

## Atypical Antipsychotics (AAPs)

### Executive Summary

- The AAPs Drug Class was first reviewed in May 2011. Risperidone and quetiapine IR and XR (Seroquel, Seroquel XR) are Basic Core Formulary (BCF). Iloperidone (Fanapt), asenapine (Saphris), and lurasidone (Latuda) are nonformulary (NF). Cariprazine (Vraylar) and brexpiprazole (Rexulti) have not been previously reviewed.
- There are currently 13 AAPs available in the United States; most are available as generics. Six branded agents remain in the class including Seroquel XR, Fanapt, Saphris, Latuda, Vraylar, and Rexulti.
- Since the last class review, many agents have become available in generic form including aripiprazole. Seroquel XR generics are expected in November 2016.
- Brexpiprazole is a new atypical antipsychotic that is FDA-approved to treat schizophrenia and as an adjunct to antidepressant therapy for major depressive disorder (MDD).
  - In schizophrenia, brexpiprazole showed individual changes from baseline in Positive and Negative Syndrome Scale (PANSS) score that were clinically significant from baseline but not when compared to placebo.
  - Limitations of the schizophrenia studies included lack of active comparators and short duration (six weeks).
  - In depression, higher doses of brexpiprazole were statistically and clinically significant but not at the lowest dose (1 mg).
- Cariprazine is a new atypical antipsychotic that is FDA-approved to treat schizophrenia and bipolar disorder.
  - In schizophrenia, cariprazine showed individual changes from baseline in PANSS score that were clinically significant but not when compared to placebo.
  - Limitations include the short duration of the studies and no head-to-head comparisons with other AAPs.
  - In bipolar disorder, cariprazine was superior to placebo but there are no head-to-head studies.
- Brexpiprazole and cariprazine have similar safety and tolerability concerns as the other drugs in the class.
- Cariprazine has an active metabolite with a long half-life (one to three weeks) that may extend adverse effects in those affected.
- Brexpiprazole and cariprazine offer no clinically compelling advantages over existing Uniform Formulary (UF) agents.
- There are no significant efficacy or safety updates since the May 2011 drug class review. The safety profiles of the individual AAPs are well known in terms of metabolic, neurologic, and cardiovascular effects. In May 2016, the FDA released safety warnings for aripiprazole (for impulse control problems) and olanzapine (for Drug Reaction with Eosinophilia and Systemic Symptoms); however, these are rare adverse events.
- According to the Institute for Quality and Efficiency in Health Care (IQWiG), manufacturer claims of fewer adverse events with lurasidone compared to risperidone, olanzapine, and quetiapine XR could not be proven. However, lurasidone is dosed once daily and is the only Pregnancy Category B drug besides clozapine.
- AAPs with new pediatric indications include asenapine for bipolar disorder (ages 10–17) and paliperidone for schizophrenia (ages 12–17), although several other drugs have similar pediatric indications.
- The safety profiles of individual AAPs in terms of metabolic, neurologic, and cardiovascular effects are well known.
- Generic AAPs currently on the UF are adequate to meet the needs of the majority of DoD patients with schizophrenia, bipolar disorder, and adjunct to MDD.
- Choice of treatment should be based on efficacy, tolerability, and individual patient characteristics.

### Previous UF Review

Risperidone and quetiapine (IR and XR) are BCF. A class review was conducted for the atypical antipsychotics in May 2011 and olanzapine, ziprasidone, and aripiprazole were added to the UF. Fanapt, Saphris, and Latuda were made NF. Currently, all of the agents on the UF are available in a generic formulation.

**Table 1. Current Formulary Status**

BCF drugs – MTFs <u>must</u> have on formulary	MTFs <u>may</u> have on formulary	MTFs <u>must not</u> have on formulary
<ul style="list-style-type: none"> <li>• risperidone</li> <li>• quetiapine (Seroquel and Seroquel XR)</li> </ul>	<ul style="list-style-type: none"> <li>• risperidone ODT</li> <li>• olanzapine (Zyprexa)</li> <li>• olanzapine/fluoxetine (Symbyax)</li> <li>• ziprasidone (Geodon)</li> <li>• aripiprazole (Abilify)</li> <li>• paliperidone (Invega)</li> </ul>	<ul style="list-style-type: none"> <li>• iloperidone (Fanapt)</li> <li>• asenapine (Saphris)</li> <li>• lurasidone (Latuda)</li> </ul>

Note: Vraylar and Rexulti have not been previously reviewed.

