

Comparison of Atypical Antipsychotics

Second generation or “atypical” antipsychotics have a lower propensity than the first generation agents to cause extrapyramidal side effects and tardive dyskinesia, but are by no means devoid of these adverse effects.⁴ Clozapine may be the most effective atypical for schizophrenia, but its use is limited due to the risk of agranulocytosis.^{1,2,13} All carry “black box” warnings regarding mortality risk in dementia-related psychosis, and suicidality if indicated for depression. Atypicals pose varying risks of QT prolongation, drug interactions, and metabolic adverse effects. **Extrapyramidal side effects** are low with quetiapine and olanzapine, and high with lurasidone, paliperidone, and risperidone.^{3-5,9,13} **Hyperprolactinemia**, associated with sexual dysfunction, gynecomastia, and irregular periods, seems most common with risperidone and paliperidone.^{4,6,13} These factors, plus cost and dosing frequency, are all considerations in choice of agent. The chart below compares atypicals in regard to adult indications and dosing, metabolic side effects, sedation, QT prolongation, CYP metabolism, and cost. Prescribers can bill for IM antipsychotic injections under their supervision using CPT code 96372, and add the medication code.

NOTE: *Usual or target daily adult dosage range may not include initial and maximum doses. Use lowest effective dose. Dosing in special populations (e.g., renal impairment) is not included. Maximum doses of oral aripiprazole, lurasidone, olanzapine, paliperidone, quetiapine XR, and risperidone are approved for once-daily administration. Divide asenapine, iloperidone, and ziprasidone twice daily.

Generic (Brand)/ Cost ^b	FDA-Approved Indication(s) for Adults and Usual or Target Adult Daily Dosage Range (mg/day) ^{*a}	Metabolic Adverse Effects ^{a,1,2,4,7,10-13}			QT Prolonging ^c	CYP450 Metabolism ^a	Sedation ^{a,8,13}
		Weight Gain	Diabetes Risk	Dyslipidemia			
Aripiprazole (Abilify, generics) 10 mg \$758.17 Oral solution & orally disintegrating tablet available.	<u>Schizophrenia</u> : 10-15 mg <u>Bipolar I disorder (manic or mixed episodes and maintenance)</u> : 15 mg (monotherapy or with lithium or valproate) <u>Major depression (adjunct)</u> : 5-10 mg	Low	Low	Low	Yes See footnotes e and h.	CYP2D6, CYP3A4 Specific dosing may be advised for CYP450 interactions.	Low

More . . .

Generic (Brand)/ Cost ^b	FDA-Approved Indication(s) for Adults and Usual or Target Adult Daily Dosage Range (mg/day) ^{a,*}	Metabolic Adverse Effects ^{a,1,2,4,7,10-13}			QT Prolonging ^c	CYP450 Metabolism ^a	Sedation ^{a,8,13}
		Weight gain	Diabetes Risk	Dyslipidemia			
Aripiprazole (Abilify injection) 9.75 mg \$27.84/dose	<u>Agitation associated with schizophrenia or bipolar I mania</u> : 9.75 mg IM (5.25 mg may be given). May repeat in 2 hours. Max daily dose 30 mg.	Low	Low	Low	Yes See footnotes e and h.	CYP2D6, CYP3A4	Low
Aripiprazole (Abilify Maintena long-acting injection) 400 mg \$1584.46	<u>Schizophrenia</u> : 400 mg IM (gluteal) once monthly. Reduce dose if CYP2D6 poor metabolizer. Avoid with CYP3A4 inducers for more than 14 days. Continue oral agent for 14 days after first dose, then stop. If >6 weeks elapse since last dose (>5 weeks if 2 nd or 3 rd dose is missed), restart oral aripiprazole x 14 days with the next dose.	Low	Low	Low	Yes See footnotes e and h.	CYP2D6, CYP3A4 Specific dosing may be advised for CYP450 interactions.	Low
Asenapine (Saphris) 10 mg \$689.66	<u>Schizophrenia</u> : 10 mg (acute), 10-20 mg (maintenance) <u>Bipolar I disorder (manic or mixed episodes)</u> : 10-20 mg • For sublingual use. Avoid food/drink for 10 min afterward.	Low to moderate	Low	Low	Yes See footnote d.	CYP1A2, CYP3A4 (minor), CYP2D6 (minor) (Weak CYP2D6 inhibitor.) Specific dosing may be advised for CYP450 interactions.	Low to Moderate
Clozapine ^f (Clozaril, etc, generics) 400 mg \$156.77 Oral suspension and generic orally disintegrating tablet available.	<u>Schizophrenia (treatment-resistant)</u> : 300-450 mg <u>Recurrent suicidal behavior risk reduction in schizophrenia & schizoaffective disorder</u> : 300-450 mg NOTE: initial dose is 12.5 mg once or twice daily (for both indications).	High	High	High	Yes See footnote h.	CYP1A2, CYP3A4, CYP2D6 Specific dosing may be advised for CYP450 interactions.	High

