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# DERP VI Surveillance: Second-Generation Antipsychotic Drugs

November 2019

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## Objectives

The purpose of this Drug Effectiveness Review Project (DERP) surveillance report is to preview the volume and nature of new research and relevant clinical information that has emerged since the last scan on second-generation antipsychotic (SGAs) drugs. The literature search for this report focused on new randomized controlled trials (RCTs), systematic reviews (with and without meta-analysis), and actions taken by the U.S. Food and Drug Administration (FDA) such as new drugs, formulations, indications, or identified serious harms since the last report. Comprehensive searches, quality assessments, and a synthesis of evidence would follow this surveillance report only if DERP participants commission an update review or another research product type for this topic. Comprehensive searches might identify additional eligible studies.

## Topic History and Context

This report is the first surveillance document on this topic since the completion of the second scan in November 2018 for the Update #5 report presented in October 2016. The search dates for the scan presented in November 2018 were through September 2018. The search dates for all previous reports are shown in Table 1.

Table 1. Recent Topic History and Search Dates

| Document Type | Date Presented | Search Dates |
|---|---|---|
| Scan #2 | November 2018 | Through September 2018 |
| Scan #1 | April 2017 | Through March 2017 |
| Update #5 Report | October 2016 | Through July 2016 |

## Key Questions

1. For adults and adolescents with schizophrenia (including a first episode) and other psychotic disorders, do second-generation antipsychotics (SGAs) differ from each other in terms of benefits (efficacy, effectiveness) or harms?
2. For adults with major depressive disorder (MDD), do SGAs differ from each other in terms of benefits (efficacy, effectiveness) or harms?
3. For adults with bipolar disorder, do SGAs differ from each other in terms of benefits (efficacy, effectiveness) or harms?
4. For children and adolescents with bipolar disorder,
    a. Do SGAs differ from placebo in terms of benefits (efficacy, effectiveness) or harms?
    b. Do SGAs differ from each other in terms of benefits (efficacy, effectiveness) or harms?
5. For children and adolescents with autism spectrum disorder (ASD),
    a. Do SGAs differ from placebo in terms of benefits (efficacy, effectiveness) or harms?
    b. Do SGAs differ from each other in terms of benefits (efficacy, effectiveness) or harms?
6. For children and adolescents with disruptive, impulse control, and conduct disorders,
    a. Do SGAs differ from placebo in terms of benefits (efficacy, effectiveness) or harms?

b. Do SGAs differ from each other in terms of benefits (efficacy, effectiveness) or harms?

7. Are there subgroups of patients based on demographics, socioeconomic status, other medications, or comorbidities for which a particular SGA is more effective or associated with fewer harms?

## PICOS

### *Population*

Diagnosis based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria is preferred, but we accepted investigator-defined criteria for diagnosis in the absence of DSM-5 criteria.

- Adults (age 18 years or older) and adolescents (age 12 to 17 years) with a diagnosis of schizophrenia or other psychotic disorders, such as schizophreniform disorder (<6 months duration of schizophrenia symptoms), delusional and schizoaffective disorders, first-episode schizophrenia, and patients refractory to treatment
- Adults (age 18 years or older), adolescents (age 12 to 17 years), and children (under age 12 years) with bipolar disorder (manic or depressive phases, rapid cycling, mixed states)
- Adults with MDD
- Children (under age 12 years) or adolescents (age 12 to 17 years) with a DSM-5 diagnosis for ASD
- Children (under age 12 years) or adolescents (age 12 to 17 years) with a DSM-5 diagnosis of disruptive, impulse control, or conduct disorders.

### *Interventions*

Table 2. Included Interventions

| Generic Name | Brand Name | Form | Initial Year Approved | Populations |
|---|---|---|---|---|
| Aripiprazole | Abilify | Oral tablet | 2002 | Schizophrenia[a,b]<br>Bipolar disorder[a,b,c]<br>ASD[b,c]<br>MDD[a] |
| | Abilify Maintena Kit | ER IM injection | 2013 | Schizophrenia[a]<br>Bipolar disorder[a] |
| | Abilify MyCite Kit | Oral tablet | 2017 | Schizophrenia[a]<br>Bipolar disorder[a]<br>MDD[a] |
| Aripiprazole Lauroxil | Aristada | ER IM injection | 2015 | Schizophrenia[a] |
| | Aristada Initio Kit | ER IM injection | 2018 | |
| Asenapine | Saphris | Sublingual tablet | 2009 | Schizophrenia[a]<br>Bipolar disorder[a,b] |
| Brexpiprazole | Rexulti | Oral tablet | 2015 | Schizophrenia[a]<br>MDD[a] |
| Cariprazine | Vraylar | Oral capsule | 2015 | Schizophrenia[a]<br>Bipolar disorder[a] |

