Texas Vendor Drug Program

Drug Use Criteria: Atypical Antipsychotics (oral)

Publication History

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Notes: Information on indications for use or diagnosis is assumed to be unavailable. All criteria may be applied retrospectively; prospective application is indicated with an asterisk [*]. The information contained is for the convenience of the public. The Texas Health and Human Services Commission is not responsible for any errors in transmission or any errors or omissions in the document.

Medications listed in the tables and non-FDA approved indications included in these retrospective criteria are not indicative of Vendor Drug Program formulary coverage.

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1 Dosage

1.1 Adults

Oral atypical antipsychotics are FDA-approved for use in schizophrenia, bipolar I disorder (BD), bipolar disorder with mixed episodes or depressive episodes, bipolar mania, schizoaffective disorder (SD), adjunctive therapy in major depressive disorder (MDD), treatment-resistant schizophrenia, and irritability associated with autism.[1-18] Cariprazine (Vraylar®) has been approved for schizophrenia and manic or mixed episodes associated with BD.[1-4, 19] Aripiprazole tablets with sensors (Abilify MyCite®) have been approved to track if the medication has been taken.[22]

Pimavanserin (Nuplazid®) is an oral atypical antipsychotic recently indicated for use to manage hallucinations and delusions seen with Parkinson's disease psychosis.[1-4, 20] Olanzapine combination therapy is FDA-approved for use in managing treatment-resistant depression as well as bipolar depression.[1-4, 21]

Maximum recommended adult doses for atypical antipsychotics are summarized in Table 1. Dosages exceeding these recommendations will be reviewed.

Table 1. Oral Atypical Antipsychotics (Monotherapy) - Adult Maximum Recommended Dosages[1-39]

Treatment Indication	Drug Name	Available Dosage Strengths	Maximum Recommended Dosage
Schizophrenia, BD	Aripiprazole(Abilify®, Abilify Discmelt®, Abilify MyCite® system)	2 mg, 5 mg, 10mg, 15 mg, 20 mg, 30 mg immediate-release (IR) tablets 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, 30 mg IR tablets with sensor# 10 mg, 15 mg orally disintegrating tablets (ODTs) 1 mg/ml oral solution	30 mg/day

Treatment Indication	Drug Name	Available Dosage Strengths	Maximum Recommended Dosage
MDD	Aripiprazole(Abilify®, Abilify Discmelt®, Abilify MyCite® system)	2 mg, 5 mg, 10mg, 15 mg IR tablets 2 mg, 5 mg, 10mg, 15 mg IR tablets with sensor# 10 mg, 15 mg ODTs 1 mg/ml oral solution	15 mg/day
Schizophrenia, BD	Asenapine (Saphris®)	2.5 mg, 5 mg, 10 mg sublingual tablets	20 mg/day, in two divided doses
Schizophrenia	Brexpiprazole (Rexulti®)	0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg tablets	4 mg once daily
MDD	Brexpiprazole (Rexulti®)	0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg tablets	3 mg once daily
Bipolar major depression	Cariprazine (Vraylar®)	1.5 mg, 3 mg, 4.5 mg 6 mg capsules	3 mg once daily
BD (acute mixed/manic episodes), schizophrenia			6 mg once daily
Schizophrenia (treatment-resistant), reducing recurrent suicidal behavior in schizophrenia and schizoaffective disorder (SD)	Clozapine (Clozaril®, generics, FazaClo®, Versacloz®)	25 mg, 50 mg, 100 mg, 200 mg IR tablets 12.5 mg, 25 mg, 100 mg, 150 mg, 200 mg ODTs 50 mg/ml oral suspension	900 mg/day, in divided doses
Schizophrenia	Iloperidone (Fanapt®)	1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg 12 mg IR tablets	24 mg/day, in divided doses
Schizophrenia	Lurasidone (Latuda®)	20 mg, 40 mg, 60 mg, 80 mg, 120 mg IR tablets	160 mg/day, with food (at least 350 calories)
Bipolar depression			120 mg/day, with food (at least 350 calories)
Schizophrenia, BD, treatment-resistant depression	Olanzapine (Zyprexa®, Zyprexa Zydis®, generics)	2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg IR tablets 5 mg, 10 mg, 15 mg, 20 mg ODTs	20 mg/day, as a single dose

