Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Class Update: Atypical Antipsychotic Medications

Month/Year of Review: March 2012
New Product for review: Lurasidone (Latuda®)
Manufacturer: Sunovion Pharmaceuticals
Last Oregon Review: Dec 2010 (Oregon HRC)

Dossier received: Yes

Source Document: DERP

Table 1. Current Voluntary PDL Preferred/Non-Preferred Atypical Antipsychotics

Current Preferred Agents:	Current Non-Preferred Agents:
Clozapine (Clozaril®)	Abilify® tablet/solution/Discmelt®/IM
Geodon® capsule/IM	Fanapt® tablet
Risperidone (Risperdal®) tablet/solution--generic	Invega® tablet
Risperidone Tab RAPDIS	Invega Sustenna®
Seroquel® (therapeutic doses) tablet/XR tablet	Risperdal Consta®
	Olanzapine (Zyprexa®) tablet--generic
	Saphris® SL tablet
	Zyprexa Relprevv®
	Zyprexa Zydis®

Reason for Review:
The Oregon Evidence-based Practice Center drug effectiveness review project (DERP) published an update to the drug class review on atypical antispychotics.[1] This was reviewed by the Oregon Health Resources Commission in December 2010 and their conclusions are listed in Appendix 1.[2] Since the last OR review, however, the Agency for Healthcare Research and Quality (AHRQ) has release an update report on the off-label use of atypical antipsychotics[3], a new atypical antipsychotic, lurasidone (Latuda®), has been FDA-approved,[4] and various systematic reviews through the Cochrane Library were done to evaluate and compare atypical antipsychotics in patients with schizophrenia.[5-9] The evidence-based practice guidelines endorsed by the American Psychiatric Association have not been updated since 2002 for the treatment of bipolar affective disorder and 2004 for the treatment of schizophrenia. This update will summarize the results from the AHRQ systematic review regarding the off-label use of atypical antipsychotics, evaluate the effectiveness, safety, and place in therapy for lurasidone, and identify any other new relevant comparative effectiveness evidence, high-quality systematic reviews, or evidence-based guidelines.

Issues:

- Is there any new evidence of effectiveness or harms that will support atypical antipsychotic management strategies or changes?
- Is there any evidence that lurasidone is more effective or safer than currently available medications in the PDL drug class including in subgroups of patients?
- What recommendations for management of the atypical antipsychotic class can be made?

Conclusions:

- No trials have been done evaluating the newest agents (asenapine, iloperidone, paliperidone, and lurasidone) for any off-label uses.
- Benefits and harms vary among atypical antipsychotics and direct comparisons of different agents for off-label conditions are rare.
- There is low quality evidence that lurasidone is safe and effective based on short-term placebo controlled trials in improving the general mental state. There is insufficient evidence to determine comparative effectiveness of lurasidone with other atypical antipsychotics.
- There is insufficient evidence to determine how maintenance lurasidone affects other clinical important outcomes in patients with schizophrenia including quality of life, improvement in social functioning, hospitalization, mortality, or adherence.
- From a recent AHRQ systematic review, there was moderate to high level of evidence available to support the following off-label use of the listed atypical antipsychotics.[3]
  - Generalized anxiety disorder: quetiapine
  - Dementia (overall): aripiprazole, risperidone
  - Dementia (psychosis): risperidone
  - Dementia (agitation): olanzapine, risperidone
  - Depression (selective serotonin reuptake inhibitor (SSRI)/ selective serotonin-norepinephrine reuptake inhibitor (SNRI) augmentation): aripiprazole, quetiapine, risperidone
  - Depression (monotherapy): quetiapine
  - Obsessive Compulsive Disorder (SSRI augmentation): risperidone
  - Post Traumatic Stress Disorder (PTSD): risperidone

Recommendations:

1. No changes are recommended for the atypical antipsychotic preferred drug class list based on safety and efficacy. Costs should be reviewed in executive session.
2. Based upon findings from the AHRQ report on off-label antipsychotics, it is recommended to maintain the current dose limit for quetiapine (limits doses <150mg for >3 months) to prevent off-label use.
3. Based on the lack of long-term comparative effectiveness data, recommend listing lurasidone a non-preferred agent on the voluntary PDL.
4. Due to the need for voluntary compliance with the PDL for this drug class, it is recommended that educational outreach interventions be considered in the management strategy.
    i. As one example, academic detailing can be used to promote appropriate utilization and minimize inappropriate off-label use.