Generic (Brand)/ Cost ^b	FDA-Approved Indication(s) for Adults and Usual or Target Adult Daily Dosage Range (mg/day) ^{a,*}	Metabolic Adverse Effects ^{a,1,2,4,7,10-13}			QT Prolonging ^c	CYP450 Metabolism ^a	Sedation ^{a,8,13}
		Weight gain	Diabetes Risk	Dyslipidemia			
Iloperidone (Fanapt) 12 mg \$942.34	<u>Schizophrenia</u> : 12-24 mg	Moderate	Low	Low	Yes See footnote g.	CYP3A4, CYP2D6 Specific dosing may be advised for CYP450 interactions.	Low
Lurasidone (Latuda) 40 mg \$769.50	<u>Schizophrenia</u> : 40-160 mg <u>Bipolar depression</u> : 20 to 120 mg • Take with food (at least 350 kcal).	Low	Low	Low	No ¹² See footnote e.	Contraindicated with strong CYP3A4 inhibitors or inducers. Specific dose decrease may be advised with moderate inhibitors.	Low to Moderate
Olanzapine (Zyprexa, generics) 10 mg \$15.68 Generic orally disintegrating tablet available.	<u>Schizophrenia</u> : 10 mg <u>Bipolar I disorder (manic or mixed episodes and maintenance)</u> : 5-20 mg (monotherapy or with lithium or valproate) <u>Bipolar depression, with fluoxetine</u> : 5-12.5 mg <u>Depression (treatment-resistant), with fluoxetine</u> : 5-20 mg	High	High	High	Yes See footnotes e and h.	CYP1A2, CYP2D6	Moderate
Olanzapine (Zyprexa Intra-Muscular) 10 mg \$39.06/dose	<u>Agitation associated with psychosis or bipolar I mania</u> : 10 mg (lower dose [5 mg, 7.5 mg] may be given). May repeat dose in two hours. A third dose may be given no sooner than four hours after the second dose.	High	High	High	Yes See footnotes e and h.	CYP1A2, CYP2D6	Moderate

Generic (Brand)/ Cost ^b	FDA-Approved Indication(s) for Adults and Usual or Target Adult Daily Dosage Range (mg/day) ^{a,*}	Metabolic Adverse Effects ^{a,1,2,4,7,10-13}			QT Prolonging ^c	CYP450 Metabolism ^a	Sedation ^{a,8,13}
		Weight gain	Diabetes Risk	Dyslipidemia			
Olanzapine (Zyprexa Relprevv) 300 mg \$1684	<u>Schizophrenia</u> : After loading regimen, dosed every 2 or 4 weeks IM (gluteal). Establish tolerability and target dose with oral olanzapine first. In clinical trial, oral agent was stopped 2-7 days before first dose. <u>Available only through a restricted distribution program requiring prescriber, facility, patient, and pharmacy enrollment.</u>	High	High	High	Yes See footnotes e and h.	CYP1A2, CYP2D6	Moderate Rare risk of post-injection delirium/sedation syndrome. Monitor for at least 3 hours post-dose.
Paliperidone (Invega) 6 mg \$849.89	<u>Schizophrenia</u> : 3-12 mg <u>Schizoaffective disorder</u> : 3-12 mg (monotherapy or adjunct to mood stabilizers or antidepressants)	Low to moderate	Low	Low	Yes See footnote d.	CYP2D6 (minor), CYP3A4 (minor)	Low
Paliperidone (Invega Sustenna) 117 mg \$967.03	<u>Schizophrenia or schizoaffective disorder</u> : IM monthly after 2 doses one week apart. Establish tolerability with oral paliperidone or risperidone before use. Stop oral agent with first dose. When switching from a long-acting injectable, start in place of the next scheduled dose. Missed <u>maintenance</u> dose: resume regular monthly dosing if up to 2 weeks late. Details on handling other missed dosing scenarios are provided in the product labeling.	Low to moderate	Low	Low	Yes See footnote d.	CYP2D6 (minor), CYP3A4 (minor)	Low