Treatment Indication	Drug Name	Available Dosage Strengths	Maximum Recommended Dosage
Schizophrenia, SD	Paliperidone (Invega®)	1.5 mg, 3 mg, 6 mg, 9 mg extended-release (ER) tablets	12 mg/day
Parkinson disease psychosis	Pimavanserin (Nuplazid®)	10 mg, 17 mg, 34 mg tablet	34 mg once daily
Schizophrenia, BD (acute manic episodes, maintenance)	Quetiapine (Seroquel®, Seroquel XR®, generics)	25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg IR tablets 50 mg, 150 mg, 200 mg, 300 mg, 400 mg ER tablets	IR: 800 mg/day, in two or three divided doses ER: 800 mg/day, as a single dose
MDD	Quetiapine (Seroquel XR®, generics)	50 mg, 150 mg, 200 mg, 300 mg, 400 mg ER tablets	ER: 300 mg/day, as a single dose
Bipolar depression	Quetiapine (Seroquel®, Seroquel XR®, generics)	25 mg, 50 mg, 100 mg 200 mg, 300 mg IR tablets 50 mg, 150 mg, 200 mg, 300 mg ER tablets	IR: 300 mg/day, at bedtime ER: 300 mg/day, as a single dose
Schizophrenia	Risperidone (Risperdal®, Risperdal M-TAB®, generics)	0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg IR tablets 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg ODTs 1 mg/ml oral solution	8 mg/day in 1 or 2 divided doses*
Bipolar mania	Risperidone (Risperdal®, Risperdal M-TAB®, generics)	0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg IR tablets 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg ODTs 1 mg/ml oral solution	6 mg/day
Schizophrenia	Ziprasidone (Geodon®, generics)	20 mg, 40 mg, 60 mg, 80 mg IR capsules	200 mg/day, in two divided doses+
BD	Ziprasidone (Geodon®, generics)	20 mg, 40 mg, 60 mg, 80 mg IR capsules	160 mg/day, in two divided doses

- # ingestible event marker (IEM) embedded in each MyCite® tablet; to be dispensed with MyCite® patch (wearable sensor that detects signal frim IEM sensor) and MyCite App

- * = Doses up to 16 mg/day have demonstrated efficacy in clinical trials; however, doses of 4 to 8 mg/day tended to produce the maximal effect
- + = Doses up to 320 mg daily have been used safely but greater efficacy not noted with higher dosages

Combination therapy with the atypical antipsychotic, olanzapine, and the selective serotonin reuptake inhibitor, fluoxetine, is FDA-approved for the management of depressive episodes associated with bipolar I disorder and treatment-resistant depression in adults. Doses exceeding the maximum adult recommended doses summarized in Table 2 will be reviewed.

Table 2. Oral Atypical Antipsychotics (Combination Therapy) – Adult Maximum Recommended Dosages[1-4, 40]

Treatment Indication	Drug Name	Available Dosage Strengths	Maximum Recommended Dosage
Bipolar depression, treatment-resistant depression	Olanzapine/ fluoxetine (Symbyax®)	Olanzapine 3 mg/fluoxetine 25 mg; olanzapine 6 mg/fluoxetine 25 mg; olanzapine 6 mg/fluoxetine 50 mg; olanzapine 12 mg/fluoxetine 25 mg; olanzapine 12 mg/fluoxetine 50 mg	Olanzapine 18 mg/ fluoxetine 75 mg once daily in evening, without regard to meals