Background:

Antipsychotic medications are approved by the U.S. FDA for treatment of schizophrenia and bipolar disorder and are divided into the older, conventional antipsychotics and the second generation atypical antipsychotics. There are currently ten different atypical antipsychotics available and approved by the FDA. Some offer a variety of dosage forms (e.g. orally disintegrating tablets or long-acting injectables) and many have an assortment of approved indications (ranging from the irritability associated with autistic disorder in children and adolescents to the maintenance treatment for schizophrenia in adults), as well as are commonly used off-label for various psychiatric conditions.[3] Appendix 2 lists FDA approved indications for the atypical antipsychotics. No consistent differences in efficacy have been demonstrated between the available agents. Side effect profiles between the agents do vary and is often an important factor in treatment selection. These side effects may include extrapyramidal symptoms, autonomic effects, increased prolactin levels, metabolic effects, and cardiac risks including increased risk of ventricular arrhythmias.

Methods:

The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, the Department of Veteran Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

Comparative Effectiveness Reviews:

AHRQ Off-Label Use of Atypical Antipsychotics: An Update (September 2011)

The AHRQ report performed a systemic review on the efficacy and safety of atypical antipsychotics for use in conditions lacking FDA approval.[3] These conditions include anxiety, attention deficit hyperactivity disorder (ADHD), dementia and severe geriatric agitation, major depressive disorder (MDD), eating disorders, insomnia, OCD, PTSD, personality disorders, substance abuse, and Tourette's syndrome. Lurasidone was not included in this review.

Key Questions and Conclusions:

1. What are the leading off-label uses of atypical antipsychotics in utilization studies? How have trends in utilization changed in recent years, including inpatient versus outpatient use? What new uses are being studied in trials?

- Atypicals have been studied as off-label treatment for the following conditions: ADHD, anxiety, dementia in elderly patients, depression, eating disorders, insomnia, obsessive compulsive disorder (OCD), personality disorder, PTSD, substance use disorders, and Tourette's syndrome.
- Off-label use of atypical antipsychotics in various settings has increased rapidly since their introduction in the 1990s; risperidone, quetiapine, and olanzapine are the most common atypicals prescribed for off-label use.
- One recent study indicated that the 2005 regulatory warning from the FDA and Health Canada was associated with decreases in the overall use of atypical antipsychotics, especially among elderly dementia patients. Use of atypicals in the elderly is much higher in long-term care settings than in the community.
- Atypicals are frequently prescribed to treat PTSD in the U.S. Department of Veterans Affairs health system.
- At least 90 percent of antipsychotics prescribed to children are atypical, rather than conventional antipsychotics. The majority of use is off-label.
- No off-label use of the newly approved atypicals (asenapine, iloperidone, and paliperidone) was reported in the utilization literature.

2. What does the evidence show regarding the efficacy and comparative effectiveness of atypical antipsychotics, for off-label indications?

- Moderate to high evidence for efficacy for the following off-label indications and atypical antipsychotics:
  - Generalized anxiety disorder: quetiapine
  - Dementia (overall): aripiprazole, risperidone
  - Dementia (psychosis): risperidone
  - Dementia (agitation): olanzapine, risperidone
  - Depression (SSRI/SRNI augmentation): aripiprazole, quetiapine, risperidone
  - Depression (monotherapy): quetiapine
  - Obsessive Compulsive Disorder (SSRI augmentation): risperidone
  - PTSD: risperidone

- Moderate to high evidence for inefficacy for the following off-label indications and atypical antipsychotics:
  - Eating Disorders: olanzapine
  - Substance Abuse (alcohol): aripiprazole
  - MDD (monotherapy): olanzapine

- A complete summary of strength of efficacy by drug and conditions is available in Appendix 3.

3. What subset of the population would potentially benefit from off-label uses? Do effectiveness and harms differ by race/ethnicity, gender, and age group? By severity of condition and clinical subtype?

- There are insufficient data regarding efficacy, effectiveness, and harms to determine what subset of the population would potentially benefit from off-label uses of atypicals.

4. What are the potential adverse effects and/or complications involved with off-label prescribing of atypical antipsychotics? How do they compare within the class and with other drugs used for the conditions?