Generic (Brand)/ Cost ^b	FDA-Approved Indications for Adults and Usual or Target Adult Daily Dosage Range (mg/day) ^{a,*}	Metabolic Adverse Effects ^{a,1,2,4,7,10-13}			QT Prolonging ^c	CYP450 Metabolism ^a	Sedation ^{a,8,13}
		Weight gain	Diabetes Risk	Dyslipidemia			
Paliperidone (Invega Trinza) 410 mg \$1004.74	<u>Schizophrenia, after adequate treatment with Invega Sustenna for at least 4 months</u> : IM every 3 months. Dose depends on previous <i>Invega Sustenna</i> dose. Can give up to 2 weeks early or up to one month late. Details on handling missed doses are provided in the product labeling.	Low to moderate	Low	Low	Yes See footnote d.	CYP2D6 (minor), CYP3A4 (minor) Avoid CYP3A4 and/or P-glycoprotein inducers, if possible.	Low
Quetiapine (Seroquel, generics) 400 mg \$23.18	<u>Schizophrenia</u> : 150-750 mg <u>Bipolar depression</u> : 300 mg <u>Bipolar mania or bipolar I maintenance (monotherapy [acute] or as an adjunct to lithium or valproate [acute, maintenance])</u> : 400-800 mg	Moderate	Moderate	Moderate	Yes See footnote d.	CYP3A4 Specific dosing may be advised for CYP450 interactions.	Moderate
Quetiapine (Seroquel XR) 400 mg \$694.69	<u>Schizophrenia</u> : 400-800 mg <u>Bipolar depression (acute)</u> : 300 mg <u>Bipolar I manic or mixed episode (monotherapy [acute] or as an adjunct to lithium or valproate [acute, maintenance])</u> : 400-800 mg <u>Major depressive disorder (adjunct to antidepressants)</u> : 150-300 mg • Take without food or with a light meal (about 300 kcal).	Moderate	Moderate	Moderate	Yes See footnote d.	CYP3A4 Specific dosing may be advised for CYP450 interactions.	Moderate

Generic (Brand)/ Cost ^b	FDA-Approved Indications for Adults and Usual or Target Adult Daily Dosage Range (mg/day) ^{a,*}	Metabolic Adverse Effects ^{a,1,2,4,7,10-13}			QT Prolonging ^c	CYP450 Metabolism ^a	Sedation ^{a,8,13}
		Weight gain	Diabetes Risk	Dyslipidemia			
Risperidone (Risperdal, generics) 4 mg \$5.09 Oral solution and orally disintegrating tablet available.	<u>Schizophrenia</u> : 4-8 mg <u>Bipolar I disorder (manic or mixed episodes)</u> : 1-6 mg	Moderate	Moderate	Low	Yes See footnotes e and h.	CYP2D6, CYP3A4 (minor) ¹⁴ Specific dosing may be advised for CYP450 interactions.	Low
Risperidone (Risperdal Consta) 25 mg \$682.76	<u>Schizophrenia</u> : 25 mg IM every 2 weeks <u>Bipolar I maintenance (monotherapy or as an adjunct to lithium or valproate)</u> : 25 mg IM every 2 weeks <ul style="list-style-type: none"> Continue oral agent for 3 weeks after first dose, then discontinue. <u>Missed dose, and <4 consecutive doses received</u> : Give injection, plus oral agent for 3 weeks. ¹⁵ <u>Missed dose, and 4 or more consecutive doses received</u> : If only 3-6 weeks have passed since last injection, give injection alone. If >6 weeks have passed since last injection, give injection, plus oral agent for 3 weeks. ¹⁵	Moderate	Moderate	Low	Yes See footnotes e and h.	CYP2D6, CYP3A4 (minor) ¹⁴ Specific dosing may be advised for CYP450 interactions.	Low

Generic (Brand)/ Cost ^b	FDA-Approved Indications for Adults and Usual or Target Adult Daily Dosage Range (mg/day) ^{a,*}	Metabolic Adverse Effects ^{a,1,2,4,7,10-13}			QT Prolonging ^c	CYP450 Metabolism ^a	Sedation ^{a,8,13}
		Weight gain	Diabetes Risk	Dyslipidemia			
Ziprasidone (Geodon, generics) 80 mg \$38.20	<u>Schizophrenia</u> : 40-160 mg <u>Bipolar manic or mixed episodes: maintenance [adjunct to lithium or valproate]</u> : 80-160 mg • Take with food.	Low	Low	Low	Yes See footnote g.	CYP3A4, CYP1A2 (minor)	Moderate
Ziprasidone (Geodon injection) 20 mg \$26.19/dose	<u>Agitation associated with schizophrenia</u> : 10 mg IM q 2 hrs or 20 mg q 4 hrs. Max 40 mg/day.	Low	Low	Low	Yes See footnote g.	CYP3A4, CYP1A2 (minor)	Moderate