1.2 Pediatrics

Risperidone has been FDA-approved to manage symptoms of irritability in autistic children greater than 5 years of age and adolescents and has recently gained FDA-approved indications for bipolar mania in children and adolescents 10 to 17 years of age and schizophrenia in adolescents 13 to 17 years of age. Aripiprazole has received recent FDA approval for treating Tourette's disorder in pediatric patients 6 to 18 years of age and is also FDA-approved for managing schizophrenia in adolescents 13 to 17 years of age, bipolar disorder with or without psychotic features in children 10 to 17 years of age, and irritability associated with autistic disorder in children 6 to 17 years of age. Olanzapine has been granted FDA approval for bipolar disorder and schizophrenia in adolescents 13 years of age and older, while quetiapine received FDA approval for acute treatment of bipolar disorder mania episodes in children and adolescents 10 to 17 years of age and schizophrenia management in adolescents 13 to 17 years of age. Paliperidone has

recently gained FDA approval for schizophrenia in adolescents 12 to 17 years of age. Brexpiprazole, cariprazine, clozapine, iloperidone, lurasidone, ziprasidone, and aripiprazole tablets with sensors (Abilify MyCite®) are not recommended for use in pediatric patients as safety and efficacy have not been established in this patient population. Additionally, pimavanserin is not approved for use in pediatric patients as Parkinson's disease is typically not observed in pediatric patients, and safety and efficacy data are not available for pimavanserin in the pediatric population. Atypical antipsychotic pediatric dosages are summarized in Table 3.[1-23]

Table 3. Atypical Antipsychotics (Monotherapy) – Pediatric Maximum Recommended Dosages[1-4, 8, 10, 12-16]

Treatment Indication	Drug Name	Available Dosage Strengths	Maximum Recommended Dosage per Age Group
Schizophrenia	Aripiprazole(Abilify®, Abilify Discmelt®)	2 mg, 5 mg, 10mg, 15 mg, 20 mg, 30 mg immediate-release (IR) tablets 10 mg, 15 mg orally disintegrating tablets (ODTs) 1 mg/ml oral solution	13-17 years of age: 30 mg once daily
BD	Aripiprazole(Abilify®, Abilify Discmelt®)	2 mg, 5 mg, 10mg, 15 mg, 20 mg, 30 mg IR tablets 10 mg, 15 mg ODTs 1 mg/ml oral solution	10-17 years of age: 30 mg once daily
Irritability associated with autism	Aripiprazole(Abilify®, Abilify Discmelt®)	2 mg, 5 mg, 10mg, 15 mg, IR tablets 10 mg, 15 mg ODTs 1 mg/ml oral solution	6-17 years of age: 15 mg/day as a single dose
Tourette's disorder	Aripiprazole(Abilify®, Abilify Discmelt®)	2 mg, 5 mg, 10mg, 15 mg, 20 mg, 30 mg IR tablets 10 mg, 15 mg ODTs 1 mg/ml oral solution	6-18 years of age: Less than 50 kg: 10 mg/day Greater than or equal to 50 kg: 20 mg/day
BD	Asenapine (Saphris®)	5 mg, 10 mg sublingual tablets	10-17 years of age: 20 mg/day, in two divided doses
Schizophrenia, BD	Olanzapine (Zyprexa®, Zyprexa Zydis®, generics)	2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg IR tablets 5 mg, 10 mg, 15 mg, 20 mg orally disintegrating tablets	13 to 17 years of age: 20 mg once daily

Treatment Indication	Drug Name	Available Dosage Strengths	Maximum Recommended Dosage per Age Group
Schizophrenia	Paliperidone (Invega®)	1.5 mg, 3 mg, 6 mg, 9 mg extended-release (ER) tablets	12-17 years of age: Less than 51 kg: 6 mg/day Greater than or equal to 51 kg: 12 mg/day
BD - acute manic episodes	Quetiapine (Seroquel®, generics, Seroquel XR®)	25 mg, 50 mg, 100 mg 200 mg, 300 mg, 400 mg IR tablets 50 mg, 150 mg, 200 mg, 300 mg, 400 mg ER tablets	10 to 17 years of age: 600 mg daily, once daily (ER tablets) or in 2 to 3 divided doses (IR tablets)
Schizophrenia	Quetiapine (Seroquel®, generics, Seroquel XR®)	25 mg, 50 mg, 100 mg 200 mg, 300 mg, 400 mg IR tablets 50 mg, 150 mg, 200 mg, 300 mg, 400 mg ER tablets	13 to 17 years of age: 800 mg daily, once daily (ER tablets) or in 2 to 3 divided doses (IR tablets)
Bipolar mania	Risperidone (Risperdal®, Risperdal M-TAB®, generics)	0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg IR tablets 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg ODTs 1 mg/ml oral solution	10-17 years of age: 6 mg daily
Schizophrenia	Risperidone (Risperdal®, Risperdal M-TAB®, generics)	0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg IR tablets 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg ODTs 1 mg/ml oral solution	13-17 years of age: 6 mg daily
Irritability in autistic disorder	Risperidone (Risperdal®, Risperdal M-TAB®, generics)	0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg IR tablets 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg ODTs 1 mg/ml oral solution	5-17 years of age: 3 mg/day (no dosing data available for pediatric patients less than 15 kg)

