDA safety communication [olanzapine], 2016; FDA safety communication [ziprasidone], 2014).
    - In September 2011, 52 cases of Type I hypersensitivity reactions were reported with SAPHRIS use. A Warning and Precaution of hypersensitivity reactions was added to the SAPHRIS prescribing information (FDA safety communication [asenapine], 2011).
    - In February 2011, a safety warning for all atypical antipsychotics was communicated after increases in the risk of EPS and withdrawal symptoms were observed in newborns whose mothers were administered antipsychotics in the third trimester of pregnancy (FDA safety communication, 2011).
- 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	Brexpiprazole	Cariprazine	Clozapine*	Iloperidone	Lurasidone	Olanzapine	Paliperidone	Quetiapine	Risperidone	Ziprasidone
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	Moderate	Moderate	Moderate	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	Low to moderate	Low	Low to moderate	Negligible to low	Negligible to low	Moderate	Low	High	Negligible to low	High	Low to moderate
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	Moderate	Moderate	Moderate	Negligible to low
Prolactin – high levels linked to gynecomastia, sexual dysfunction, menstrual disruption, acne, amenorrhea, hirsutism, osteoporosis, increased risk of hip fracture, etc.	Low	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	Low	Negligible to low	Low	Moderate	Negligible to low	Low	Low	Low	Low	Moderate

Abbrv: 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).

(Altinbas et al, 2013; FDA/CBER summary review [VRAYLAR], 2015; Jibson et al, 2016)

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose: Adult	Usual Recommended Dose: Pediatric	Other Dosing Considerations	Administration Considerations
Aripiprazole (ABILIFY,†† ABILIFY DISMELT, ABILIFY MAINTENA)	Orally disintegrating tablet: 10 mg 15 mg Oral Tablet: 2 mg 5 mg 10 mg 15 mg 20 mg 30 mg Long-acting injection (vial or syringe): 300 mg 400 mg Oral Solution: 1 mg/mL	Bipolar disorder – manic or mixed episodes: Oral formulations and monotherapy: initial, 15 mg PO daily; recommended dose, 15 mg PO daily; max, 30 mg PO daily tablet Adjunct to lithium or valproate (oral formulations): initial dose may range from 10 mg to 15 mg PO daily Schizophrenia: Oral formulations: initial or target, 10 to 15 mg PO daily; max, 30 mg PO daily tablet; dose increases should generally not be made before 2 weeks; daily doses > 15 mg were not shown to be more efficacious than 15 mg PO daily Long-acting injection: initial or maintenance, 400 mg IM once a month; max, 400 mg/month; take 14 days of concurrent oral aripiprazole (10 to 20 mg) or current oral antipsychotic in conjunction with the first injection Adjunctive treatment of major depressive disorder: Oral formulations: initial, 2 to 5 mg PO daily; recommended dose, 2 to 15 mg (or 5 to 10 mg) PO daily; max, 15 mg PO daily; dose adjustments up to 5 mg/day should occur at intervals of ≥ 1 week. Dosing of oral solution: May be substituted for tablets on an mg-per-mg basis up to 25 mg. Tablet doses of 30 mg should receive 25 mg of solution.	Bipolar mania – manic or mixed episodes as monotherapy or as adjunct to lithium or valproate (10 to 17 years): Oral formulations: initial, 2 mg PO daily; target dose, 10 mg PO daily; max, 30 mg PO daily tablet; titrate every 2 days Schizophrenia (13 to 17 years): Oral formulations: initial, 2 mg PO daily; target dose, 10 mg PO daily; max, 30 mg PO daily tablet; titrate every 2 days; daily doses of 30 mg daily were not shown to be more efficacious than 10 mg daily Autistic disorder with irritability (6 to 17 years): Oral formulations: initial, 2 mg PO daily; target dose, 5 to 15 mg PO daily; max, 15 mg PO daily; dose adjustments up to 5 mg/day should occur at intervals of ≥ 1 week. Tourette's Disorder (6 to 18 years): Oral formulations: initial, 2 mg PO daily; recommended dose, 5 mg PO daily for patients < 50 kg and 10 mg PO daily for patients ≥ 50 kg; max, 10 mg PO daily for patients < 50 kg and 20 mg PO daily for patients ≥ 50 kg; dose adjustments should occur gradually at intervals of ≥ 1 week.	Dose adjustments are recommended in known CYP2D6 poor metabolizers, or with concomitant CYP2D6 inhibitors, and/or CYP3A4 inhibitors/inducers.*	Oral formulations should be administered once daily without regard to meals. Aripiprazole-naïve patients should establish tolerability with oral formulations prior to initiating long-acting injections. Long-acting injection may be administered in the deltoid or gluteus by a healthcare professional only.