| Generic Name | Brand Name | Form | Initial Year Approved | Populations |
|---|---|---|---|---|
| Clozapine | Clozaril | Oral tablet | 1989 | Schizophrenia[a] |
| | Fazaclo | ODT | 2004 | |
| | Versacloz | Oral suspension | 2013 | |
| Iloperidone | Fanapt | Oral tablet | 2009 | Schizophrenia[a] |
| Lurasidone | Latuda | Oral tablet | 2010 | Schizophrenia[a,b]<br>Bipolar disorder[a,b,c] |
| Olanzapine | Zyprexa | Oral tablet | 1996 | Schizophrenia[a,b]<br>Bipolar disorder[a,b] |
| | | IM injection | 2004 | Schizophrenia[a]<br>Bipolar disorder[a] |
| | Zyprexa Zydis | ODT | 2000 | Schizophrenia[a,b]<br>Bipolar disorder[a,b] |
| Olanzapine Pamoate | Zyprexa Relprevv | ER IM injection | 2009 | Schizophrenia[a] |
| Paliperidone | Invega | ER oral tablet | 2006 | Schizophrenia[a,b]<br>Schizoaffective disorder[a] |
| Paliperidone Palmitate | Invega Sustenna | ER IM injection | 2009 | Schizophrenia[a]<br>Schizoaffective disorder[a] |
| | Invega Trinza | ER IM injection | 2015 | Schizophrenia[a] |
| Quetiapine | Seroquel | Oral tablet | 1997 | Schizophrenia[a,b]<br>Bipolar disorder[a,b,c] |
| | Seroquel XR | ER oral tablet | 2007 | Schizophrenia[a,b]<br>Bipolar disorder[a,b,c]<br>MDD[a] |
| Risperidone | Risperdal | Oral tablet<br>Oral solution | 1993<br>1996 | Schizophrenia[a,b]<br>Bipolar disorder[a,b,c]<br>ASD[b,c] |
| | Risperdal M-TAB | ODT | 2003 | |
| | Risperdal Consta | Long-acting IM injection | 2003 | Schizophrenia[a]<br>Bipolar disorder[a] |
| | Perseris Kit | ER SC suspension | 2018 | Schizophrenia[a] |
| Ziprasidone | Geodon | Oral capsule | 2001 | Schizophrenia[a]<br>Bipolar disorder[a] |
| | | IM injection | 2002 | Schizophrenia[a] |

*Note. * Overview of populations with FDA-approved indications; full details available in product labels. [a] Adults, [b] adolescents, [c] children. Abbreviations. ASD: autism spectrum disorder; ER: extended-release; IM: intramuscular; Max: maximum; MDD: major depressive disorder; ODT: orally disintegrating tablet; SC: subcutaneous; XR: extended-release.*

### *Comparators*

- Head-to-head
  - All populations
- Placebo

- Children and adolescents with bipolar disorder, ASD, or disruptive, impulse control, or conduct disorders
- Adults with MDD (add-on or background therapy)

### *Efficacy Outcomes*

#### *All populations*

- Quality of life (validated scales)
- Functional capacity (i.e., social, academic, activities of daily living, employment, and encounters with the legal system)
- Hospitalization (due to mental illness and all-cause), emergency department visits
- Persistence (i.e., ability to continue taking medication over time)

Excluded: very short term studies that focused exclusively on treatment of acute agitation associated with schizophrenia or bipolar disorder

#### *Adults and adolescents with schizophrenia and other psychotic disorders, first-episode schizophrenia, bipolar disorder, and MDD*

- Mortality
- Symptom response (e.g., global state, mental state, positive and negative symptoms), response rates, duration of response, remission, relapse, speed of response, and time to discontinuation of medication

#### *Children and adolescents with disruptive, impulse control, and conduct disorders*

- Symptom response (e.g., global state, irritability, aggressiveness, self-injurious behavior), response rates, duration of response, remission, relapse, speed of response, time to discontinuation of medication

#### *Children and adolescents with disruptive, impulse control, and conduct disorders*

- Symptom response (e.g., global state, irritability, noncompliance, aggressive conduct, property damage, theft)
- Disciplinary consequences (e.g., detention, suspension, encounters with the legal system)

### *Harms Outcomes*

- Overall adverse events
- Withdrawals due to adverse events, time to withdrawal due to adverse events
- Specific adverse events
  - Major: those that are life-threatening, result in long-term morbidity, or require medical intervention to treat (e.g., mortality, cardiovascular, and cerebrovascular disease-related events, development of diabetes mellitus, diabetic ketoacidosis, neuroleptic malignant syndrome, seizures, tardive dyskinesia, cardiomyopathies and cardiac arrhythmias, agranulocytosis)
  - General: incidence of extrapyramidal adverse events, clinically important weight change, metabolic syndrome, and incidence and severity of adverse sexual events

### *Study Designs*

- RCTs

## Methods

Generally, surveillance documents aim to identify studies conducted between the last search date used in the previous research document through the present. However, given the size and scope of this topic, we expanded the search date to include the period beginning on the last search date used in the last systematic review and ending on the present day. Using the PICOS outlined above, we searched for eligible RCTs in ClinicalTrials.gov, the ISRCTN Registry, and the FDA website. Using relevant clinical trial numbers and other identifiers, we then searched Epub Ahead of Print, Ovid MEDLINE, and Ovid MEDLINE In-Process & Other Non-Indexed Citations from January 1, 2015, through September 5, 2019. We used Google Search to identify studies published since the implementation of the search strategy in the last scan (November 2018). We used limits for English language and human participants. We also searched reference lists of relevant systematic reviews published within the last 3 years to capture additional relevant trials not registered elsewhere. We searched the FDA website to identify newly approved drugs, formulations, indications, and new serious harms (e.g., boxed warnings) or warnings for included interventions. To identify new drugs, we used Google and searched CenterWatch, a privately-owned database of clinical trials information.

## Findings

### New Drugs or Formulations

No new drugs or formulations were identified within the surveillance period.