- In elderly patients, adverse effects included an increased risk of death (NNH 87), stroke (NNH 53 for risperidone), extrapyramidal symptoms (NNH 10 for olanzapine, 20 for risperidone), and urinary symptoms.
- In nonelderly adults, adverse events included weight gain (especially with olanzapine), fatigue, sedation, akithisia (for aripiprazole), and extrapyramidal symptoms.
- In elderly patients, a metaanalysis found a small but statistically significant difference in the risk of death for atypicals compared to placebo and found no difference between drugs in the class.

5. What is the effective dose and time limit for off-label indications?

- There are too few studies comparing doses of atypical antipsychotic medications to draw a conclusion about a minimum dose needed.
    - Most trials used flexible dosing, resulting in patients taking a wide range of doses.
    - According the meta-analysis conducted by AHRQ, using the percentage of remitters and responders according to the Montgomery-Asperg Depression Rating Scale (MADRS) as an outcome, 150 mg quetiapine daily augmentation has equal efficacy as augmentation with 300 mg for patients with MDD who respond inadequately to SSRIs.
    - More trials examining different doses of other atypicals for MDD are needed as are dosage trials for treating conditions such as OCD, PTSD, and anxiety disorder.
- Though there is some trial data regarding duration of treatment in PTSD, eating disorders, and borderline personality disorder, the outcome of treatment appears to be the same regardless of reported follow-up time.

Cochrane Reviews:

Five systematic reviews were also identified from the Cochrane Library evaluating quetiapine, olanzapine, risperidone, clozapine, and ziprasidone versus other atypical antipsychotics for schizophrenia.[5-9] It was clear across all of the reviews that it remains difficult to draw strong conclusions due to the high rates of attrition in these groups (risperidone 46.9%, olanzapine 49.2%, ziprasidone 59.1%, quetiapine 57.6%). Differences in efficacy were small and most often seen in general mental state. Most differences are seen in side effects and toleratibility profiles between the different medications.

Other conclusions from these reviews include:

- Olanzapine may be a more efficacious drug in improving the general mental state than some other atypical antipsychotics (aripiprazole, risperidone, quetiapine, and ziprasidone), but this small superiority in efficacy needs to be considered that it can be associated with more weight gain and metabolic problems than other medications in the class, except clozapine.
- Ziprasidone may be a slightly less efficacious antipsychotic drug based on the Positive and Negative Syndrome Scale (PANSS) than olanzapine (4 RCTs, n=1291, MD 8.32 CI 5.64 to 10.99) and risperidone (3 RCTs, n=1016, MD 3.91 CI 0.27 to 7.55). Its main advantage is the low propensity to induce weight gain and associated adverse effects.
- Risperidone seems to produce somewhat more extrapyramidal side effects and clearly more prolactin increase than most other second generation antipsychotics.
- Risperidone improved the general mental state (PANSS score) slightly less than olanzapine (15 RCTs, n = 2390, MD 1.94 CI 0.58 to 3.31), but slightly more than quetiapine (9 RCTs, n = 1953, MD -3.09 CI -5.16 to -1.01) and ziprasidone (3 RCTs, n =1016, MD -3.91 CI -7.55 to -0.27).
- Clozapine differs more clearly in adverse effects from other second generation antipsychotics and the side-effect profile could be key in the selection of treatment depending on the clinical situation and patient's preferences. Data on other important outcomes such as cognitive functioning, quality of life, death or service use are currently largely missing, making further large and well-designed trials necessary
- Efficacy data favored olanzapine and risperidone compared with quetiapine (PANSS total score versus olanzapine: 10 RCTs, n=1449, WMD 3.66 CI 1.93 to 5.39; versus risperidone: 9 RCTs, n=1953, WMD 3.09 CI 1.01 to 5.16), but clinical meaning is unclear. There were no clear mental state differences when quetiapine was compared with clozapine or ziprasidone.
- Most data that has been reported within existing comparisons of quetiapine are of very limited value because of assumptions and biases within them. There is much scope for further research into the effects of this widely used drug.