**Table 2. Oral Atypical Antipsychotics Available in the United States<sup>1,2</sup>**

Active Ingredient	Brand (Manufacturer)	Strengths	FDA Approval	Patent Exp Date
Clozapine	Clozaril, FazaClo (Novartis, generics)	12.5, 25, 50, 100, 200 mg tabs; 12.5, 25, 50, 100, 150, 200 mg ODT tabs	9/26/89	-
Risperidone	Risperdal (OMJ, generics)	0.25, 0.5, 1, 2, 3, 4 mg tabs; 0.25, 0.5, 1, 2, 3, 4 mg ODT tabs; 1mg/mL oral solution	12/29/93	-
Olanzapine	Zyprexa, Zyprexa Zydis (Eli Lilly & Co, generics)	2.5, 5, 7.5, 10, 15, 20 mg tabs; Zydis: 5, 10, 15, 20 mg ODT tabs	9/30/96 4/06/00	-
Quetiapine	Seroquel, <b>Seroquel XR</b> (Astra Zeneca, generics)	25, 50, 100, 150, 200, 300, 400 mg tabs 50, 150, 200, 300, 400 mg XR tabs	9/26/97 5/17/07	generics Nov 2016
Ziprasidone	Geodon (Pfizer, generics)	20, 40, 60, 80 mg caps; 10 mg/mL oral solution	2/5/01	-
Aripiprazole	Abilify (Otsuka)	2, 5, 10, 15, 20, 30 mg tabs 10, 15 mg ODT tabs; 1mg/mL soln	11/15/02	-
Olanzapine/ Fluoxetine	Symbyax (Eli Lilly & Co, generics)	3-25, 6-25, 6-50, 12-25, 12-50 mg caps	12/24/03	-
Paliperidone	Invega (OMJ, generics)	1.5, 3, 6, 9, 12 mg XR tabs	12/19/06	-
Iloperidone	<b>Fanapt</b> (Vanda Pharmaceuticals)	1, 2, 4, 6, 8, 10, 12 mg tabs	5/6/09	11/15/2011
Asenapine	<b>Saphris</b> (Actavis)	5, 10 mg SL tabs	8/13/09	06/09/2015
Lurasidone	<b>Latuda</b> (Sunovion)	40, 80 mg tabs	10/28/10	2019
Brexiprazole	<b>Rexulti</b> (Otsuka Pharm)	0.25, 0.5, 1, 2, 3, 4 mg tabs	7/10/2015	-
Cariprazine	<b>Vraylar</b> (Actavis)	1.5, 3, 4.5, 6 mg caps	9/17/2015	-

OMJ=Ortho McNeil Janssen; BMS=Bristol-Myers Squibb

**Products in bold are still branded**

## Indications

All AAPs are indicated to treat schizophrenia. Olanzapine, quetiapine, risperidone, cariprazine, asenapine, ziprasidone, and aripiprazole are also indicated for bipolar disorder. Quetiapine, brexpiprazole, aripiprazole, and olanzapine/fluoxetine are indicated as adjunctive therapy for MDD in addition to antidepressants.

## Efficacy Measures

The primary measure of efficacy in schizophrenia studies is the PANSS. For bipolar disorder, the Young Mania Rating Scale (YMRS) is frequently the primary efficacy measure. The Montgomery-Asberg Depression Rating Scale (MADRS) measures efficacy in MDD or for agents seeking an indication as adjunctive therapy in MDD. See Table 3 for more details about each scale and the corresponding minimal clinically important difference (MCID).

**Table 3. Efficacy Measures Commonly Used in Schizophrenia, Bipolar Disorder, and MDD**

Clinical Measure	Criteria	Minimal Clinically Important Difference (MCID)
Positive and Negative Syndrome Scale (PANSS)	<ul style="list-style-type: none"> <li>Point rating scale in which 30 different symptoms are rated from 1-7</li> <li>Scores range from 30-210 (30 representing no symptoms and 210 representing worst symptoms)</li> </ul>	<p>≥ 20% reduction in score</p> <p>~20 points in most studies with a baseline PANSS of ~100</p>
Young Mania Rating Scale (YMRS)	<ul style="list-style-type: none"> <li>Clinician-administered 11-item instrument used for assessment/severity of mania</li> </ul>	<p>≥ 50% total score improvement</p> <p>~6-7 point reduction</p>
Montgomery-Asberg Depression Rating Scale (MADRS)	<ul style="list-style-type: none"> <li>10-item clinical-rating scale used to assess the degree of depressive symptomatology</li> <li>Scores range from 0-60 (0 representing no symptoms and 60 representing worst symptoms)</li> </ul>	<p>≥ 50% reduction in overall score</p> <p>~2 point reduction</p>

## Efficacy

### New Agents

There have been two new agents approved since the May 2011 class review: cariprazine (Vraylar) and brexpiprazole (Rexulti).