### New Indications

In May 2019, cariprazine (Vraylar) received a new indication for the treatment of depressive episodes associated with bipolar I disorder in adults.[1] Previously, use of cariprazine in adults with bipolar disorder had been limited to acute treatment of manic or mixed episodes.

### New Serious Harms or Warnings

We identified numerous serious harms and warnings related to several drugs included in this surveillance period, which are detailed in Table 3.

Table 3. New Serious Harms or Warnings

| Generic Name | Brand Name(s) | Date | Summary of Harm or Warning |
|---|---|---|---|
| Aripiprazole | Abilify | 8/7/2019 | Potential presence in maternal breastmilk; poor weight gain in breastfed infants[2] |
| Aripiprazole lauroxil | Aristada | 11/30/2018 | Increased risk of death for elderly patients with dementia-related psychosis[3] |
| Cariprazine | Vraylar | 5/24/2019 | Increased risk of suicidal thoughts or behaviors in children, adolescents, and young adults (patients < 24 years)[4] |
| Paliperidone/ Paliperidone palmitate | Invega, Invega Sustenna, Invega Trinza | 1/25/2019 | Somnambulism (sleepwalking)[5-7] |
| Quetiapine | Seroquel, Seroquel XR | 8/26/2019 | Potential for infertility due to increased serum prolactin levels[8,9] |
| Risperidone | Risperdal, Risperdal Consta | 1/25/2019 | Somnambulism (sleepwalking)[10,11] |

| Generic Name | Brand Name(s) | Date | Summary of Harm or Warning |
|---|---|---|---|
| Ziprasidone | Geodon | 11/5/2018 | Increased risk of cerebrovascular adverse reactions (e.g., stroke) and death in elderly patients with dementia-related psychosis[12] |

*Abbreviation. XR, extended release.*

## Randomized Controlled Trials

We identified 6 new RCTs in this surveillance period (Table 4), including 3 head-to-head trials and 3 placebo-controlled trials.

All 3 head-to-head trials were conducted in adolescents and/or adults with schizophrenia and study samples ranged from 101 to 1,016 participants. Two head-to-head trials evaluated oral formulations of aripiprazole, cariprazine, quetiapine, risperidone, and ziprasidone. The other head-to-head trial compared long-acting injectable formulations of aripiprazole and paliperidone.

Of the 3 placebo-controlled trials, 1 study (N = 321) evaluated the use of oral asenapine in children and adolescents with bipolar disorder. The other 2 placebo-controlled trials (N = 394 and 812) evaluated the use of oral brexpiprazole and cariprazine as treatment adjunctive to antidepressants in adults with MDD.

Table 4. Randomized Controlled Trials

| Author, Year<br>NCT | N<br>Duration<br>Population | Intervention<br>Comparison(s) | Outcomes |
|---|---|---|---|
| **Schizophrenia** | | | |
| Gomez-Revuelta, 2018[13]<br>NCT02526030 | N = 202<br>3 years<br>Adolescents and adults | Aripiprazole oral tablet 5 to 30 mg/day<br><br>Quetiapine oral tablet 100 to 600 mg/day<br><br>Ziprasidone oral capsule 40 to 160 mg/day | Time to discontinuation, symptom severity, adverse events |
| Cuomo, 2018[14] | N = 101<br>1 year<br>Adults with comorbid SUD[a] | Aripiprazole long-acting injectable 400 mg once-monthly<br><br>Paliperidone palmitate long-acting injectable 100 mg once-monthly | Symptom severity, quality of life, adverse events |
| Nemeth, 2017[15] | N = 461<br>26 weeks<br>Adults with predominantly negative symptoms | Cariprazine oral capsule 3 to 6 mg/day<br><br>Risperidone oral 3 to 6 mg/day | Symptom severity, adverse events |

| Author, Year<br>NCT | N<br>Duration<br>Population | Intervention<br>Comparison(s) | Outcomes |
|---|---|---|---|
| **Bipolar Disorder** | | | |
| Findling, 2016[16]<br>NCT01349907 | N = 321<br>50 weeks<br>Children and adolescents (10 to 17 years) | Asenapine sublingual tablet 2.5 to 10 mg twice daily<br><br>Placebo | Long-term safety (e.g., adverse events) |
| **Major Depressive Disorder** | | | |
| Hobart, 2018[17]<br>NCT02196506 | N = 394<br>6 weeks<br>Adults | Brexpiprazole oral tablet 2 mg/day*<br><br>Placebo*<br><br>(*Adjunct to antidepressants) | Symptom severity, disability, adverse events |
| Durgam, 2016[18]<br>NCT01469377 | N = 812<br>8 weeks<br>Adults | Cariprazine oral capsule 1 to 4.5 mg/day*<br><br>Placebo*<br><br>(*Adjunct to antidepressants) | Symptom severity, response or remission, adverse events |

*Abbreviations. SUD: substance use disorder. Notes. [a] Includes schizophrenia spectrum and other psychotic disorders and bipolar disorder with psychotic features comorbid with a DSM-5 SUD. [b] Flexible and fixed dosing depending on stage of trial.*

## Ongoing Studies

We identified 16 ongoing studies in this surveillance period (Table 5). More than half of all ongoing studies (N = 10) pertained to SGA use in adults with schizophrenia. Three of 4 studies pertaining to MDD were placebo-controlled trials evaluating the use of SGAs as adjuncts to antidepressant therapy in adults. We identified 1 placebo-controlled trial of aripiprazole in children and adolescents with ASD, and 1 trial comparing aripiprazole, paliperidone, or usual treatment in adolescents and adults with substance use disorder and psychosis. Based on the date of estimated primary study completion, we estimate that 8 of these studies may be published within the next year.