Another recent Cochrane Review attempted to assess the effects of atypical antipsychotics in people who are diagnosed with both schizophrenia and depression and concluded that there is insufficient evidence to make any definitive conclusions or recommendations. Only three studies were included in their review and evaluation.[10]

New Drug Review[11,12]

FDA approved indications: Lurasidone is an atypical antipsychotic agent indicated for the treatment of patients with schizophrenia.

Clinical Trial Data:[12]

Efficacy: The efficacy of lurasidone was established in four short term (six-week), randomized, placebo-controlled studies in 1307 adults with schizophrenia and who were hospitalized for an acute exacerbation and had a duration of illness for at least one year.[12] Table 2 provides a summary of the evidence findings for the two published and peer-reviewed studies.[13,14] The remaining two have not been published or peer-reviewed and were not included because they could not be assessed for quality or risk of bias. There are no head-to-head comparative trials comparing lurasidone with any other atypicals. Among the measures used to deem effectiveness were Positive and Negative Syndrome Scale (PANSS), Brief Psychiatric Rating Scale derived (BPRSd), and Clinical Global Impression severity scale (CGI-S). These are all validated measures. Endpoints were measured at the end of week six. All studies had a high discontinuation rates (34%-65.8%).

In one fair-quality study (n=180) phase II study, lurasidone 80 mg daily was found to be superior to placebo in the mean change inf BPRSd total score and CGI-S.[14] The mean change was -8.9 and -4.2 for the 80mg and placebo groups (p= 0.018). A total of 99 (55%) patients completed the study. The proportion of subjects experiencing ≥1 AE was not significantly higher in the lurasidone group (76.7%) than in the placebo group (68.9%). In another fair-quality randomized controlled trial (n=473), patients were randomized to an active control of olanzapine 15mg, lurasidone 40 mg, 120 mg, or placebo. A total of 298 subjects (62%) completed the double-blind study phase. All three active arms were superior to placebo on the PANSS total score and CGI-S.[13] The mean change in the PANSS total score was -25.7, -23.6, -28.7 and -16 for the 40mg, 120mg, olanzapine and placebo groups respectively and the difference from placebo in mean change was significant in the lurasidone 40mg group and the lurasidone 120mg group (p= 0.002 and 0.022 respectively). There was no improved efficacy with the 120mg dose compared to 40mg dose, and an increased risk of adverse events.

Two other randomized short term trials were evaluated by the FDA for the approval of lurasidone. In one study, a total of 488 participants were randomized to lurasidone 80mg, lurasidone 160 mg, placebo, or quetiapine XR 600mg as an active comparator. The difference from placebo in the mean change in the PANSS total score from baseline to week 6 was significant in the lurasidone 80 mg group (-11.9, $p<0.001$) and the lurasidone 160 mg group (-16.2, $p<0.001$). A randomized study (n=489) evaluated lurasidone 40, 80, and 120 mg daily compared to placebo.[12] Only the 80 mg daily dose demonstrated superiority to placebo in the primary endpoint of PANSS total score and CGI-S. The 120 mg daily dose did not have additional benefit over lower daily doses. The mean change in the PANSS score was -19.2, -23.4, -20.5, -17 in the 40mg, 80mg, 120mg and placebo groups respectively (p=0.591, 0.034, and 0.391) .[12] A third published study assessing performance and interview-based cognitive change in lurasidone versus ziprasidone is also available, but because it does not measures common efficacy endpoints it is not included in the following evidence table.[15] There was a fifth study (049) that failed to distinguish either lurasidone (at any of 3 doses: 20, 40, or 80 mg/day) or haloperidol (10 mg/day) from placebo and was not further reviewed by the FDA.

Safety: Commonly observed adverse effects (incidence ≥5% and at least twice the rate of placebo) include: somnolence, akathisia, nausea, parkinsonism, and agitation. Electrocardiogram changes exceeding 500 milliseconds were not reported. In short-term trials, weight gain, fasting glucose, and lipid levels appear to be similar to placebo. The mean change in fasting glucose was 1.4 mg/dL in the lurasidone group, 0.6 mg/dL in the placebo group and 9 mg/dL in the olanzapine group. Mean increases in TC, LDL, and TC was not noted in the lurasidone group. Latuda has the same warnings and precautions as other atypical antipsychotics such as increased mortality in the elderly, neuroleptic malignant syndrome, tardive dyskinesia, and metabolic side effects. Mean increases in weight was 0.75 kg in the lurasidone group, 0.26 kg for placebo and 4.1 kg for olanzapine.[4]

Consideration in Subpopulations:

Pediatrics: Several atypical are approved for use in pediatrics. Lurasidone has not been studied in patients less than 18 years of age.