Drug	Dosage Form: Strength	Usual Recommended Dose: Adult	Usual Recommended Dose: Pediatric	Other Dosing Considerations	Administration Considerations
			Dosing of oral solution: May be substituted for tablets on a mg-per-mg basis up to 25 mg. Tablet doses of 30 mg should receive 25 mg of solution.		
Aripiprazole lauroxil (ARISTADA)	Long-acting injection (pre-filled syringe): 441 mg 662 mg 882 mg	Schizophrenia: Initial or maintenance, 441 mg, 662 mg, or 882 mg IM once a month or 882 mg IM once every 6 weeks; take 21 days of concurrent oral aripiprazole in conjunction with the first injection	Not FDA-approved	Dose adjustments are recommended in known CYP2D6 poor metabolizers, or in patients taking concomitant CYP2D6 inhibitors, and/or CYP3A4 inhibitors/inducers for more than 2 weeks.*	Aripiprazole-naïve patients should establish tolerability with oral formulations prior to initiating long-acting injections. The 441 mg dose can be injected into the deltoid or gluteal muscle, but the 662 mg and 882 mg doses can only be administered in the gluteal muscle by a healthcare professional.
Asenapine (SAPHRIS)	Sublingual tablet: 2.5 mg 5 mg 10 mg	Bipolar disorder– manic or mixed episodes: Acute and maintenance monotherapy: initial, target and max dose, 10 mg SL twice daily; dose can be decreased to 5 mg SL twice daily if adverse effects occur. Adjunct to lithium or valproate: initial dose, 5 mg SL twice daily; max dose, 10 mg SL twice daily Schizophrenia: Acute treatment: initial, 5 mg SL twice daily; target dose, 5 mg SL twice daily; max dose, 10 mg SL twice daily; the safety	Bipolar disorder– manic or mixed episodes (10 to 17 years): Initial, 2.5 mg SL twice daily; target dose, 2.5 to 10 mg SL twice daily; max dose, 10 mg SL twice daily; titrate 2.5 to 5 mg every 3 days	Pediatric patients appear to be more sensitive to dystonia with initial dosing when the recommended titration schedule is not followed.	Do not swallow sublingual tablets. Sublingual tablets should be placed under the tongue and left to dissolve completely. The sublingual tablet will dissolve in saliva within seconds. Eating and drinking should be avoided for

Drug	Dosage Form: Strength	Usual Recommended Dose: Adult	Usual Recommended Dose: Pediatric	Other Dosing Considerations	Administration Considerations
		of doses above 10 mg SL twice daily has not been evaluated Maintenance treatment: initial, 5 mg SL twice daily; target dose, 5 to 10 mg SL twice daily; max dose, 10 mg SL twice daily			10 minutes after administration.
Brexpiprazole (REXULTI)	Oral Tablet: 0.25 mg 0.5 mg 1 mg 2 mg 3 mg 4 mg	Adjunctive treatment of major depressive disorder: Initial, 0.5 to 1 mg PO once daily; maintenance, 2 mg once daily; max, 3 mg once daily Schizophrenia: Initial, 1 mg PO once daily; maintenance, 2 to 4 mg once daily; max, 4 mg once daily	Not FDA-approved	Dose adjustments are recommended in known CYP2D6 poor metabolizers, concomitant moderate to strong CYP2D6 and/or CYP3A4 inhibitors, and/or CYP3A4 inducers.*	Take with or without food
Cariprazine (VRAYLAR)	Capsule: 1.5 mg 3 mg 4.5 mg 6 mg Titration pack: 1.5 mg and 3 mg	Schizophrenia: Initial, 1.5 mg PO once daily; maintenance, 1.5 to 6 mg PO once daily; titrate by 1.5 to 3 mg once daily to target dose; max, 6 mg once daily. Bipolar disorder – manic or mixed episodes: Initial, 1.5 mg PO once daily; maintenance, 3 to 6 mg PO once daily; titrate by 1.5 to 3 mg once daily to target dose; max, 6 mg once daily.	Not FDA-approved	Due to the long half-life, dose changes may not be reflected for several weeks. Monitor for adverse events and response for several weeks. Dose adjustments are recommended with concomitant CYP3A4 inhibitors.*	Take with or without food Discontinuation of treatment may not be immediately reflected in the patient. No data addressing switching patients to another treatment is available.
Clozapine (CLOZARIL, FAZACLO, VERSACLOZ)	Orally disintegrating tablet: 12.5 mg 25 mg 100 mg 150 mg 200 mg Tablet:	Treatment-resistant schizophrenia: Initial, 12.5 mg PO once or twice daily;* target dose, 300 to 450 mg daily (in divided doses); max, 900 mg PO daily; titrate by 25 to 50 mg daily to target dose by the end of 2 weeks, after 2 weeks then may titrate by ≤ 100 mg no more frequently than once or twice weekly.	Not FDA-approved	In the event of planned termination of therapy, gradual reduction in dose is recommended over a 1 to 2 week period. Dose adjustments are recommended in patients with	Prior to initiating, a baseline ANC must be ≥ 1,500/µL (≥ 1,000/µL for patients with Benign Ethnic Neutropenia [BEN]). To continue treatment, ANC must be monitored regularly.

