BlueCross BlueShield of Alabama

Atypical Antipsychotics Step Therapy and Quantity Limit Program Summary

This step therapy program applies to Commercial, GenPlus, NetResults A series, SourceRx and Health Insurance Marketplace.

OBJECTIVE

The intent of the Atypical Antipsychotic Step Therapy (ST) program is to encourage the use of cost-effective generic atypical antipsychotic agents over brand atypical antipsychotic agents and to accommodate for use of brand atypical antipsychotic agents when generic atypical antipsychotic agents cannot be used due to previous trial, documented intolerance, FDA labeled contraindication, or hypersensitivity. The criteria for Abilify and Abilify Discmelt encourage the use of cost-effective generic atypical antipsychotic agents or generic FDA approved agents for Tourette's Disorder, and accommodate for the use of Abilify and Abilify Discmelt when generic atypical antipsychotic agents or generic FDA approved Tourette's Disorder agents cannot be used due to previous trial, documented intolerance, FDA labeled contraindication, or hypersensitivity. The use of these agents for the off-label use "dementia-related psychosis" will be accommodated for shorter approval timeframes, due to concerns with safety of their use in the dementia population and based on published regulations and guidelines. The program also allows for continuation of therapy if a patient has been previously stabilized on the requested brand atypical antipsychotic. All dosage forms of the brand atypical antipsychotics listed will be included as targets in the step therapy program.

TARGET AGENTS

Abilify® (aripiprazole)[a]
Abilify Discmelt® (aripiprazole)[c]
Abilify Maintena™ (aripiprazole)
Aripiprazole ODT
Aristada™ (aripiprazole lauroxil)
Aristada Initio™ (aripiprazole lauroxil extended reléase)
Clozaril® (clozapine)[a]
Fanapt® (iloperidone)
FazaClo®, **clozapine ODT**[a,b] (clozapine)
Geodon® (ziprasidone)[a]
Invega® (paliperidone)[a]
Invega Sustenna® (paliperidone)
Invega Trinza® (paliperidone injection)
Latuda® (lurasidone)
Rexulti® (brexpiprazole)
Risperdal® (risperidone)[a]
Risperdal® **M-Tab®** (risperidone)[a]
Risperdal Consta® (risperidone)
Risperidone Orally Disintegrating Tablet
Saphris® (asenapine)
Seroquel® (quetiapine)[a]
Seroquel XR® (quetiapine)[a]
Versacloz™ (clozapine)
Vraylar™ (cariprazine)
Zyprexa® (olanzapine)[a]
Zyprexa® **Zydis®** (olanzapine)[a]
Zyprexa® **Relprevv™** (olanzapine)

a – generic available; not a target in step therapy program

b – MSC M product available; included as target in step therapy program
c – MSC Y product available only; not a target in step therapy program

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

Brand Atypical Antipsychotics will be approved when ONE of the following is met:

1. The patient is requesting Abilify OR Abilify Discmelt for Tourette's Disorder **AND** ONE of the following:
    a. The patient's medication history includes the use of haloperidol OR pimozide in the past 90 days
    OR
    b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to either generic haloperidol OR pimozide

    OR
2. The patient's medication history includes use of a generic atypical antipsychotic agent in the past 90 days

    OR
3. There is documentation that the patient is currently being treated with the requested agent

    OR
4. The prescriber states the patient is being treated with the requested agent AND is at risk if therapy is changed

    OR
5. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to at least one generic atypical antipsychotic agent

Length of approval: for dementia-related psychosis: 3 months for initial approval; 6 months for renewals
for all other indications: 12 months

NOTE: If Quantity Limit program also applies, please refer to Quantity Limit documents.