Table 5. Ongoing Studies

| NCT<br>Study Name | Estimated Enrollment<br>Duration<br>Population | Intervention<br>Comparison(s) | Outcomes | Estimated Primary Completion |
|---|---|---|---|---|
| **Schizophrenia** | | | | |
| NCT02360319<br><br>PRELAPSE | N = 488<br>2 years<br>Adults | Aripiprazole long-acting injection | Hospitalization, symptom severity, quality of life | March 2019 |

| NCT<br>Study Name | Estimated Enrollment<br>Duration<br>Population | Intervention<br>Comparison(s) | Outcomes | Estimated Primary Completion |
|---|---|---|---|---|
| | | Treatment as usual (any FDA approved antipsychotic) | | |
| NCT03345979 | N = 200<br>25 weeks<br>Adults | Aripiprazole lauroxil long-acting injection<br><br>Paliperidone palmitate long-acting injection | Symptom severity | March 2019 |
| NCT03465787 | N = 206<br>6 weeks<br>Adults | Lurasidone oral tablet<br><br>Quetiapine extended-release oral tablet | Symptom severity | March 2019 |
| NCT03090503 | N = 200<br>3 years<br>Adolescents and adults; first-episode psychosis | Aripiprazole oral tablet<br><br>Risperidone oral tablet | Discontinuation, symptom severity | June 2019 |
| NCT03874494 | N = 370<br>6 weeks<br>Adults | Brexpiprazole oral tablet<br><br>Aripiprazole oral tablet | Symptom severity, response rate | June 2019 |
| NCT02431702<br><br>DREaM<br><br>Conference Abstract<br><br>Conference Poster | N = 337<br>18 months<br>Adults | Aripiprazole<br><br>Olanzapine<br><br>Paliperidone extended-release oral tablet<br><br>Quetiapine<br><br>Risperidone oral tablet<br><br>Paliperidone palmitate extended-release injection (once monthly)<br><br>Paliperidone palmitate extended-release | Treatment failure, cognitive performance, symptom severity, adverse events | October 2019 |

| NCT<br>Study Name | Estimated Enrollment<br>Duration<br>Population | Intervention<br>Comparison(s) | Outcomes | Estimated Primary Completion |
|---|---|---|---|---|
| | | injection (once every 3 months) | | |
| NCT03883204 | N = 115<br>3 years<br>Adolescents and adults; first-episode psychosis | Aripiprazole oral tablet<br><br>Risperidone oral tablet | Cognitive functioning | December 2019 |
| NCT03345342 | N = 841<br>1 year<br>Adults | Paliperidone palmitate extended-release injection (every 6 months)<br><br>Paliperidone palmitate extended-release injection (every 3 months at 350 mg)<br><br>Paliperidone palmitate extended-release injection (every 3 months at 525 mg)<br><br>Paliperidone palmitate extended-release injection (once monthly) | Relapse, symptom severity, remission | July 2020 |
| NCT03510325 | N = 1,260<br>1 year<br>Adults; first-episode psychosis | Olanzapine oral tablet<br><br>Risperidone oral tablet<br><br>Aripiprazole oral tablet<br><br>Paliperidone long-acting injection (once monthly) | Symptom severity | September 2020 |
| NCT03198078 | N = 480<br>6 weeks<br>Adolescents | Brexpiprazole oral tablet<br><br>Aripiprazole oral tablet | Symptom severity, adverse events | November 2021 |

| NCT<br>Study Name | Estimated Enrollment<br>Duration<br>Population | Intervention<br>Comparison(s) | Outcomes | Estimated Primary Completion |
|---|---|---|---|---|
| **Major Depressive Disorder** | | | | |
| NCT03148509 | N = 300<br>8 weeks<br>Adolescents and adults | Risperidone<br><br>Aripiprazole | Symptom severity | December 2019 |
| NCT03738215<br>NCT03739203 | N = 750<br>6 weeks<br>Adults | Cariprazine oral capsule*<br><br>Placebo*<br><br>(*Adjunct to antidepressant therapy) | Symptom severity | July 2021 |
| NCT03697603 | N = 720<br>14 weeks<br>Adults | Brexpiprazole oral tablet*<br><br>Placebo*<br><br>(*Adjunct to antidepressant therapy) | Symptom severity | July 2022 |
| NCT03538691 | N = 1,450<br>46 weeks<br>Adults | Brexpiprazole oral tablet*<br><br>Placebo*<br><br>(*Adjunct to antidepressant therapy) | Relapse, disability | September 2022 |
| **Autism Spectrum Disorder** | | | | |
| NCT03487770 | N = 100<br>8 weeks<br>Children and adolescents | Aripiprazole oral solution<br><br>Placebo | Symptom severity, response | April 2020 |
| **Comorbid Populations** | | | | |
| NCT03485417 | N = 240<br>3 years<br>Adolescents and adults; substance use disorder and psychosis | Aripiprazole oral or depot<br><br>Paliperidone oral or depot (Invega Sustenna or Invega Trinza)<br><br>Treatment as usual | Psychosis relapse, cognitive function | December 2021 |

*Abbreviation. FDA: U.S. Food and Drug Administration.*

## Summary

Since the completion of the most recent updated DERP systematic review in October 2016, we identified the following:

- 14 new RCTs (6 in this surveillance document)
  - 7 head-to-head studies (3 in this surveillance document)
  - 7 placebo-controlled trials (3 in this surveillance document)
- 16 ongoing studies
  - 12 head-to-head studies
  - 4 placebo-controlled trials
- 3 new indications (1 in this surveillance document)
  - Cariprazine oral capsule (Vraylar) for depressive episodes associated with bipolar I disorder in adults (in this surveillance document)
  - Aripiprazole extended-release injection (Abilify Maintena Kit) for maintenance monotherapy treatment of bipolar disorder in adults
  - Lurasidone oral tablet (Latuda) for monotherapy treatment of bipolar disorder in pediatric patients ages 10 to 17 years
- 7 new serious harms or warnings
  - Implications for use in pregnant women (presence in breastmilk)
  - Increased adverse effects in the elderly (stroke, death) as well as children, adolescents, and young adults (suicidality)
  - Occurrences of sleepwalking
  - Potential risk of infertility
- 3 new formulations
  - Aripiprazole (Abilify MyCite Kit) oral tablet (drug-device combination, daily administration)
  - Aripiprazole lauroxil (Aristada Initio Kit) extended-release intramuscular injection (treatment initiation)
  - Risperidone (Perseris Kit) extended-release subcutaneous suspension (monthly administration)

Using the *Is There a There There Scale* (ITS) (Table 6), we rated this topic as *Yes* (see Appendix B for ratings and definitions).

Table 6. Summary and ITS Rating

| Clinical Evidence | Yes<br>How many? | No |
|---|---|---|
| New Comparative Trial | ☑<br>7 (11 publications) | |
| New Placebo-Controlled Trial (if needed) | ☑<br>7 | |
| New Meaningful[a] Study | ☑<br>2 | |
| Ongoing Study Likely to be Published in the Next Year | ☑<br>8 | |

| FDA Actions | Yes<br>Description | No |
|---|---|---|
| New Drug or Formulation | ☑<br>3 new formulations | |
| New Indication | ☑<br>3 | |
| New Serious Harm or Warning | ☑<br>7 | |
| ITS Rating: *Yes* | | |

*Abbreviation. ITS: Is There a There There Scale. Note.* [a] *Large studies (≥ 1,000 participants), studies that have long-term follow-up (≥ 12 months), studies that compare one drug with another that is considered the standard of care or has not been reported and is clinically important, and studies that include an intervention or outcome that is not previously reported in the literature or is clinically important (e.g., mortality) and adds to the body of literature.*

## References


1. U.S. Food and Drug Administration. Cariprazine (Vraylar) product label. 2019; https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/204370s006lbl.pdf. Accessed September 5, 2019.

2. U.S. Food and Drug Administration. Aripiprazole (Abilify) drug safety-related labeling change. 2019; https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=38. Accessed September 5, 2019.

3. U.S. Food and Drug Administration. Aripiprazole lauroxil (Aristada) drug safety-related labeling changes. 2018; https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=291. Accessed September 5, 2019.

4. U.S. Food and Drug Administration. Cariprazine (Vraylar) drug safety-related labeling change. 2019; https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=857. Accessed September 5, 2019.

5. U.S. Food and Drug Administration. Paliperidone palmitate (Invega Sustenna) drug safety-related labeling change. 2019; https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=68. Accessed September 5, 2019.

6. U.S. Food and Drug Administration. Paliperidone (Invega) drug safety-related labeling change. 2019; https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=67. Accessed September 5, 2019.

7. U.S. Food and Drug Administration. Paliperidone palmitate (Invega Trinza) drug safety-related labeling change. 2019; https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=69. Accessed September 5, 2019.

8. U.S. Food and Drug Administration. Quetiapine (Seroquel) drug safety-related labeling changes. 2019; https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=141. Accessed September 5, 2019.

9. U.S. Food and Drug Administration. Quetiapine (Seroquel XR) drug safety-related labeling changes. 2019; https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=142. Accessed September 5, 2019.

10. U.S. Food and Drug Administration. Risperidone (Risperdal) drug safety-related labeling changes. 2019; https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=76. Accessed September 5, 2019.

11. U.S. Food and Drug Administration. Risperidone (Risperdal Consta) drug safety-related labeling change. 2019; https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=79. Accessed September 5, 2019.

12. U.S. Food and Drug Administration. Ziprasidone (Geodon) drug safety-related labeling changes. 2018; https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=858. Accessed September 5, 2019.

13. Gomez-Revuelta M, Pelayo-Teran JM, Juncal-Ruiz M, et al. Long-Term Antipsychotic Effectiveness in First Episode of Psychosis: A 3-Year Follow-Up Randomized Clinical Trial Comparing Aripiprazole, Quetiapine, and Ziprasidone. *Int J Neuropsychopharmacol.* 2018;21(12):1090-1101. doi: 10.1093/ijnp/pyy082.

14. Cuomo I, Kotzalidis GD, de Persis S, et al. Head-to-head comparison of 1-year aripiprazole long-acting injectable (LAI) versus paliperidone LAI in comorbid psychosis and substance use disorder: impact on clinical status, substance craving, and quality of life. *Neuropsychiatr Dis Treat.* 2018;14:1645-1656. doi: 10.2147/ndt.S171002.

15. Nemeth G, Laszlovszky I, Czobor P, et al. Cariprazine versus risperidone monotherapy for treatment of predominant negative symptoms in patients with schizophrenia: a randomised, double-blind, controlled trial. *Lancet.* 2017;389(10074):1103-1113. doi: 10.1016/s0140-6736(17)30060-0.