Drug	Dosage Form: Strength	Usual Recommended Dose: Adult	Usual Recommended Dose: Pediatric	Other Dosing Considerations	Administration Considerations
	25 mg 50 mg 100 mg 200 mg Suspension: 50 mg/mL	Reduce the risk of recurrent suicidal behavior in schizophrenia or schizoaffective disorder: Same dosing as above. Mean dose is ~300 mg daily.		renal/hepatic impairment, CYP2D6 poor metabolizers, taking concomitant CYP2D6, CYP1A2, CYP3A4 inhibitors and/or CYP3A4, CYP1A2 inducers.*	Shake oral suspension for 10 seconds prior to each use.
Iloperidone (FANAPT)	Tablet: 1 mg 2 mg 4 mg 6 mg 8 mg 10 mg 12 mg	Schizophrenia: Initial, 1 mg twice daily; maintenance, increase to reach the target dose range of 6 to 12 mg twice daily with daily dosage adjustments not to exceed 2 mg twice daily; max, 12 mg twice daily	Not FDA-approved	Dose adjustments are recommended in patients with renal/hepatic impairment, CYP2D6 poor metabolizers, taking concomitant CYP2D6 and/or CYP3A4 inhibitors.*	Control of symptoms may be delayed during the first 1 to 2 weeks. Some adverse effects are dose related.
Lurasidone (LATUDA)	Tablet: 20 mg 40 mg 60 mg 80 mg 120 mg	Schizophrenia: Initial, 40 mg PO once daily;† max, 160 mg PO once daily Bipolar disorder - depressive episodes: Monotherapy or as adjunct to lithium or valproate: initial, 20 mg PO once daily; maintenance 20 to 120 mg once daily; max, 120 mg once daily; in the monotherapy study, daily doses of 80 to 120 mg were not shown to be more efficacious than 20 to 60 mg daily.	Not FDA-approved	Recommended starting dose is 20 mg and the max dose is 80 mg with concomitant use with a moderate CYP3A4 inhibitor, or moderate to severe hepatic or renal impairment.	Administer with food (≥ 350 calories).
Olanzapine (ZYPREXA, ZYPREXA ZYDIS, ZYPREXA RELPREVV)	Orally disintegrating tablet: 5 mg 10 mg 15 mg 20 mg	Schizophrenia: Oral formulations: initial, 5 to 10 mg PO daily; maintenance, 10 mg PO daily; max, 20 mg PO daily; adjust in increments of 5 mg daily. Long-acting injection: initial (during the first 8 weeks), 210 to 300 mg IM every 2 weeks	Schizophrenia (13 to 17 years): Oral formulations: initial, 2.5 to 5 mg PO daily; target, 10 mg PO daily; max, 20 mg PO daily; adjust in increments of 2.5 to 5 mg.	Lower starting dose recommended in debilitated or pharmaco-dynamically sensitive patients or patients with predisposition to	Be aware that there are 2 olanzapine injectable formulations with different dosing schedules.

Drug	Dosage Form: Strength	Usual Recommended Dose: Adult	Usual Recommended Dose: Pediatric	Other Dosing Considerations	Administration Considerations
	Tablet: 2.5 mg 5 mg 7.5 mg 10 mg 15 mg 20 mg Short-acting injection (vial): 10 mg Long-acting injection (vial): 210 mg 300 mg 405 mg	or 405 mg IM every 4 weeks depending upon target oral olanzapine dose; maintenance (after the first 8 weeks of ZYPREXA RELPREVV), 150 to 300 mg IM every 2 weeks or 300 to 405 mg IM every 4 weeks depending upon target oral olanzapine dose; doses > 405 mg every 4 weeks or > 300 mg every 2 weeks have not been evaluated.* <u>Bipolar disorder– manic or mixed episodes:</u> Monotherapy (oral formulations): initial, 10 or 15 mg PO daily; maintenance, 5 to 20 mg PO daily; max, 20 mg PO daily; adjust in increments of 5 mg daily. Adjunct to lithium or valproate (oral formulations): initial, 10 mg PO daily; maintenance, 5 to 20 mg PO daily; max, 20 mg PO daily. <u>Bipolar disorder - depressive episodes (in combo with fluoxetine):</u> Oral formulations: initial, 5 mg PO daily in combination with fluoxetine 20 mg PO daily; maintenance, 5 to 12.5 mg PO daily in combination with fluoxetine 20 to 50 mg PO daily; doses > 18 mg olanzapine with 75 mg of fluoxetine have not been evaluated. <u>Agitation associated with schizophrenia and bipolar I mania</u>: Short-acting injection: initial, 2.5 to 10 mg IM up to every 2 hours; target dose, 10 mg IM (lower dose to 5 to 7.5 mg when clinical factors warrant); max, 30 mg IM daily	<u>Bipolar disorder– manic or mixed episodes (13 to 17 years):</u> Oral formulations: initial, 2.5 or 5 mg PO daily; target, 10 mg PO daily; max, 20 mg PO daily; adjust in increments of 2.5 to 5 mg. <u>Bipolar disorder - depressive episodes (in combo with fluoxetine) (10 to 17 years)</u>: Oral formulations: initial, 2.5 mg PO daily in combination with fluoxetine 20 mg PO daily; maintenance, 2.5 to 12 mg PO daily in combination with fluoxetine 20 to 50 mg PO daily; doses > 12 mg olanzapine with 50 mg of fluoxetine have not been evaluated.	hypotensive reactions, or with potential slowed metabolism. Recommended dosing for the powder for injection is based on correspondence to oral olanzapine doses.	Administer ZYPREXA without regard to meals. ZYPREXA RELPREVV is available only through a restricted distribution program and must be administered by a healthcare professional; patient observation required for at least 3 hours after injection due to the potential for Post-Injection Delirium/Sedation Syndrome. Establish tolerability with oral olanzapine prior to initiating therapy with ZYPREXA RELPREVV.