FDA APPROVED INDICATIONS AND DOSAGE[1-21,34]

Agent	Schizophrenia (acute)	Schizophrenia (maintenance)	Schizoaffective (acute)	Acute agitation [d]	Resistant Schizophrenia	Risk of Recurrent suicidal behavior	BPD (acute manic/mixed)	BPD (acute depressive)	BPD (maintenance)	Autism (irritability) [e]	MDD	Tourette's Disorder	Dosing
Abilify, (aripiprazole) ‡ tablet, oral solution, IM injection	✓	✓		✓ IM			✓		✓ [bc]	✓	✓ [c]	✓	**Doses/Day –** 1 dose/day **Schizophrenia and BPD (mania):** Start 10-15 mg/day; maximum 30 mg/day. **MDD (adjunctive):** Start 2-5 mg/day. Range: 2-15 mg/day. **Autism:** Start 2 mg/day, increase if needed. Range: 5-15 mg/day. **Acute agitation** (IM): 9.75 mg (recommended dose); range is 5.25 – 15 mg. Safety of total daily dose >30 mg or dosing interval <2 hours not evaluated. **Tourette's Disorder:** Patients < 50 kg – initial 2 mg/day, recommended 5 mg/day, maximum 10 mg/day Patients > 50 kg – initial 2 mg/day, recommended 10 mg/day, maximum 20 mg/day
aripiprazole ODT oral disintegrating tablet	✓	✓					✓		✓ [bc]	✓	✓ [c]	✓	**Doses/Day –** 1 dose/day **Schizophrenia and BPD (mania):** Start 10-15 mg/day; maximum 30 mg/day. **MDD (adjunctive):** Start 2-5 mg/day. Range: 2-15 mg/day. **Autism:** Start 2 mg/day, increase if needed. Range: 5-15 mg/day. **Tourette's Disorder:** Patients < 50 kg – initial 2 mg/day, recommended 5 mg/day, maximum 10 mg/day Patients > 50 kg – initial 2 mg/day, recommended 10 mg/day, maximum 20 mg/day

Agent	Schizophrenia (acute)	Schizophrenia (maintenance)	Schizoaffective (acute)	Acute agitation [d]	Resistant Schizophrenia	Risk of Recurrent suicidal behavior	BPD (acute manic/mixed)	BPD (acute depressive)	BPD (maintenance)	Autism (irritability) [e]	MDD	Tourette's Disorder	Dosing
Abilify Maintena (aripiprazole extended-release) IM injection		✓											Tolerability should be established with oral aripiprazole prior to starting treatment with Abilify Maintena. The recommended starting/maintenance dose of Abilify Maintena is 400 mg monthly (no sooner than 26 days after the previous injection). After the first injection, continue treatment with oral aripiprazole or other oral antipsychotic for 14 consecutive days. If there are adverse reactions with the 400 mg dosage, consider reducing the dosage to 300 mg once monthly.
Aristada (aripiprazole lauroxil) IM injection		✓											441 mg, 662 mg, or 882 mg per month; or 882 mg every 6 weeks; or 1064 mg every 8 weeks

Agent	Schizophrenia (acute)	Schizophrenia (maintenance)	Schizoaffective (acute)	Acute agitation [d]	Resistant Schizophrenia	Risk of Recurrent suicidal behavior	BPD (acute manic/mixed)	BPD (acute depressive)	BPD (maintenance)	Autism (irritability) [e]	MDD	Tourette's Disorder	Dosing
Aristada Initio (aripiprazole lauroxil) extended release IM injection		✓											Administer one 675 mg injection and one 30 mg dose of oral aripiprazole in conjunction with the first Aristada injection
Clozaril, FazaClo (clozapine)‡ tablet, oral disintegrating tablet					✓	✓							**Doses/Day** – 2-3 divided doses Start 12.5 mg once or twice daily, titrate up to 300-450 mg/day over two weeks, then up to maximum 600-900 mg/day, based on response.
Fanapt (iloperidone) tablet	✓*												**Doses/Day** – 2 divided doses Start 1 mg twice daily, titrate to 12 mg twice daily over 7 days; control of symptoms delayed due to titration. Target dose: 12-24 mg/day.
Geodon (ziprasidone) ‡ capsule, IM injection	✓*	✓		✓ IM			✓		✓[c]				**Doses/Day** – 2 divided doses **Schizophrenia:** Start 20 mg twice daily; titrate up to 80 mg twice daily. **BPD (mania):** Start 40 mg twice daily. Range: 40-80 mg twice daily. **Acute agitation** (IM): 10 mg every 2 hours; 20 mg every 4 hours; up to maximum of 40 mg/day.
Invega (paliperidone ER)‡ tablet	✓	✓	✓										**Doses/Day –** 1 dose/day Start 6 mg/day (tab); range 3-12 mg/day (maximum).