- Per U.S. product information: *Abilify* (December 2014), *Abilify Maintena* (December 2014), *Saphris* (March 2015), *Clozaril* (December 2014), *Fanapt* (April 2014), *Latuda* (July 2013), *Zyprexa* and *Zyprexa IntraMuscular* (December 2014), *Zyprexa Relprevv* (December 2014), *Invega* (April 2014), *Invega Sustenna* (February 2015), *Invega Trinza* (May 2015), *Seroquel* (October 2013), *Seroquel XR* (October 2013), *Risperdal* (April 2014), *Risperdal Consta* (June 2014), *Geodon* (December 2014).
- Wholesale average cost of 30-day supply of dose (daily if oral) specified of generic, if available.
- Per FDA-approved product labeling and www.crediblemeds.org. A “yes” in the QT column means, at minimum, QT prolongation has been reported in patients taking the medication, regardless of causality. Some of these medications have contraindications or recommendations to avoid use related to QT prolongation (see pertinent footnotes).
- Avoid use in patients with long QT syndrome, or history of cardiac arrhythmias, or with medications that prolong the QT interval. Avoid in patients with risk factors for QT prolongation (e.g., bradycardia, hypomagnesemia, hypokalemia, etc).
- Aripiprazole, olanzapine, and lurasidone may pose relatively lower torsades risk vs other antipsychotics based on product labeling and literature review. Risperidone may pose more moderate risk vs higher-risk atypical antipsychotics. In a QT study, lurasidone was associated with QT prolongation vs baseline at 120 mg and 600 mg daily.

- f. Clozapine is associated with agranulocytosis, seizures, and myocarditis. Hematological monitoring required. Clozapine is only available through manufacturer-specific registration and distribution systems. Prescribers may obtain details by calling the number in the manufacturer's product information.
- g. Consider relatively strong capacity to prolong QT interval when selecting an atypical agent. Avoid in patients with significant cardiovascular disease (e.g., QT prolongation, cardiac arrhythmia, uncompensated heart failure, recent heart attack), or with drugs that prolong the QT interval. Use iloperidone with caution with drugs that inhibit its metabolism (e.g., CYP2D6 and CYP3A4 inhibitors), and in patients with reduced CYP2D6 activity. Check baseline and periodic potassium and magnesium levels in patients at risk for electrolyte disturbance.
- h. Product labeling does not advise to avoid in long QT syndrome, but www.crediblemeds.org does (accessed June 9, 2015).

Users of this PL Detail-Document are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and internet links in this article were current as of the date of publication.

Project Leader in preparation of this PL Detail-Document: *Melanie Cupp, Pharm.D., BCPS*

References

1. American Diabetes Association; American Psychiatric Association; American Association of Clinical Endocrinologists; North American Association for the Study of Obesity. Consensus Development Conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care* 2004;27:596-601.
2. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* 2005;353:1209-23.
3. Rummel-Kluge C, Komossa K, Schwarz S, et al. Second-generation antipsychotic drugs and extrapyramidal side effects: a systematic review and meta-analysis of head-to-head comparisons. *Schizophr Bull* 2012;38:167-77.
4. McDonagh MS, Peterson K, Carson S, et al. Drug class review: atypical antipsychotic drugs: final report update 3 [Internet]. Portland, OR: Oregon Health & Science University, June 2010. <http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0009352/pdf/TOC.pdf>. (Accessed May 31, 2015).
5. Chwieduk CM, Keating GM. Paliperidone extended release: a review of its use in the management of schizophrenia. *Drugs* 2010;70:1295-317.
6. Correll CU. Antipsychotic use in children and adolescents: minimizing adverse effects to maximize outcomes. *J Am Acad Child Adolesc Psychiatry* 2008;47:9-20.
7. Fowler JA, Bettinger TL, Argo TR. Paliperidone extended-release tablets for the acute and maintenance treatment of schizophrenia. *Clin Ther* 2008;30:231-48.
8. Miller DD. Atypical antipsychotics: sleep, sedation, and efficacy. *Prim Care Companion J Clin Psychiatry* 2004;6(Suppl 2):3-7.
9. Caccia S, Pasina L, Nobili A. New atypical antipsychotics for schizophrenia: iloperidone. *Drug Des Devel Ther* 2010;4:33-48.
10. Bishara D, Taylor D. Upcoming agents for the treatment of schizophrenia: mechanism of action, efficacy and tolerability. *Drugs* 2008;68:2269-92.
11. Potkin SG, Cohen M, Panagides J. Efficacy and tolerability of asenapine in acute schizophrenia: a placebo- and risperidone-controlled trial. *J Clin Psychiatry* 2007;68:1492-500.
12. Citrome L. Lurasidone for schizophrenia: a brief review of a new second-generation antipsychotic. *Clin Schizophr Relat Psychoses* 2011;4:251-7.
13. Leucht S, Cipriani A, Spineli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet* 2013;382:951-62.
14. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc; 2015. <http://www.clinicalpharmacology.com>. (Accessed June 10, 2015).
15. Janssen Medical Information. *Risperdal Costa* (risperidone). Dosing-dosage and administration. http://www.janssenmedicalinformation.com/assets/pdf/products/files/Risperdal%20Consta/clinical_replies/RC-PSY-DA%20General.pdf. (Accessed June 12, 2015).