Drug	Dosage Form: Strength	Usual Recommended Dose: Adult	Usual Recommended Dose: Pediatric	Other Dosing Considerations	Administration Considerations
		Treatment-resistant depression (in combo with fluoxetine): Oral formulations: initial, 5 mg PO daily in combination with fluoxetine 20 mg PO daily; maintenance, 5 to 20 mg PO daily in combination with fluoxetine 20 to 50 mg PO daily; doses > 18 mg olanzapine with 75 mg of fluoxetine have not been evaluated.			
Olanzapine/ fluoxetine (SYMBYAX)	Capsule: 3/25 mg 6/25 mg 6/50 mg 12/25 mg 12/50 mg	Bipolar disorder - depressive episodes and treatment-resistant depression: Initial, 6/25 mg once daily in the evening; maintenance, adjust dosage according to efficacy and tolerability; max, doses > 18/75 mg have not been evaluated	Bipolar disorder - depressive episodes (10 to 17 years): Capsule: initial, 3/25 mg once daily in the evening; maintenance, adjust dosage according to efficacy and tolerability; max, doses > 12/50 mg have not been evaluated	Discontinue treatment gradually.	Neonates exposed to SSRIs late in the third trimester have required prolonged hospitalizations, respiratory support, and tube feeding. Consider tapering dose for pregnant women during the third trimester.
Paliperidone (INVEGA, INVEGA SUSTENNA, INVEGA TRINZA)	Extended-release tablet: 1.5 mg 3 mg 6 mg 9 mg Long-acting injection: Once-a-month (INVEGA SUSTENNA): 39 mg 78 mg 117 mg 156 mg 234 mg Once every 3 months	Schizophrenia: Oral formulation:† initial, 6 mg PO daily; maintenance, 3 to 12 mg PO daily; max, 12 mg PO daily; titrate by 3 mg, increases > 6 mg should occur at intervals > 5 days and only after reassessment. Long-acting injection (INVEGA SUSTENNA): initial, 234 mg administered on treatment day one, followed by 156 mg one week later; maintenance, 117 mg (range, 39 to 234 mg) administered once monthly; max, 234 mg administered once monthly. Long-acting injection (INVEGA TRINZA): To be initiated only after 4 months of INVEGA SUSTENNA. INVEGA TRINZA dose depends on INVEGA SUSTENNA dose; INVEGA SUSTENNA 78 mg, 117	Schizophrenia (12 to 17 years) weighing < 51 kg: Oral formulation:† initial, 3 mg PO daily; maintenance, 3 to 6 mg PO daily; max, 6 mg PO daily; titrate by 3 mg at intervals > 5 days and only after reassessment; in one study, daily doses of 6 mg were not shown to be more efficacious. Schizophrenia, adolescents (12 to 17 years) weighing ≥ 51 kg: Oral formulation:† initial, 3 mg PO daily; maintenance, 3 to 12 mg PO daily; max, 12 mg PO daily; titrate by 3 mg at intervals > 5 days and only after reassessment; in one study,	For patients who have never taken oral paliperidone or oral or injectable risperidone, tolerability should be established with oral paliperidone or risperidone prior to initiating treatment with long-acting injectable paliperidone.	Tablets should be swallowed whole and should not be chewed, divided, or crushed. Administer the first 2 INVEGA SUSTENNA doses in the deltoid muscle. Following the second INVEGA SUSTENNA dose, doses can be administered in either the deltoid or gluteal muscle.

Drug	Dosage Form: Strength	Usual Recommended Dose: Adult	Usual Recommended Dose: Pediatric	Other Dosing Considerations	Administration Considerations
	(INVEGA TRINZA): 273 mg 410 mg 546 mg 819 mg	mg, 156 mg, or 234 mg doses administered once monthly should be converted to INVEGA TRINZA 273 mg, 410 mg, 546 mg, or 819 mg doses administered once every 3 months, respectively; conversion from the INVEGA SUSTENNA 39 mg dose has not been studied. Schizoaffective disorder (monotherapy or adjunct to mood stabilizers or antidepressants): Oral formulation:† initial, 6 mg PO daily; maintenance, 3 to 12 mg PO daily; max, 12 mg PO daily; titrate by 3 mg in increments of > 4 days and only after reassessment. Long-acting injection (INVEGA SUSTENNA): initial, 234 mg administered on treatment day one, followed by 156 mg one week later; maintenance, 78 to 234 mg administered once monthly; max, 234 mg administered once monthly; the 39 mg dose has not been studied.	daily doses of 12 mg were not shown to be more efficacious.		
Quetiapine (SEROQUEL, SEROQUEL XR)	Extended-release tablet: 50 mg 150 mg 200 mg 300 mg 400 mg Immediate-release tablet: 25 mg 50 mg 100 mg 200 mg	Bipolar disorder - depressive episodes: Immediate-release tablet: initial, 50 mg PO once daily at bedtime; maintenance, 300 mg PO daily*; max, 300 mg PO daily Extended-release tablet: initial, 50 mg PO once daily; maintenance, 300 mg once PO daily*; max, 300 mg PO daily Bipolar disorder - manic episodes: Immediate-release tablet (monotherapy or as an adjunct to lithium or divalproex): initial, 50 mg PO twice daily; maintenance,	Bipolar disorder - manic episodes (10 to 17 years): Immediate-release tablet (monotherapy): initial, 25 mg PO twice daily; maintenance, 200 to 300 mg PO twice daily*; max, 600 mg PO daily Extended-release tablet (monotherapy): initial, 50 mg PO daily; recommended, 400 to 600 mg PO daily*; max, 600 mg PO daily	Dose titration is required.	Extended-release tablets should be swallowed whole and not split, chewed, or crushed. Administer extended-release tablets without food or with a light meal. Extended-release tablets should be administered once