Agent	Schizophrenia (acute)	Schizophrenia (maintenance)	Schizoaffective (acute)	Acute agitation [d]	Resistant Schizophrenia	Risk of Recurrent suicidal behavior	BPD (acute manic/mixed)	BPD (acute depressive)	BPD (maintenance)	Autism (irritability) [e]	MDD	Tourette's Disorder	Dosing
Invega Sustenna (paliperidone extended-release) IM injection	✓	✓											Tolerability should be established with oral paliperidone or oral risperidone prior to initiating Invega Sustenna. Initially, 234 mg on day 1 and 156 mg one week later. Recommended monthly maintenance dose is 117 mg; may benefit from lower or higher doses. Recommended range 39 mg to 234 mg based on tolerability/efficacy.
Invega Trinza (paliperidone extended-release) IM injection	✓												273-829 mg once every 3 months
Latuda (lurasidone) tablet	✓							✓					**Doses/Day** 1 dose/day **Schizophrenia**: Start at 40 mg/day; Maximum recommended dose 160 mg/day. **BPD (depression)**: Start at 20 mg/day; Maximum recommended dose 120 mg/day
Rexulti (brexpiprazole) tablet	✓	✓									✓C		**MDD:** Start at 0.5-0.1 mg/day; Recommended at 2 mg/day; Maximum of 3 mg/day **Schizophrenia:** 1 mg/day; Recommended at 2-4 mg/day; Maximum of 4 mg/day
Risperdal (risperidone) ‡ tablet, oral disintegrating tablet, solution	✓	✓					✓			✓			**Doses/Day** 1-2 divided doses **Schizophrenia**: Start 2 mg/day; Effective dose range: 4-16 mg/day. **BPD (mania):** Start 2-3 mg/day; Effective dose range: 1-6 mg/day. **Autism:** Start 0.25 – 0.5 mg/day; target dose 0.5 – 1 mg/day. Effective dose range 0.5-3 mg/day. *(autism dosing is weight based)*

Agent	Schizophrenia (acute)	Schizophrenia (maintenance)	Schizoaffective (acute)	Acute agitation [d]	Resistant Schizophrenia	Risk of Recurrent suicidal behavior	BPD (acute manic/mixed)	BPD (acute depressive)	BPD (maintenance)	Autism (irritability) [e]	MDD	Tourette's Disorder	Dosing
Risperdal Consta (risperidone long-acting) IM injection	✓	✓					✓		✓				Tolerability should be established with oral risperidone prior to starting treatment with Risperdal Consta. Give oral risperidone (or other antipsychotic) with first Risperdal Consta injection and continue for 3 weeks (then stop oral). Dosed 25 mg IM every 2 weeks. If no response, may use 37.5 mg or 50 mg. Maximum is 50 mg IM every 2 weeks. Do not make upward dose adjustment more frequently than every 4 weeks.
Saphris (asenapine) sublingual tablet	✓	✓					✓ [b,c]						**Doses/Day** – 2 divided doses **Schizophrenia:** Start and target dose is 5 mg twice daily. **BPD Adults**: Start and target dose 5-10 mg twice daily. **BPD Pediatrics:** Starting dose of 2.5 mg twice daily with target dose of 2.5-10 mg twice daily
Seroquel (quetiapine) ‡ tablet	✓	✓					✓	✓	✓ [c]				**Doses/Day** - 2 divided doses **Schizophrenia**: Start 25 mg twice daily and titrate up to 300-400 mg/day Range: 150-750 mg/day. **BPD (mania):** Titrate from 100 mg to, 400 mg on first 4 days. Range: 400-800 mg/day. **BPD (depression):** Start 50 mg; titrate to recommended dose 300 mg.