The olanzapine/fluoxetine combination has been approved for use in pediatric patients 10-17 years of age with depression associated with BD. Recommended pediatric dosages are summarized in Table 4.

Table 4. Oral Atypical Antipsychotics (Combination Therapy) – Pediatric Maximum Recommended Dosages[1-4, 40]

Treatment Indication	Drug Name	Available Dosage Strengths	Maximum Recommended Dosage per Age Group
Bipolar depression	Olanzapine/ fluoxetine (Symbyax®)	Olanzapine 3 mg/fluoxetine 25 mg; olanzapine 6 mg/fluoxetine 25 mg; olanzapine 6 mg/fluoxetine 50 mg; olanzapine 12 mg/fluoxetine 25 mg; olanzapine 12 mg/fluoxetine 50 mg	*10-17 years of age:* olanzapine 12 mg/ fluoxetine 50 mg once daily in evening, without regard to meals

2 Duration of Therapy [1-40]

Atypical antipsychotics are indicated for use in the management of schizophrenia and psychotic disorders. Therefore, there is no basis for limiting treatment duration with these atypical antipsychotics as these agents are utilized in the management of chronic disorders.

3 Duplicative Therapy

Combined therapy with multiple antipsychotic medications has been evaluated in patients with treatment-resistant schizophrenia. Open studies, case reports, and clinical trials have observed favorable results following concurrent therapy with either atypical antipsychotics plus conventional antipsychotic agents, or clozapine in conjunction with an additional atypical antipsychotic in clozapine-refractory patients. Further controlled trials are necessary to identify patients and circumstances in which combination therapy should be utilized as well as risks and benefits of concurrent therapy.

Neuroleptics should be used concomitantly during transitional periods lasting up to four weeks when switching patients to a different antipsychotic agent.

4 Drug-Drug Interactions

Patient profiles will be assessed to identify those drug regimens which may result in clinically significant drug-drug interactions. Drug interactions considered clinically relevant for atypical antipsychotics are summarized in Table 5. Only those drug-drug interactions classified as clinical significance level 1 or those considered life-threatening which have not yet been classified will be reviewed:

Table 5. Select Drug-Drug Interactions for Oral Atypical Antipsychotics[1-4, 41]