Geriatrics: Older patients may be more likely to experience adverse effects due to lower renal and hepatic function. All atypical have a warning of increased risk of death in elderly patients with dementia-related psychosis.

Gender, race, ethnicity: Subgroup analyses for these 4 studies based on gender and race generally showed consistency in the results across these subgroups.[12] There is no known difference in clinical efficacy or safety based on gender, race, or ethnicity.

COMPARATIVE CLINICAL EFFICACY:

Relevant Endpoints in schizophrenia:

- Mortality
- Quality of Life
- Functional Capacity
- Hospitalization
- Efficacy as measured by symptom response
- Withdrawals due to adverse events and time to withdrawal
- Major adverse events

Study Primary Endpoints:

- Meltzer et al: Positive and Negative Syndrome Scale (PANSS)
- Nakamura et al: Brief Psychiatric Rating Scale (BPRSd)

Table 2. Lurasidone Comparative Evidence Table

Ref./ Study Design	Drug Regimens	Patient Population	N	Duration	Efficacy Results[2] (CI, p-values)	ARR / NNT[3]	Safety Results^ (CI, p-values)	ARR/ NNH[3]	Quality Rating[4]; Comments
1.Meltzer, et al. Prospective, multicenter, DB, PG study Lurasidone vs Placebo Olanzapine vs Placebo	1. Lurasidone 40mg 2. Lurasidone 120mg 3. Olanzapine 15mg 4. Placebo All dosed QD	Recently admitted inpatients with schizophrenia with an acute exacerbation of psychotic sx illness duration of at least 1 year and to have been hospitalized for ≤2 weeks for an acute exacerbation of psychotic symptoms	478	6-weeks	<u>PANSS total score (change from baseline to week 6):</u> Lurasidone 40mg = -25.7 Placebo = -16.0 p-value = 0.002 Lurasidone 120mg = -23.6 Placebo = -16.0 p-value = 0.022 Olanzapine 15mg = -28.7 Placebo = -16.0 p-value <0.001	N/A	<u>Discontinuations due to adverse events:</u> Lur 40mg : 8 (6.7%) Lur 120mg: 14 (11.8%) Olan 15mg: 8 (6.5%) Placebo 10 (8.6%)	N/A	Fair; *Placebo controlled, not head-to-head* *No dose-response relationship was observed between 40mg and 120mg of lurasidone* *Manufacturer sponsored trial* *Short-term trial* *Rates of Attrition:* *32%-45% lurasidone* *39% placebo*
2.Nakamura, et al. DB, PC, RCT	1. Lurasidone 80mg 2. Placebo	Age 18-64 yrs, hospitalized for an acute exacerbation of schizophrenia Minimum illness duration of at least 1 year 75.6% male Mean age 39.7	N=90 N=90	6-weeks	<u>BPRSd (change from baseline to week 6):</u> Lurasidone 80mg = -8.9 (CI= -11.5 to -6.2) Placebo = -4.2 (CI = -6.9 to -1.5) p-value = 0.0118 PANSS (change from baseline) Lurasidone: -14.1 Placebo: -5.5 P=0.004	N/A N/A	Discontinuations due to adverse events: Lur 80mg : 6 (6.7%) Placebo: 1(1.1%) P=0.118 Severe Adverse Events: Lur 80mg: 7 (7.8%) Placebo: 5 (5.6%)	NS NS	Fair; Unknown methods for allocation concealment *CIs appear to cross for efficacy measure BPRSd* *Manufacturer sponsored trial* *Short-term trial* *High rates of Attrition:* *48% placebo* *42% lurasidone*

[1]**Study design abbreviations:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover.
[2]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval
[3]**NNT/NNH** are reported only for statistically significant results
[4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)

Table 3. Lurasidone Dose & Availability

STRENGTH	FORM	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
40mg	Tab	PO	Daily	Max 40mg/d (CrCl 10-50 ml/min)	Max 40mg/d Child-Pugh Class B or C	Not Established	None	Should be given with food
80mg	Tab	PO	Daily					

Pharmacology

Lurasidone is a benzoisothiazol derivative thought to work through a combination of central Dopamine Type 2 (D2) and serotonin Type 2 (5HT2A) receptor antagonism.