Agent	Schizophrenia (acute)	Schizophrenia (maintenance)	Schizoaffective (acute)	Acute agitation [d]	Resistant Schizophrenia	Risk of Recurrent suicidal behavior	BPD (acute manic/mixed)	BPD (acute depressive)	BPD (maintenance)	Autism (irritability) [e]	MDD	Tourette's Disorder	Dosing
Seroquel XR‡ (quetiapine extended-release) tablet	✓	✓					✓	✓	✓ [c]		✓ [c]		**Doses/Day –** 1 dose/day **Schizophrenia:** Start 300 mg/day. Range: 400-800 mg/day. **BPD (mania):** Start with 300 mg and 600 mg on days 1 and 2, respectively. Then range of 400-800 mg/day. **BPD (depression):** Start 50 mg; titrate to recommended dose 300 mg. **MDD (adjunctive):** Start 50 mg (days 1 & 2); then 150 mg (days 3 & 4). Range: 150-300 mg/day.
Versacloz (clozapine) oral suspension					✓	✓							**Doses/Day** – in divided doses Start 12.5 mg once or twice daily, titrate up to 300-450 mg/day over two weeks, then up to maximum 900 mg/day, in 100 mg increments once or twice weekly, based on response.
Vraylar (cariprazine) capsule		✓					✓						**Doses/Day** - 1 dose/day **Schizophrenia:** Start: 1.5 mg/day Range: 1.5-6 mg/day **Acute Manic Mixed BPD:** Start: 1.5 mg/day Range: 3-6 mg/day
Zyprexa (olanzapine) ‡ tablet, oral disintegrating tablet, IM injection	✓	✓		✓ IM			✓	✓ [a]	✓ [b]		✓ [a]		**Doses/Day** – 1 dose/day **Schizophrenia:** Start 5-10 mg once daily. Target 10 mg/day. **BPD (mania):** Start 10-15 mg once daily. **BPD (depression) and Treatment resistant MDD:** Start 5 mg olanzapine w/ 20 mg fluoxetine once daily. **Acute agitation** (IM): 10 mg Maximum 3 doses 2 to 4 hours apart.

Agent	Schizophrenia (acute)	Schizophrenia (maintenance)	Schizoaffective (acute)	Acute agitation [d]	Resistant Schizophrenia	Risk of Recurrent suicidal behavior	BPD (acute manic/mixed)	BPD (acute depressive)	BPD (maintenance)	Autism (irritability) [e]	MDD	Tourette's Disorder	Dosing
Zyprexa Relprevv (olanzapine extended release) IM injection	✓	✓											Tolerability should be established with oral olanzapine prior to treatment with Zyprexa Relprevv Dose range is 150 mg to 300 mg IM every 2 weeks or 405 mg IM every 4 weeks. Doses > 300 mg every 2 weeks or 405 mg every 4 weeks not studied. Dosing chart in PI.

MDD=major depressive disorder
BPD=bipolar disorder
a= adjunctive with fluoxetine
b= monotherapy
c= adjunctive
d= associated with schizophrenia or BPD
e= age ≥5
*Iloperidone and ziprasidone may have greater capacity to prolong QT/QTc interval compared to other antipsychotic drugs. Whether ziprasidone or iloperidone will cause torsade de pointes or increase rate of sudden death is not yet known.
‡ Generics available