Cariprazine was approved in September 2015 and is indicated for schizophrenia and manic or mixed episodes associated with bipolar I disorder. The efficacy of cariprazine for the treatment of schizophrenia was studied in three phase 3, parallel-group, randomized, double-blind, placebo-controlled, active-controlled studies enrolling approximately 1,750 patients over a period of six weeks.<sup>1,3,4</sup> The primary endpoint measured was change in the PANSS. In all three trials, cariprazine showed a statistically significant improvement in PANSS total score from baseline compared to placebo.

Efficacy of cariprazine for the treatment of bipolar I disorder was evaluated in three phase 3, parallel-group, randomized, double-blind, placebo-controlled studies enrolling approximately 1,040 patients over three weeks.<sup>5-7</sup> The primary endpoint measured was the change in the YMRS. Cariprazine showed a statistically significant improvement in YMRS score compared to placebo in all three studies. While the improvement in the YMRS score met the MCID, the average scores did not reflect achievement of remission.

Brexpiprazole was approved in July 2015 and is indicated for adjunctive treatment of MDD and schizophrenia. Two studies with brexpiprazole for the treatment of schizophrenia were included in this review: both were randomized, double-blind, placebo-controlled clinical trials in patients who met DSM-IV-TR criteria for schizophrenia.<sup>8,9</sup> The primary endpoint measured was the change in the PANSS score. Both trials showed a statistically significant improvement in PANSS total score compared to placebo.

Brexpiprazole was also evaluated for the treatment of MDD in two double-blind, placebo-controlled, fixed-dose trials over a period of six weeks.<sup>10,11</sup> The primary endpoint measured was the change in MADRS score from baseline. Brexpiprazole 2 mg and 3 mg demonstrated superior efficacy versus placebo, while brexpiprazole 1 mg did not show efficacy versus placebo in patients with MDD.

## Systematic Reviews

Systematic reviews by Asmal, Komossa, and Khanna were completed to determine the comparative efficacy of specific AAPs in treating schizophrenia. The primary outcome measured was the PANSS score. The Komossa systematic review included a comparison of olanzapine with amisulpride, aripiprazole, clozapine, quetiapine, risperidone, and ziprasidone.<sup>12</sup> Results showed olanzapine was superior to all AAPs in the study except for clozapine for the treatment of schizophrenia. Asmal and colleagues conducted another systematic review that compared quetiapine with risperidone and paliperidone.<sup>13</sup> Results showed quetiapine was superior to all AAPs in the study for the treatment of schizophrenia. The Khanna review compared aripiprazole with olanzapine, risperidone, and ziprasidone.<sup>14</sup> Results in this study showed olanzapine was superior to all AAPs for the treatment of schizophrenia.

Citrome and colleagues conducted a systematic review and meta-analysis including 26 randomized controlled trials comparing the branded AAPs.<sup>15</sup> These agents included iloperidone, asenapine, lurasidone, cariprazine, and brexpiprazole. The primary outcome measures for these trials were the Brief Psychiatric Rating Scale (BPRS) and PANSS. Results showed that iloperidone had similar efficacy to ziprasidone and haloperidol but lower efficacy than risperidone. Asenapine was superior to placebo in mean change in PANSS score and its efficacy was comparable to other AAPs. Lurasidone had similar efficacy outcomes to olanzapine, quetiapine XR, and ziprasidone. Cariprazine and brexpiprazole were not compared head-to-head to other AAPs but were shown to be effective over placebo based on phase III randomized controlled trials (RCTs).

## Additional Safety Concerns

- AAPs are known to have neurologic, endocrine, and cardiovascular adverse effects. Some of these adverse effects include, but are not limited to, diabetes, extrapyramidal symptoms, elevated prolactin, QTc prolongation, and weight gain.
- Cariprazine and brexpiprazole interact with drugs that are metabolized by CYP3A4 and CYP2D6.

## References

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## Abbreviations

The following abbreviations are used in this review:

AAPs	– Atypical Antipsychotics Drug Class
BCF	– Basic Core Formulary
BPRS	– Brief Psychiatric Rating Scale
DoD	– Department of Defense
FDA	– U.S. Food and Drug Administration
IQWiG	– Institute for Quality and Efficiency in Health Care
MADRS	– Montgomery-Asberg Depression Rating Scale
MCID	– minimal clinically important difference
MDD	– major depressive disorder
PANSS	– Positive and Negative Syndrome Scale
RCTs	– randomized controlled trials
UF	– Uniform Formulary
YMRS	– Young Mania Rating Scale