Table 4. Lurasidone Pharmacokinetics

Parameter	Result
Oral Bioavailability	9-19% (increased w/food)
Cmax	1-3 hours
Protein Binding	~99%
Elimination	Feces 80% Urine 9%
Half-Life	18 hours
Metabolism	CYP3A4 2 active; 2 inactive metabolites

ADVERSE EFFECTS:[4] Adverse reactions observed in >2% of patients and greater incidence than placebo treated patients

	Icatibant (N=1004)	***Placebo (N=455)***
System Organ Class	***Subjects (%)***	***Subjects (%)***
Gastrointestinal Disorders		
Nausea	*12*	*6*
Vomiting	*6*	*8*
Dyspepsia	*8*	*6*
Nervous System Disorders		
Somnolence	*22*	*10*
Akathisia	*15*	*3*
Parkinsonism	*11*	*5*
Dystonia	*5*	*1*
Dizziness	*5*	*3*
Psychiatric Disorders		
Insomnia	*8*	*7*
Agitation	*6*	*3*
Anxiety	*6*	*3*
Restlessness	*3*	*2*

Appendix 1

Previous Conclusions by DERP[1,2]:

Schizophrenia:

1. No consistent differences in efficacy were found between clozapine, olanzapine, quetiapine, risperidone, ziprasidone, Iloperidone, asenapine or aripiprazole in shorter-term trials of inpatients or outpatients.
2. There is insufficient evidence to draw conclusions regarding the impact of medications in this class on suicide death.
3. There is no evidence of a clinically meaningful difference in rates of rehospitalization for the included drugs.
4. Good quality evidence shows olanzapine is superior to quetiapine for reduction in relapse rate. Evidence for olanzapine vs. risperdone was mixed for relapse rate. No evidence was found for the other included drugs
5. There was no evidence to differentiate between drugs in this class for quality of life. Olanzapine, quetiapine, risperdone, ziprasidone and clozapine were the only drugs compared.
6. In a single 12 month study (n=108) no difference was seen between clozapine and risperdone for social functioning. There is insufficient evidence to draw conclusions about differences between quetiapine, risperidone, clozapine, and extended release palinperidone for social functioning.
7. There is insufficient evidence to draw conclusions regarding the impact of this class of drugs on:
    - Employment, Global assessment of functioning, Violent behavior, Rates of discontinuation or time to discontinuation, Inpatient outcome, Aggressive behavior, Length of stay, Time to onset of efficacy, Nursing burden in inpatient setting, Comparative differences in extrapyramidal symptoms, Metabolic syndrome, Subgroups of race, age, and gender
8. There was consistent evidence that showed no difference for medications in this class for response rates. Asenapine and iloperidone had no published studies.
9. One good quality study of first episode schizophrenia (n=400) found no statistically significant differences in overall discontinuation rates (primary outcome) or symptom response for olanzipine, immediate release quetiapine, and risperidone.
10. Weight gain was 6 to 13 pounds greater with olanzapine than the other atypical antipsychotics over periods of 1.5 to 18 months of treatment.
11. There was no evidence of clinically meaningful differences in rates of sexual dysfunction for the included drugs.
12. Evidence indicates that clozapine is more sedating than risperidone and olanzapine.

Bipolar Disorder

1. There is insufficient evidence to determine a clinically meaningful difference between drugs in this class for bipolar disorder.
2. The strength of evidence for efficacy and comparative difference between drugs in this category is low.

Major Depressive Disorder

1. No atypical antipsychotic had evidence of providing a significant long-term benefit when used as an adjunctive treatment for augmentation of antidepressant therapy in adults with treatment resistant depression.

Dementia

1. There was no consistent evidence that any atypical antipsychotic was superior to haloperidol for treating behavioral and psychological symptoms of dementia.
2. There were no significant differences between drugs or between drug and placebo on a variety of evaluation scales.
3. The incidence of Parkinsonism is higher with olanzapine and risperidone compared to immediate release quetiapine and placebo in patients with dementia.