Drug	Dosage Form: Strength	Usual Recommended Dose: Adult	Usual Recommended Dose: Pediatric	Other Dosing Considerations	Administration Considerations
	300 mg 400 mg	400 to 800 mg PO daily*; max, 800 mg PO daily Bipolar disorder – manic or mixed episodes: Extended-release tablet (monotherapy or as an adjunct to lithium or divalproex): initial, 300 mg PO once daily; maintenance, 400 to 800 mg PO once daily*; max, 800 mg PO daily Major depressive disorder: Extended-release tablet (as an adjunct to antidepressants): initial, 50 mg PO once daily; maintenance, 150 to 300 mg PO once daily*; max, 300 mg PO daily Schizophrenia: Immediate-release tablet: initial, 25 mg PO twice daily; maintenance, 150 to 750 mg PO daily*; max, 750 mg PO daily for acute treatment (≤ 6 weeks) and 800 mg PO daily for maintenance dosing Extended-release tablet: initial, 300 mg PO once daily; maintenance, 400 to 800 mg PO once daily*; max, 800 mg PO daily	Schizophrenia (13 to 17 years): Immediate-release tablet: initial, 25 mg PO twice daily; recommended, 200 to 400 mg PO twice daily*; max, 800 mg PO daily Extended-release tablet: initial, 50 mg PO daily; recommended, 400 to 800 mg PO daily*; max, 800 mg PO daily		daily, preferably in the evening. Administer immediate-release tablets without regard to food.
Risperidone (RISPERDAL, RISPERDAL CONSTA, RISPERDAL M-TAB)	Orally disintegrating tablet: 0.25 mg 0.5 mg 1 mg 2 mg 3 mg 4 mg Solution: 1 mg/mL	Bipolar – manic or mixed episodes:‡: Oral formulations: initial, 2 to 3 mg PO daily; target, 1 to 6 mg PO daily; max, 6 mg PO daily Long-acting injection (monotherapy or as an adjunct to lithium or valproate): 25 mg IM every 2 weeks; maintenance, 25 to 50 mg IM every 2 weeks; max, 50 mg IM every 2 weeks Schizophrenia:	Bipolar – manic or mixed episodes (10 to 17 years): Oral formulations: initial, 0.5 mg PO once daily; dosage adjustments, if indicated, at intervals not less than 24 hours, in increments of 0.5 mg or 1 mg PO daily, as tolerated, to a recommended dose of 2.5 mg PO daily; no additional benefit was seen above 2.5 mg PO	For the treatment of bipolar mania in adults, there is no clinical data supporting maintenance dosing. For the treatment of bipolar mania in children and adolescents, no	For the treatment of bipolar mania, risperidone should be administered once daily. For the treatment of schizophrenia, risperidone should be administered once or twice daily.

Drug	Dosage Form: Strength	Usual Recommended Dose: Adult	Usual Recommended Dose: Pediatric	Other Dosing Considerations	Administration Considerations
	Tablet: 0.25 mg 0.5 mg 1 mg 2 mg 3 mg 4 mg Long-acting injection: 12.5 mg 25 mg 37.5 mg 50 mg	Long-acting injection: 25 mg IM every 2 weeks; maintenance, 25 to 50 mg IM every 2 weeks; max, 50 mg IM every 2 weeks Oral formulations: initial, 2 mg PO once daily or 1 mg PO twice daily; target, 4 to 16 mg PO per day (divided into once or twice daily dosing); maintenance therapy, 2 to 8 mg PO daily; max, 16 mg PO daily; daily doses of > 6 mg per day for twice daily dosing were not were not shown to be more efficacious than lower doses.	daily; doses higher than 6 mg PO daily were not studied <u>Irritability associated with autistic disorder, children and adolescents aged 5 to 16 years</u>§: Orally disintegrating tablet, oral solution, tablet: initial, 0.25 mg PO daily for patients < 20 kg and 0.5 mg daily for patients ≥ 20 kg; max, 1 mg PO daily in patients < 20 kg, 2.5 mg in patients ≥ 20 kg <u>Schizophrenia, adolescents aged 13 to 17 years:</u> Orally disintegrating tablet, oral solution, tablet: initial, 0.5 mg PO once daily; dosage adjustments, if indicated, at intervals not less than 24 hours, in increments of 0.5 mg or 1 mg PO daily, as tolerated, to a recommended dose of 3 mg PO daily; max, 6 mg PO daily	additional benefit was seen with doses > 2.5 mg/day, and doses > 6 mg/day were not evaluated. Titrate the dose of RISPERAL CONSTA no sooner than every 4 weeks; clinical effects are observed ≥ 3 weeks after injection.	Oral RISPERDAL (or another antipsychotic) should be given with the first injection of RISPERDAL CONSTA, and continued for 3 weeks (and then discontinued) to ensure adequate concentrations of RISPERDAL CONSTA.
Ziprasidone (GEODON)	Capsule: 20 mg 40 mg 60 mg 80 mg Short-acting injection: 20 mg/mL	<u>Acute agitation in schizophrenia</u>: Injection: initial, 10 mg IM every 2 hours or 20 mg every 4 hours; max, 40 mg IM daily¶ <u>Bipolar disorder – manic or mixed episodes</u>: Capsule (monotherapy): initial, 40 mg PO twice daily; maintenance (monotherapy), 60 to 80 mg PO twice daily on day 2; maintenance (adjunct to lithium or valproate), 40 to 80 mg PO twice daily <u>Schizophrenia</u>: Capsule: initial, 20 mg PO twice daily; maintenance, 20 to 80 mg PO twice daily;	Not FDA-approved	Not applicable.	Administer capsules with food. Administration of short-acting injection for more than 3 consecutive days has not been studied. If long term therapy is indicated, oral therapy should replace the injection as soon as possible.

Drug	Dosage Form: Strength	Usual Recommended Dose: Adult	Usual Recommended Dose: Pediatric	Other Dosing Considerations	Administration Considerations
		max, 100 mg PO twice daily; no additional benefit for doses > 20 mg twice daily			Coadministration of capsules and injection is not recommended.