CLINICAL RATIONALE

Schizophrenia

Schizophrenia is a psychiatric disorder that involves chronic or recurrent psychosis. Antipsychotic medications are first-line medication treatment for schizophrenia.[22] Antipsychotics have been shown to reduce positive symptoms of schizophrenia, such as hallucinations, delusions, and suspiciousness.[22,23] Negative symptoms of schizophrenia, such as diminished emotional expression and lack of motivation, have proven particularly difficult to treat.[22] Clozapine is generally considered the most effective antipsychotic drug for the treatment of schizophrenia, but is usually reserved for refractory disease due to adverse effects. Olanzapine maybe slightly more effective than other antipsychotic drugs, except clozapine, but its adverse metabolic effects may make it unacceptable for long-term use. Olanzapine has been more effective than aripiprazole, quetiapine, risperdone, or ziprasidone in reducing psychotic symptoms. Other second-generation antipsychotics are not clearly more effective than less expensive first generation drugs but they are less likely to cause tardive dyskinesia. The more recently approved antipsychotic drugs: paliperidone, asenapine, iloperidone, lurasidone, brexpiprazole, and cariprazine, maybe more effective for some patients, but their efficacy and safety relative to older drugs remain to be established.[23]

Bipolar Disorder

Bipolar disorder is a mood disorder that is characterized by episodes of mania, hypomania, and major depression. Initiation of maintenance therapy is recommended to prevent relapse, minimize suicide attempts, and maybe associated with reduced rates of violent

behavior. First line maintenance therapy is recommended to consist of the same regimen that successfully treated the acute bipolar mood episode. Second line therapy is reserved for those who do not tolerate first-line maintenance pharmacotherapy. Lithium, valproate, quetiapine, and lamotrigine are recommended as second-line therapy. These agents are listed in order of preference based upon efficacy in reducing the risk of suicide, number of trials conducted, risk of side effects, and cost.[24]

Second-generation antipsychotics, lithium, and valproate are effective for treatment of acute manic episodes. Both lithium and valproate may take days to weeks to have a full therapeutic effect. Treatment of an acute manic episode with these agents generally requires addition of an antipsychotic drug.[25]

Quetiapine and lurasidone and combination olanzapine/fluoxetine have been shown to be effective in treating bipolar depression. Antidepressant drugs (e.g., SSRIs or bupropion can be effective for treatment of bipolar depression, but they can precipitate mania and generally should be used only as an adjunct to mood-stabilizing drugs such as lithium. Lithium has been shown to have protective effects against suicide and self-harm when used for treatment of bipolar depression. Lamotrigine may be modestly effective for this indication, but its usefulness in treating an acute episode is limited by the amount of time required for safe titration to an effective dose.[25]

Antipsychotics can cause somnolence, weight gain, diabetes, extrapyramidal symptoms, QT interval prolongation, and hyperprolactinemia. Bipolar patients are particularly susceptible to extrapyramidal effects; quetiapine appears to have the lowest risk. Lurasidone appears to have minimal metabolic effects, but more studies are needed. DRESS (drug reaction with eosinophilia and systemic symptom syndrome) has been reported rarely with olanzapine and ziprasidone. [25]

Major Depressive Disorder

Major depressive disorder (MDD), also known as unipolar major depression, is diagnosed when a patient has suffered at least one major depressive episode and have no history of mania or hypomania. Goal of initial treatment for depression is symptom remission and restoring baseline functioning.[26] Selective serotonin reuptake inhibitors (SSRIs) along with serotonin norepinephrine reuptake inhibitors (SNRIs), bupropion, and mirtazapine are considered first line treatment options for adults with major depressive disorder (MDD).[27] Guidelines do not consider antipsychotics as a first line treatment of major depressive disorder without psychosis. However, they suggest that psychotic depression typically responds better to the combination of an antipsychotic and an antidepressant medication rather than either component alone, although some research has shown comparable responses for anti-depressive treatment or antipsychotic treatment alone. [28]

Autism

Practice Parameters-American Academy of Child and Adolescent Psychiatry (AACAP, 2014) suggest pharmacotherapy may be offered when there is a specific target symptom or comorbid condition, potentially increasing patient ability to profit from educational and other interventions, and allow less restrictive environments through management of severe and challenging behaviors. Frequent targets for pharmacologic intervention include associated comorbid conditions (e.g., anxiety, depression) and other features (e.g., aggression, self-injurious behavior, hyperactivity, inattention, compulsive-like behaviors, repetitive or stereotypic behaviors, and sleep disturbances). Various considerations (e.g., adverse effects) should inform pharmacologic treatment. Risperidone and aripiprazole have been FDA approved for the treatment of irritability (e.g., physical aggression, severe tantrum behavior) associated with autism. There is a growing body of controlled evidence for pharmacologic intervention. The guideline provides a summary chart of medications

supported by RCTs for use in children with autism spectrum disorder (ASD), including target symptoms, ages, dosing, potential adverse effects, and outcomes.[29]