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level[#]
Aripiprazole	Citalopram	Increased risk of QT prolongation and serotonin syndrome because aripiprazole is a partial agonist of 5-HT1A and citalopram is a selective serotonin reuptake inhibitor	Avoid use	Major (DrugReax) 2-major(CP)
Atypical antipsychotics (AAs)	Antihypertensive agents	Potential for enhanced antihypertensive effects due to AA-associated alpha$_1$-adrenergic receptor antagonism	Use cautiously together; monitor for amplified hypotensive effects	3-moderate (CP)
AAs	CNS depressants	Potential for additive CNS effects	Use cautiously together; observe patients for enhanced CNS adverse effects	Major (DrugReax) 3-moderate (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level[#]
AAs (except pimavanserin)	Drugs affecting seizure threshold (e.g., tramadol)	Increased seizure risk as AAs have been associated with seizures (incidence varies)	Avoid drug combination if possible; if combination necessary, closely monitor patients for seizure activity and discontinue therapy as indicated	Major (DrugReax) 2-major (CP)
AAs	Metoclopramide	Adjunctive therapy enhances potential for increased extrapyramidal symptoms (EPS) and neuroleptic malignant syndrome (NMS) as both agents block dopamine receptors	Combination contraindicated by metoclopramide manufacturer; if combination necessary, monitor for signs/ symptoms of EPS or NMS-discontinue metoclopramide if symptoms develop	Contraindicated (DrugReax) 1-severe (CP)
Clozapine	Myelopsuppressive (antineoplastic) drugs	Potential for additive bone marrow suppressive effects	Concurrent administration contraindicated	1-severe (CP)
Clozapine	Carbamazepine	Increased risk of additive bone marrow-suppressing effects, including agranulocytosis	Avoid concurrent use; choose alternative anticonvulsant	Major (DrugReax) 2-major (CP)
Select AAs (clozapine, olanzapine)	CYP1A2 inducers (e.g., carbamazepine**, phenobarbital, phenytoin, ritonavir*, rifampin)	Potential for reduced clozapine, olanzapine serum concentrations and worsening of psychosis	Monitor clozapine, olanzapine efficacy in patients; adjust doses as necessary when CYP1A2 inducer added, deleted, or changed to therapeutic regimen	Moderate (DrugReax) 2-major (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level[#]
Select AAs (asenapine, clozapine, olanzapine)	CYP1A2 inhibitors (e.g., ciprofloxacin, fluvoxamine)	Potential for decreased AA clearance, increased AA serum concentrations and enhanced pharmacologic/ adverse effects (seizures, hypotension) as clozapine, olanzapine metabolized by CYP1A2	If drug combination necessary, used reduced clozapine dosages and closely monitor for adverse events	Moderate (DrugReax) 2-major (CP)
Select AAs (aripiprazole, brexpiprazole, cariprazine, clozapine, iloperidone, pimavanserin, quetiapine, ziprasidone)	CYP3A4 inhibitors (e.g., ketoconazole, ritonavir*)	Potential for decreased AA clearance, increased AA serum concentrations, and enhanced pharmacologic/ adverse effects as select AAs metabolized by CYP3A4	Monitor for enhanced AA pharmacologic/ adverse effects and adjust doses as necessary (50% dose reduction recommended for aripiprazole, brexpiprazole, iloperidone)	Moderate (DrugReax) 2-major, 3-moderate (CP)
Select AAs (aripiprazole, brexpiprazole, clozapine, olanzapine, pimavanserin, quetiapine, risperidone, ziprasidone)	CYP3A4 inducers (e.g., carbamazepine**, phenytoin)	Potential for significant reductions in AA plasma concentrations (by as much as 50%) due to enhanced AA hepatic microsomal metabolism	Monitor AA efficacy in patients; adjust doses as necessary when CYP3A4 inducer added, deleted, or changed to therapeutic regimen (brexpiprazole dose should be doubled over 1-2 weeks when prescribed with CYP3A4 inducer)	Moderate (DrugReax) 2-major, 3-moderate (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level[#]
Select AAs (aripiprazole, brexpiprazole, iloperidone, risperidone)	CYP2D6 inhibitors (e.g., quinidine, select SSRIs, ritonavir)	Potential for decreased AA clearance and increased AA serum concentrations and enhanced pharmacologic/ adverse effects as select AAs metabolized by CYP2D6	Monitor for enhanced AA pharmacologic/ adverse effects and adjust doses as necessary (recommended to reduce aripiprazole, brexpiprazole, iloperidone doses by 50% when administered in conjunction with CYP2D6 inhibitor)	Moderate (DrugReax) 2-major, 3-moderate (CP)
Select AAs (aripiprazole, asenapine, clozapine, iloperidone, olanzapine, paliperidone, pimavanserin, quetiapine, risperidone, ziprasidone)	QTc interval-prolonging medications	Potential for increased cardiotoxicity (e.g., torsades de pointes, cardiac arrest) due to additive QT interval prolongation	Avoid concurrent use; if combination necessary, closely monitor cardiac function; discontinue therapy in patients with QTc measurements > 500 msec	Major (DrugReax) 1-severe, 2-major (CP)

- [#] CP = Clinical Pharmacology
- * - Ritonavir inhibits clozapine metabolism through CYP3A4 inhibition but induces olanzapine metabolism through CYP1A2 enzyme induction.
- ** = Carbamazepine induces olanzapine metabolism through CYP1A2 enzyme induction and induces clozapine metabolism through CYP3A4 induction.

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