Abbrv: ANC = absolute neutrophil count, BEN = Benign Ethnic Neutropenia, CBC = complete blood count, CYP = cytochrome isoenzyme, IM = intramuscularly, PO = orally, SL = sublingually, WBC = white blood count

*Please refer to individual package insert for dose titration and/or tapering guidance.

†Initial dose titration is not required.

‡There is no clinical data supporting maintenance dosing.

§No dosing data is available for children who weighed less than 15 kg.

¶Administration for more than 3 consecutive days has not been studied.

**In combination with fluoxetine 20 mg (adults and children)

††Short-acting injection is FDA-approved and guidance outlined in prescribing information; however, formulation has been discontinued.

SPECIAL POPULATIONS

Table 5. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy/ Nursing
Aripiprazole*	No dosage adjustment is recommended for elderly patients. Safety and effectiveness of aripiprazole lauroxil extended-release injection in patients > 65 years of age have not been evaluated.	Safety and effectiveness in pediatric patients < 13 years with schizophrenia, patients < 10 years with bipolar mania, and patients < 6 years with Tourette's or with irritability associated with autism have not been established. PK in patients aged 10 to 17 years was similar to adults. The long-acting injections have not been studied in children.	No dosage adjustment is required in subjects with renal impairment.	No dosage adjustment is required in subjects with hepatic impairment.	May cause EPS and/or withdrawal symptoms in neonates with third trimester exposure; discontinue drug or nursing.
Asenapine	Clinical studies did not include sufficient numbers of elderly patients to determine whether or not they respond differently than younger patients.	Safety and efficacy in the treatment of bipolar disorder in patients < 10 years of age, and patients with schizophrenia aged < 12 years have not been evaluated.	No dosage adjustment is required in subjects with renal impairment.	Contraindicated in patients with severe hepatic impairment.	May cause EPS and/or withdrawal symptoms in neonates with third trimester exposure; discontinue drug or nursing.
Brexpiprazole*	Has not been studied in patients aged ≥ 65 years; PK studies showed similar results to adults for MDD.	Safety and effectiveness have not been established. Antidepressants increase the risk of suicidal thoughts and behaviors in pediatric patients.	In moderate, severe, or end-stage renal impairment (CrCL < 60 mL/min), the max dose for MDD is 2 mg once daily and in schizophrenia is 3 mg once daily.	In moderate to severe hepatic impairment, the max dose for MDD is 2 mg once daily and in schizophrenia is 3 mg once daily.	May cause EPS and/or withdrawal symptoms in neonates with third trimester exposure; discontinue drug or nursing.
Cariprazine	Clinical studies did not include sufficient numbers of elderly patients to determine whether or not they respond differently	Safety and effectiveness have not been established.	Not recommended in severe renal impairment (CrCL < 30 mL/min).	Not recommended in severe hepatic impairment (Child-Pugh 10 to 15).	No adequate studies in pregnant women; use only if clearly needed. Drug is present in the milk