16. Findling RL, Landbloom RL, Mackle M, et al. Long-term Safety of Asenapine in Pediatric Patients Diagnosed With Bipolar I Disorder: A 50-Week Open-Label, Flexible-Dose Trial. *Paediatr Drugs.* 2016;18(5):367-378. doi: 10.1007/s40272-016-0184-2.

17. Hobart M, Skuban A, Zhang P, et al. A Randomized, Placebo-Controlled Study of the Efficacy and Safety of Fixed-Dose Brexpiprazole 2 mg/d as Adjunctive Treatment of Adults With Major Depressive Disorder. *J Clin Psychiatry.* 2018;79(4). doi: 10.4088/JCP.17m12058.

18. Durgam S, Earley W, Guo H, et al. Efficacy and safety of adjunctive cariprazine in inadequate responders to antidepressants: a randomized, double-blind, placebo-controlled study in adult patients with major depressive disorder. *J Clin Psychiatry.* 2016;77(3):371-378. doi: 10.4088/JCP.15m10070.

## Appendix A. Abstracts of New Eligible Studies

**Cuomo I, Kotzalidis GD, de Persis S, et al. Head-to-head comparison of 1-year aripiprazole long-acting injectable (LAI) versus paliperidone LAI in comorbid psychosis and substance use disorder: impact on clinical status, substance craving, and quality of life. *Neuropsychiatr Dis Treat*. 2018;14:1645-1656.**

Background: To overcome nonadherence in patients with psychosis switch to long-acting injectable (LAI) antipsychotic formulations is adopted. Most oral versus LAI comparisons showed similar antipsychotic responses. Psychoses often overlap with substance use disorder (SUD). Head-to-head LAI comparisons have hitherto focused only on non-comorbid populations. Objective: The objective of this study was to compare two LAIs, administered for 12 months, in initially hospitalized patients with psychosis comorbid with SUD in their clinical and quality of life (QoL) outcomes. Patients and methods: Inpatients were recruited during 2016 and switched randomly to 400 mg intramuscular aripiprazole monohydrate (AM) (N=50) or to 100 mg intramuscular paliperidone palmitate (PP) once-monthly (N=51); patients were discharged and followed up for 12 months. Patients were rated at baseline and after 1 year through the Clinical Global Impression scale - severity (CGIs), substance craving intensity was rated through a visual analog scale for substance craving, and QoL through the World Health Organization (WHOQOL-BREF) scale. We addressed confounders with backward stepwise logistic regression and three-way analysis of variance. Results: PP were older and had more cases of schizophrenia spectrum and less bipolar disorders than AM, but AM had a stronger craving for substances at baseline. Both LAIs were associated with significant improvements in all outcomes, with AM displaying stronger effect sizes than PP. The two groups did not differ on baseline WHOQOL-BREF scores in any domain, but at the 1-year follow-up, AM fared better on all domains. The two groups did not differ in final severity, but PP scored higher than AM in craving at the 1-year endpoint. Limitation: The CGIs is not a refined tool for severity and the substance craving may be subject to recall bias. Conclusion: 1-year AM and PP was followed by improved clinical status and QoL and reduced substance craving in a population with psychosis and SUD comorbidity. AM, compared to PP, improved craving and QoL at the 1-year follow-up.

**Durgam S, Earley W, Guo H, et al. Efficacy and safety of adjunctive cariprazine in inadequate responders to antidepressants: a randomized, double-blind, placebo-controlled study in adult patients with major depressive disorder. *J Clin Psychiatry*. 2016;77(3):371-378.**

BACKGROUND: Cariprazine is an atypical antipsychotic currently under investigation as adjunctive therapy in patients with major depressive disorder (MDD) who have inadequate response to standard antidepressant therapy. METHOD: A randomized, double-blind, placebo-controlled, flexible-dose study was conducted from December 2011 to December 2013 in adults who met DSM-IV-TR criteria for MDD and had an inadequate antidepressant response. Eligible patients were randomized to 8-week adjunctive treatment with placebo (n = 269), cariprazine 1-2 mg/d (n = 274), or cariprazine 2-4.5 mg/d (n = 276). The primary efficacy parameter was change from baseline to week 8 in Montgomery-Asberg Depression Rating Scale (MADRS) total score; P values were adjusted for multiple comparisons. Safety assessments included adverse events, clinical laboratory tests, vital signs, electrocardiograms (ECGs), and suicidality. RESULTS: Compared with placebo, reduction in MADRS total score at week 8 was significantly greater with adjunctive cariprazine 2-4.5 mg/d (least squares mean difference [LSMD] = -2.2; adjusted P =

.0114), but not with cariprazine 1-2 mg/d (LSMD = -0.9; adjusted P = .2404). Significant LSMDs for MADRS total score change were detected at all earlier study visits (weeks 2, 4, 6) in the 2- to 4.5-mg/d group and at weeks 2 and 4 in the 1- to 2-mg/d group (all P values < .05). Treatment-emergent adverse events reported in >/= 10% of patients in either cariprazine dosage group were akathisia (22.3%), insomnia (13.6%), and nausea (12.8%) (all in 2- to 4.5-mg/d group). Mean changes in metabolic parameters, vital signs, and ECG parameters were generally similar between groups. No suicide-related adverse events were reported. DISCUSSION: These results show that adjunctive cariprazine 2-4.5 mg/d was effective and generally well tolerated in adults with MDD who had inadequate responses to standard antidepressants. Further clinical studies to confirm these results are warranted. TRIAL REGISTRATION: ClinicalTrials.gov identifier: NCT01469377.