- Antipsychotics supported by RCTs showing positive effects on various target symptoms in ASD include aripiprazole, haloperidol, olanzapine, and risperidone.
- Combining medication with parent training is moderately more efficacious than medication alone for decreasing serious behavioral disturbance and modestly more efficacious for adaptive functioning. Individuals with ASD may be nonverbal, so treatment response is often judged by caregiver report and observation of specific behaviors. Although this may help document the effectiveness of the selected medication, an overall goal of treatment is to facilitate the child's adjustment and engagement with educational intervention.

Despite many randomized trials, confidence in reported improvements remains low for most interventions. Risperidone and aripiprazole improved challenging behavior in the short term (<6 months) but also significant harms including weight gain, appetite changes, and EPS.[30]

Dementia-Related Psychosis (off-label use)
The American Psychiatric Association (APA) recommends that nonpharmacologic interventions be attempted before a trial of antipsychotic drug therapy and that the interventions attempted be guided by the patient's level of distress and the risk to the patients and caregiver. In addition, the FDA states that physicians who prescribe antipsychotics to elderly patients with dementia-related psychosis should discuss the risk of increased mortality with their patients, patients' families, and caregivers.[31]

The APA Guideline Watch (2014) states new evidence indicates that antipsychotics provide weak benefits for the treatment of psychosis and agitation in patients with dementia. Adverse effects of antipsychotics include sedation, metabolic effects, and cognitive impairment. For many patients with Alzheimer's disease, antipsychotics can be tapered and discontinued without significant signs of withdrawal or return of behavioral symptoms.[32]

Antipsychotic drug therapy generally is reserved for patients who have severe symptoms or when associated agitation, combativeness, or violent behavior puts the patient or others in danger. Current evidence indicates that the atypical antipsychotics can provide modest improvement in behavioral manifestations; some evidence suggests that efficacy may be better for psychosis than for other manifestations. Antipsychotic efficacy appears to be similar among available agents and therefore the choice of agent should be based on adverse effect profile and other patient considerations; to minimize adverse effects, the lowest possible effective dose should be used.[31]

Tourette's Disorder
A review (2015) on treatment of Tourette's syndrome suggests alpha-2 agonists (clonidine and guanfacine) are less effective than antipsychotics but are usually recommended as initial pharmacotherapy due to low side effects. Atypical neuroleptics (aripiprazole or risperidone) are typically used if the alpha-2 agonists are ineffective or intolerable.[33]

The American Academy of Child & Adolescent Psychiatry states that atypical antipsychotics are effective in Tourette's Disorder (TD). At the time the guidelines were published, no atypical antipsychotics were FDA approved, and only haloperidol and pimozide had been approved for TD. However, most clinicians use atypical antipsychotics prior to the two approved agents. The guidelines found that risperidone is the most well studied non-FDA labeled atypical antipsychotic for the treatment of TD. Risperidone was found to be at least as effective as clonidine, haloperidol, and pimozide; with less frequent and severe side effects. The most common adverse reaction with risperidone therapy was mild to moderate sedation. No clinically significant extrapyramidal symptoms were observed. Ziprasidone

showed efficacy compared to placebo in one randomized controlled trial. However, ECG screenings are recommended if ziprasidone treatment is considered. Olanzapine was studied in several open-label trials and 1 double-blind crossover study with pimozide. Although olanzapine was shown to be effective, weight gain was observed. Due to the metabolic effects, olanzapine, it is not recommended as a first line medication for TD.[34]

For additional clinical information see Prime Therapeutics Formulary Chapter 9.3B: Atypical Antipsychotics.

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