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy/ Nursing
	than younger patients.				of animal models; discontinue drug or nursing.
Clozapine*†	Clinical studies did not include sufficient numbers of elderly patients to determine whether or not they respond differently than younger patients. Elderly are more susceptible to hypotension, tachycardia, anticholinergic effects, and tardive dyskinesia.	Safety and effectiveness in pediatric patients have not been established.	Dose reductions may be needed in patients with renal impairment.	Dose reductions may be needed in patients with hepatic impairment.	No adequate studies in pregnant women; however, in general neonates with third trimester exposure have EPS and/or withdrawal symptoms with antipsychotic use. Drug is present in human milk; discontinue drug or nursing.
Iloperidone*	Clinical studies did not include sufficient numbers of elderly patients to determine whether or not they respond differently than younger patients.	Safety and effectiveness in pediatric patients have not been established.	Renal impairment (CrCL < 30 mL/min) had minimal effect on PK parameters.	Not recommended in severe impairment.	No adequate studies in pregnant women; use only if clearly needed. Drug is present in the milk of animal models; do not breastfeed.
Lurasidone	Clinical studies did not include sufficient numbers of elderly patients to determine whether or not they respond differently than younger patients.	Safety and effectiveness in pediatric patients have not been established.	PK bounds varied moderately in mild to severe impairment; dose should not exceed 80 mg/day in patients with CrCL < 50.	In severe impairment AUC was much higher than in mild to moderate impairment; dose reduction to max 40 mg/day recommended.	No adequate studies in pregnant women; use only if benefit outweighs risk. Discontinue drug or nursing.
Olanzapine	Consider a lower starting dose (2.5 mg to 5 mg short-acting injection) for any elderly patient if factors are present that might decrease PK clearance or increase the PD response. Clinical studies did not include sufficient numbers of elderly	Safety and effectiveness in pediatric patients with schizophrenia or manic/mixed bipolar I disorder < 13 years of age and < 10 years in combination with fluoxetine for acute treatment of depressive episodes have not been established.	No dosage adjustment is required in subjects with renal impairment. Has not been studied in long-acting injection formulations.	May reduce clearance; however a small study (N = 6) of cirrhosis patients showed very little PK effects. Has not been studied in long-acting injection formulations.	No adequate studies in pregnant women; use only if benefit outweighs risk. May cause EPS and/or withdrawal symptoms in neonates with third trimester exposure. Drug is present in human milk; do not breastfeed.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy/ Nursing
	patients in long-acting injection studies to determine whether or not they respond differently than younger patients.	Safety and effectiveness of the long-acting injection have not been established. Adolescents treated with oral olanzapine are more prone to weight gain, sedation, metabolic changes, prolactin, and AST increases.			
Olanzapine/ fluoxetine	Clinical studies did not include sufficient numbers of elderly patients to determine whether or not they respond differently than younger patients. Certain factors might decrease PK clearance or increase PD response; consider a lower starting dose (3/25 mg or 6/25 mg).	Safety and efficacy in pediatric patients with bipolar depression < 10 years have not been established. Safety and efficacy in treatment resistant depression has not been established. Adolescents treated with oral olanzapine are more prone to weight gain, sedation, metabolic changes, prolactin, and AST increases.	No dosing recom-mendations	Consider lower initial doses of SYMBYAX (3/25 mg or 6/25 mg) in hepatic impairment. Caution is advised when using SYMBYAX in patients with diseases or conditions that could affect its metabolism.	No adequate studies in pregnant women; fluoxetine exposure in the first trimester has had inconsistent results and the third trimester have resulted in complications requiring prolonged hospitalizations, respiratory support, and tube feeding. Use only if benefit outweighs risk. Drug is present in human milk; do not breastfeed.
Paliperidone Paliperidone palmitate‡	Because elderly patients may have diminished renal function, dose adjustment may be required according to their renal function status. In general, the recommended dosing for elderly patients with healthy renal function is the same as for younger adult patients with	Safety and effectiveness in pediatric patients with schizophrenia < 12 years of age have not been established. Safety and effectiveness in pediatric patients with schizoaffective disorder and other conditions have not been established.	Adjust dose to 3 to 6 mg once daily in mild renal impairment (CrCL 50 to 80 mL/ min); 1.5 to 3 mg once daily in moderate to severe impairment (CrCL 10 to 50 mL/ min). For mild impairment, SUSTENNA should be dosed at 156 mg on day 1 followed by 117	For patients with mild to moderate hepatic impairment no dose adjustment is recom-mended. Not studied in patients with severe hepatic impairment.	No adequate studies in pregnant women; however, in general neonates with third trimester exposure have EPS and/or withdrawal symptoms with antipsychotic use. Drug is present in human milk; discontinue drug or nursing.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy/ Nursing
	healthy renal function.	Safety and effectiveness of the long-acting injection in patients < 18 years of age have not been established.	mg one week later; subsequent dose should be 78 mg every month. TRINZA should be transitioned after stabilized on SUSTENNA. For moderate to severe impair-ment, long-acting injections are not recommended.		
Quetiapine	For elderly patients, consider a slower rate of dose titration and a lower target dose; when indicated, dose escalation should be performed with caution in these patients.	Safety and effectiveness in pediatric patients with schizophrenia < 13 years, and bipolar mania < 10 years have not been established. Increases in systolic and diastolic BP occurred in pediatric patients. Safety and effectiveness in bipolar depression have not been established.	Dosage adjustment not needed.	Start at a low dose of 50 mg for extended-release (XR) and 25 mg immediate-release (IR). Increase by 25 to 50 mg for IR and 50 mg for XR formulations.	Based on animal data, may cause fetal harm. Limited human data; only use if the benefit justifies the risk. Drug is present in human milk; discontinue drug or nursing.
Risperidone‡	Clinical studies did not include sufficient numbers of elderly patients to determine whether or not they respond differently than younger patients. Lower doses may be considered as elderly are susceptible to hypotension and risperidone is highly excreted by the kidneys.	Safety and effectiveness in pediatric patients with schizophrenia < 13 years, bipolar disorder < 10 years, and autistic disorder < 5 years have not been established. Pediatric patients treated with oral risperidone are prone to tardive dyskinesia, weight gain, somnolence,	For severe impairment (CrCL < 30 mL/min), start at 0.5 mg twice daily (see PI for dose titration). Long-acting injection should be initiated after patient is stable on the oral formulation.	For severe impairment (Child-Pugh C), start at 0.5 mg orally twice daily (see PI for dose titration). Long-acting injection should be initiated after patient is stable on the oral formulation.	Reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, feeding disorder, and corpus callosum were reported in neonates exposed in the third trimester. No data is available in humans with the long-acting injection. Drug is present in human milk;

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy/ Nursing
		and elevated prolactin levels. Safety and efficacy of the long-acting injection in pediatric patients have not been established.			discontinue drug or nursing.
Ziprasidone	Consider a lower starting dose, slower titration, and careful monitoring during the initial dosing period for some elderly patients. Ziprasidone IM has not been studied in this group.	Safety and effectiveness in pediatric patients have not been established.	Caution should be used in renal impairment with administration of IM formulations due to cyclodextrin, which is renally filtered.	Dose adjustments are not required but PK changes have been observed. Ziprasidone IM has not been studied in this group.	Based on animal data, may cause fetal harm. Limited human data; only use if the benefit justifies the risk. Drug is present in the milk of animal models; do not breastfeed.

Abbrv: AST = hepatic aminotransferase, ANC = absolute neutrophil count, AUC = area under the curve, BP=blood pressure, CrCL = creatinine clearance, EPS = extrapyramidal symptoms, IM = intramuscular, MDD = major depressive disorder, NMS = neuroleptic malignant syndrome, PD = pharmacodynamic, PI = prescribing information, PK = pharmacokinetic
*For CYP2D6 poor metabolizers dosage adjustments are recommended.
†For hospice patients (life expectancy ≤ 6 months), consider reducing the ANC monitoring frequency to once every 6 months.
‡Patients with Parkinson's disease or Dementia with Lewy Bodies can have increased sensitivity to long-acting injections, which may result in confusion, EPS, NMS, obtundation, and instability with frequent falls.