Children with Pervasive Developmental Disorder or Disruptive Behavior Disorder

1. There is insufficient evidence to draw conclusions regarding the impact of medications in this class on patients with pervasive developmental disorder or disruptive behavior disorder.
2. The conclusions that could be drawn from these reviews were limited by the small numbers of available trials and lack of long-term follow-up data.

Serious Harms

1. While clozapine has been shown to be associated with an increased risk of seizures (2.9% and 4.2% in two separate studies) and agranulocytosis (13 studies reported incidence of 0-2.4%), differences among the drugs in other serious harms have not been clearly shown.

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Appendix 2:[17]

FDA Approved Indications for Atypical Antipsychotics

Indication	*Abilify*	*Risperdal*	*Seroquel*	*Seroquel XR*	*Zyprexa*	*Geodon*	*Invega*	*Fanapt*	*Saphris*
Acute Treatment of Schizophrenia in Adults	X	X	X	X	X	X	X	X	X
Maintenance Treatment for Schizophrenia in Adults	X	X		X	X	X	X		
Acute Treatment of Schizophrenia in Adolescents (13-17 yrs)	X	X	X		X≠				
Acute Treatment of Bipolar Mania in Adults	X	X	X	X	X	X			X
Acute Treatment of Bipolar Mania in Adults—Adjunct to Lithium/Valproate	X	X	X	X	X				
Acute Treatment of Bipolar Mania in Pediatric Patients (10-17 yrs)	X	X			X≠				
Acute Treatment of Bipolar Mania in Pediatric Patients (10-17 yrs)—Adjunct to Lithium/Valproate	X								
Maintenance Treatment of Bipolar Mania in Adults	X				X				
Maintenance Treatment of Bipolar Mania in Adults—Adjunct to Lithium/Valproate			X	X		X			
Acute Treatment of Agitation Associated with Schizophrenia in Adults*	X				X	X			
Treatment of Depressive Episodes Associated with Bipolar Disorder in Adults			X	X					
Irritability Associated with Autistic Disorder in Children and Adolescents (5-16 yrs)	X	X							
Acute Treatment of Depressive Episodes Associated with Bipolar Disorder in Combination with Fluoxetine					X				
Acute Treatment of Treatment Resistant Depression in Adults in Combination with Fluoxetine					X				
Adjunctive Therapy to Antidepressants for Acute Treatment of Major Depressive Disorder in Adults	X			X					
Acute Treatment of Schizoaffective Disorder as Monotherapy							X		
Acute Treatment of Schizoaffective Disorder—Adjunct to Mood Stabilizers and/or Antidepressants							X		

≠Zyprexa label suggests trial of other drugs first in adolescents
*Injectable formulations for IM use only

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Appendix 3: Summary of Strength of Evidence of Efficacy By Drug and Condition[3]

	Aripiprazole	Olanzapine	Quetiapine	Risperidone	Ziprasidone
Generalized Anxiety Disorder	0	-	++	-	-
Social Phobia	0	+	-	0	0
ADHD (no co-occurring disorders)	0	0	0	+	0
ADHD (bipolar children)	-	0	0	0	0
ADHD (mentally retarded children)	0	0	0	+	0
Dementia (overall)	++	+	+	++	0
Dementia (psychosis)	+	+/-	+/-	++	0
Dementia (agitation)	+	++	+/-	++	0
Depression (SSRI/SNRI augmentation)	++	+	++	++	+
Depression (monotherapy)	0	-	++	0	0
Eating Disorders	0	--	-	0	0
Insomnia	0	0	-	0	0
Obsessive Compulsive Disorder (SSRI augmentation)	0	+	--	++	-
Obsessive Compulsive Disorder (citalopram augmentation)	0	0	+	+	0
Personality Disorder (borderline)	+	+/-	+	0	-
Personality Disorder (schizotypal)	0	0	0	+/-	0
PTSD	0	+/-	+	++	0
Substance Abuse (alcohol)	--	-	-	0	0
Substance Abuse (cocaine)	0	-	0	-	0
Substance Abuse (methamphetamine)	-	0	0	0	0
Substance Abuse (methadone clients)	0	0	0	-	0
Tourette's Syndrome	0	0	0	+	-

Key: (++=mod or high evidence of efficacy) (+=low or very low evidence of efficacy) (+/-=mixed results) (-=low or very low evidence of inefficacy) (--=moderate or high evidence of inefficacy) (0=no trials)

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