**Findling RL, Landbloom RL, Mackle M, et al. Long-term safety of asenapine in pediatric patients diagnosed with bipolar I disorder: a 50-week open-label, flexible-dose trial. *Paediatr Drugs.* 2016;18(5):367-378.**

BACKGROUND: Sublingually administered asenapine was approved in March 2015 by the United States Food and Drug Administration for patients aged 10-17 years with an acute manic or mixed episode associated with bipolar I disorder (BP-1). This is the first long-term safety and tolerability study of asenapine in this population. METHODS: Following the 3-week randomized, double-blind, placebo-controlled trial of patients aged 10-17 years with an acute manic or mixed episode associated with BP-1, patients could enroll in this flexible-dose (2.5-10 mg twice daily) open-label extension (OLE) study for an additional 50 weeks, conducted from August 2011 to September 2014 in the United States and Russia. Treatment-emergent adverse events (TEAEs) were assessed and predefined TEAEs of interest reported in addition to metabolic and anthropometric parameters. The Young Mania Rating Scale (YMRS) and Clinical Global Impressions scale in bipolar illness (CGI-BP) were used to assess effectiveness. RESULTS: A total of 321 patients (lead-in study treatment: placebo, n = 80; asenapine, n = 241) were included; 267 (83.2 %) reported one or more TEAE and 181 (56.4 %) discontinued early, 48 (15.0 %) due to TEAEs. Of the predefined TEAEs of interest, combined somnolence/sedation/hypersomnia occurred most frequently (42.4 %) followed by oral hypoesthesia/dysgeusia (7.5 %). In total, 109 (34.8 %) patients experienced clinically significant weight gain (>/=7 % increase). No clinically meaningful changes were noted for laboratory parameters measured. Eighteen patients met the criteria for new-onset metabolic syndrome (MBS) post-baseline during the extension study, whereas 10 patients who met MBS criteria at baseline did not meet MBS criteria at endpoint. A total of 12 patients met MBS at baseline and endpoint. Mean change in YMRS total score from OLE baseline was -9.2 points at week 50, and change in CGI-BP severity overall score was similar among all treatment groups (those who initially received asenapine and those who initially received placebo). After 26 weeks of treatment in the OLE, 79.2 % of patients were classified as YMRS 50 % responders relative to acute trial baseline. CONCLUSIONS: Asenapine was generally well tolerated in pediatric patients with BP-1 during </=50 weeks of open-label treatment; among predefined TEAEs of interest, the combination of somnolence/sedation/hypersomnia was the most common. Trial registration ClinicalTrials.gov: NCT01349907.

**Gomez-Revuelta M, Pelayo-Teran JM, Juncal-Ruiz M, et al. Long-term antipsychotic effectiveness in first episode of psychosis: a 3-year follow-up randomized clinical trial**

**comparing aripiprazole, quetiapine, and ziprasidone. *Int J Neuropsychopharmacol.* 2018;21(12):1090-1101.**

Background: Different effectiveness profiles among second-generation antipsychotics may be a key point to optimize treatment in patients suffering a first episode of psychosis to affect long-term outcome. The aim of this study was to compare the clinical effectiveness of aripiprazole, ziprasidone, and quetiapine in the treatment of first episode of psychosis at 3-year follow-up. Method: From October 2005 to January 2011, a prospective, randomized, open-label study was undertaken. Two hundred-two first-episode, drug-naive patients were randomly assigned to aripiprazole (n=78), ziprasidone (n =62), or quetiapine (n=62) and followed-up for 3 years. The primary effectiveness measure was all cause of treatment discontinuation. In addition, an analysis based on the intention-to-treat principle was conducted in the analysis for clinical efficacy. Results: The overall dropout rate at 3 years reached 19.3%. Treatment discontinuation rates were significantly different among treatment groups (aripiprazole=73.08%, ziprasidone=79.03%, and quetiapine=95.16%) (chi2=11.680; P=.001). Statistically significant differences in terms of nonefficacy, nonadherence, and side effects were observed among treatment groups along the 3-year follow-up determining significant differences in time to all-cause discontinuation (log-rank=32.260; P=.001). Significant differences between treatments were found in the categories of sleepiness/sedation (chi2=9.617; P=.008) and increased sleep duration (chi2=6.192; P=.004). No significant differences were found in the profile of extrapyramidal symptoms. Patients on aripiprazole were more likely to be prescribed benzodiazepines. Conclusions: First-episode psychosis patients on quetiapine were more likely to discontinue treatment due to nonefficacy. Identifying different discontinuation patterns may contribute to optimize treatment selection after first episode of psychosis.