CONCLUSION

- The antipsychotics are divided into 2 distinct classes: typical antipsychotics, also called first generation antipsychotics, and atypical antipsychotics, also called second generation antipsychotics (Miyamato 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 autism, bipolar disorder, Tourette's disorder, major depressive disorder, schizophrenia, and schizoaffective disorder. FDA-approved atypical agents include (Drugs@FDA, 2017):
  - Generic agents – aripiprazole, clozapine, iloperidone, olanzapine, paliperidone, quetiapine immediate- and extended-release, risperidone, ziprasidone, and olanzapine/fluoxetine
  - Branded agents – GEODON® (short-acting injection only), LATUDA®, REXULTI®, SAPHRIS®, VERSACLOZ® (oral suspension), and VRAYLAR™
  - Long-acting injections – ABILIFY MAINTENA®, ARISTADA™ , INVEGA SUSTENNA®, INVEGA TRINZA® (the only once every 3 months injection), RISPERDAL CONSTA®, and ZYPREXA RELPREVV®
- In terms of the pharmacology of the atypical antipsychotics, different chemical entities have different properties. Most atypical antipsychotics have a fairly long half-life (≥ 24 hours), except lurasidone, quetiapine, and ziprasidone. Aripiprazole lauroxil is the prodrug of aripiprazole, and paliperidone is the active metabolite of risperidone. The newly FDA-approved agent, cariprazine, has the longest half-life in the oral class (1 to 3 weeks for active metabolite); therefore, delayed adverse events have been reported. Clozapine can be highly toxic; therefore, clinicians should check plasma levels before exceeding a 600 mg dose. For the long-acting injectable agents, drug tolerability should be established prior to initiating the long-acting injectable treatment; a patient's response to an adjusted dose may not be seen for some time due to the long half-life. RISPERDAL CONSTA serum concentrations may not be seen until

approximately 3 weeks after injection. In certain slow metabolizers careful dose adjustment should be made as is the case with iloperidone and CYP2D6 slow metabolizers (Clinical Pharmacology, 2016; Micromedex 2.0, 2016).

- FDA-approved 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, 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 REXULTI. RISPERDAL CONSTA is the only long-acting injectable indicated for the treatment of bipolar disorder. Aripiprazole, olanzapine/fluoxetine, risperidone, quetiapine, and SAPHRIS 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, REXULTI, and SEROQUEL XR 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 is 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 extrapyramidal symptoms (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 (with the exception of clozapine), making them a generally better-tolerated treatment option (Abou-Setta et al, 2012; Lehman et al, 2004; Seida et al, 2012[a]; Seida et al, 2012[b]; VA Pharmacy Benefits Management Services, 2012). However, certain atypical antipsychotic agents appear to have varying levels of risk according to the side effect profile (Jibson et al, 2016; Micromedex 2.0, 2016). 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 versus 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 ≥ 10% of adult patients, but somnolence/fatigue and insomnia were reported in ≥ 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. In 2015, the FDA made changes to the recommended monitoring within the clozapine REMS program around severe neutropenia (FDA Drug Safety Communication [clozapine], 2015).
- Hypersensitivity – Olanzapine and ziprasidone have a specific warning for a fatal drug reaction with eosinophilia and systemic symptoms or DRESS. In 2011, the FDA issued an alert on serious allergic reactions after 52 cases of Type I hypersensitivity reactions were reported with asenapine use (FDA Drug Safety Communication [Saphris], 2011).

- Newly FDA-approved agent, cariprazine, has demonstrated safe and effective use in doses ≤ 6mg/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. Although, 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 to 9 mg daily during maintenance therapy (Durgam et al, 2016[a]; Durgam et al, 2016[b]).
- 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, 2015; 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 major depressive disorder (MDD), aripiprazole, REXULTI (brexpiprazole), and SEROQUEL XR (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. REXULTI is the newest agent FDA-approved and has not been included in MAs. Primary efficacy results demonstrate efficacy vs placebo, and the safety profile appears to be similar to aripiprazole (Thase et al, 2015). One meta-analysis 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 meta-analysis concluded aripiprazole and quetiapine may have an advantage in reducing remission (NNT, 9) compared to olanzapine/fluoxetine (NNT, 19) (Spielmans 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 SAPHRIS are FDA-approved for manic or mixed episodes, although only quetiapine and olanzapine/fluoxetine have been studied for depressive episodes. In an AHRQ SR, aripiprazole, olanzapine, ziprasidone, quetiapine, and risperidone were associated with greater improvements in response rates (NNT, 3 to 7) and increased remission rates (NNT, 2 to 12) compared to placebo (Seida et al, 2012[a]; Seida et al, 2012[b]). For depressive episodes, evidence is less clear, but point to efficacy with the FDA approved agents (Findling et al, 2014; Detke et al, 2015). In adult patients with bipolar disorder, selection of agents should be based on the adverse event profile and individual patient characteristics as all FDA-approved agents have demonstrated efficacy (Abou-Setta et al, 2012; Muralidharan et al, 2013). 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; Perlis et al, 2006[b]; Riedel et al, 2010; Seida et al, 2012[a]; Seida et al, 2012[b]; 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 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). The European Society for the Study of Tourette Syndrome guideline recommends risperidone as first-line treatment, aripiprazole for treatment-refractory patients, and clonidine for patients with co-morbid ADHD (Roessner et al, 2011).

- 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.

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