**Hobart M, Skuban A, Zhang P, et al. A randomized, placebo-controlled study of the efficacy and safety of fixed-dose brexpiprazole 2 mg/d as adjunctive treatment of adults with major depressive disorder. *J Clin Psychiatry.* 2018;79(4).**

OBJECTIVE: To assess the efficacy, safety, and tolerability of brexpiprazole as adjunct to antidepressant treatment (ADT) in adults with major depressive disorder (MDD) and inadequate response to ADTs. METHODS: Outpatients with inadequate response to 1-3 ADTs during their current depressive episode (DSM-IV-TR criteria) were administered prospective, open-label ADT. Those patients with inadequate response to prospective ADT were randomized to double-blind, adjunctive brexpiprazole 2 mg/d or placebo. The primary efficacy end point was the change from baseline (randomization) to week 6 in Montgomery-Asberg Depression Rating Scale (MADRS) total score. Key secondary efficacy end points were the change in Sheehan Disability Scale (SDS) mean score for all patients and the change in MADRS total score for subgroups with minimal response to prospective ADT and DSM-5-defined anxious distress. The study was conducted from July 2014 to May 2016. RESULTS: Adjunctive brexpiprazole (n = 191) improved MADRS total score from baseline to week 6 versus placebo (n = 202; least squares mean difference [95% confidence limits]: -2.30 [-3.97, -0.62]; P = .0074). There was no separation between groups for the SDS mean score (-0.22 [-0.66, 0.23]; P = .33). Adjunctive brexpiprazole also improved MADRS total score versus placebo in the subgroups with minimal response to prospective ADT (-2.25 [-4.23, -0.27]; P = .026) and anxious distress (-2.98 [-5.24, -0.72]; P = .0099). Treatment with adjunctive brexpiprazole was well tolerated with no unexpected side effects.

CONCLUSIONS: This study adds to the substantial body of evidence for the efficacy and tolerability of brexpiprazole as adjunctive treatment in patients with MDD and inadequate response to ADTs. TRIAL REGISTRATION: ClinicalTrials.gov identifier: NCT02196506; EudraCT number: 2014-000062-22.

**Nemeth G, Laszlovszky I, Czobor P, et al. Cariprazine versus risperidone monotherapy for treatment of predominant negative symptoms in patients with schizophrenia: a randomised, double-blind, controlled trial. *Lancet*. 2017;389(10074):1103-1113.**

BACKGROUND: Although predominant negative symptoms of schizophrenia can be severe enough to cause persistent impairment, effective treatment options are lacking. We aimed to assess the new generation antipsychotic cariprazine in adult patients with predominant negative symptoms. METHODS: In this randomised, double-blind, phase 3b trial, we enrolled adults aged 18-65 years with long-term (>2 year), stable schizophrenia and predominant negative symptoms (>6 months) at 66 study centres (mainly hospitals and university clinics, with a small number of private practices) in 11 European countries. Patients were randomly assigned (1:1) by an interactive web response system to 26 weeks of monotherapy with fixed-dose oral cariprazine (3 mg, 4.5 mg [target dose], or 6 mg per day) or risperidone (3 mg, 4 mg [target dose], or 6 mg per day); previous medication was discontinued over 2 weeks. The primary outcome was change from baseline to week 26 or end of treatment on the Positive and Negative Syndrome Scale factor score for negative symptoms (PANSS-FSNS) analysed in a modified intention-to-treat population of patients who had follow-up assessments within 5 days after last receipt of study drugs with a mixed-effects model for repeated measures. Safety was assessed in all patients who received at least one dose of study drug. This study is registered with EudraCT, number 2012-005485-36. FINDINGS: Between May 27, 2013, and Nov 17, 2014, 533 patients were screened and 461 (86%) patients were randomised to treatment (230 for cariprazine and 231 for risperidone); 460 were included in the safety population (one patient discontinued before study drug intake). 227 (99%) of 230 patients in the cariprazine group and 229 (99%) of 230 patients in the risperidone group were included in the modified intention-to-treat population (178 [77%] in each group completed 26 weeks of treatment). Mean daily doses were 4.2 mg (SD 0.6) for cariprazine and 3.8 mg (0.4) for risperidone. Treatment-emergent adverse events (eg, insomnia, akathisia, worsening of schizophrenia, headache, anxiety) were reported in 123 (54%) patients treated with cariprazine and 131 (57%) patients treated with risperidone. Use of cariprazine led to a greater least squares mean change in PANSS-FSNS from baseline to week 26 than did risperidone (-8.90 points for cariprazine vs -7.44 points for risperidone; least squares mean difference -1.46, 95% CI -2.39 to -0.53; p=0.0022; effect size 0.31). One patient in the risperidone group died of a cause regarded as unrelated to treatment. INTERPRETATION: Our results support the efficacy of cariprazine in the treatment of predominant negative symptoms of schizophrenia. FUNDING: Gedeon Richter Plc.

## Appendix B. ITS Ratings and Definitions

The *Is There a There There Scale* (ITS) consists of 3 ratings: *no*, *maybe*, and *yes*. The definitions of these ratings and methods for selection are described below. Center for Evidence-based Policy (Center) researchers use these definitions to rate each surveillance topic. The assigned rating is offered as guidance and does not require DERP participants to follow this recommendation. Each rating is strictly based on the identified new research and clinical information and is not comprehensive to all aspects of policy decision making, such as competing priorities, budget, contracting, or internal and external state agency needs.

### *No*

- We did not find clinical evidence or information that would indicate a need to update the report or develop a derivative research product.
- A rating of No is typically given when there are few new studies and/or no new meaningful studies, and no new serious harms.

### *Maybe*

- We found some clinical evidence or information that might suggest a need to update the report or develop a derivative research product.
- A rating of Maybe is typically given when there are multiple new comparative trials or at least 1 new meaningful study or serious harm.

### *Yes*

- We found clinical evidence or information that suggests a need to update the report or develop a derivative research product.
- A rating of Yes is typically given when there are multiple new comparative trials and meaningful studies and/or new serious harms, drugs, formulations, or indications.