Cite this document as follows: *PL Detail-Document, Comparison of Atypical Antipsychotics. Pharmacist's Letter/Prescriber's Letter. July 2015.*



Evidence and Recommendations You Can Trust...



3120 West March Lane, Stockton, CA 95219 ~ TEL (209) 472-2240 ~ FAX (209) 472-2249

Copyright © 2015 by Therapeutic Research Center

Subscribers to the *Letter* can get *PL Detail-Documents*, like this one, on any topic covered in any issue by going to www.PharmacistsLetter.com, www.PrescribersLetter.com, or www.PharmacyTechniciansLetter.com

Off-Label Use of Atypical Antipsychotics in Adults

Sixty percent of atypical prescriptions are for an off-label use. But don't assume that just any atypical will work for a given indication; evidence does not support a class effect.⁷ Weight gain and metabolic effects are of concern with atypicals, especially olanzapine,¹⁷ and very few of these off-label uses are backed by large, high-quality, randomized controlled trials. Consider other drug options with more data and fewer side effects first (e.g., antidepressants). If an atypical is used, suggested monitoring includes weight, glucose, and lipids. Monitoring for metabolic side effects is outlined in the product labeling, and in expert recommendations. Also see our *PL Chart, Lab Monitoring for Common Medications*. Although these agents pose a lower risk of extrapyramidal side effects (e.g. agitation) and tardive dyskinesia than first-generation agents, they are not devoid of these side effects.¹⁷ **The following chart lists common off-label uses for atypicals with at least level B evidence**, and therapeutic considerations. See our *PL Chart, Comparison of Atypical Antipsychotics* (U.S. subscribers; Canadian subscribers), for approved adult indications, side effects, and CYP interactions.

- a. Inclusion means medication has at least level B evidence. But inclusion does not mean agent is effective for studied indication. See Therapeutic Considerations column for details.

Use	Off-Label Medication ^a	Therapeutic Considerations
Depression, treatment-resistant, adjunct	Risperidone (<i>Risperdal</i> , generics)	<ul style="list-style-type: none"> • When a patient doesn't respond to an antidepressant, see our <i>PL Charts, Choosing and Switching Antidepressants</i> and <i>Combining and Augmenting Antidepressants</i>. • One more patient in nine will respond when an atypical is added to antidepressant therapy compared to placebo.¹⁹ • <i>Abilify</i> (aripiprazole), <i>Seroquel XR</i> (quetiapine), and <i>Zyprexa</i> (olanzapine, with fluoxetine [<i>Symbyax</i>]) are FDA-approved for adjunctive treatment of treatment-resistant major depressive disorder.¹⁻³ In Canada, <i>Abilify</i> is approved as an adjunct,¹⁸ and <i>Seroquel XR</i> is approved as monotherapy for treatment-resistant depression.⁴ • Risperidone's efficacy may be similar to aripiprazole or quetiapine,^{5,19} but study results are inconsistent.²² • Ziprasidone has not proven effective.^{20,21}
	Ziprasidone (<i>Geodon</i> , generics; <i>Zeldox</i> [Canada])	
Dementia behaviors	Aripiprazole (<i>Abilify</i> , generics [U.S.]	<ul style="list-style-type: none"> • Small benefits on agitation in dementia. Risperidone and olanzapine have the best evidence of efficacy.⁵ • Use about one-quarter to one-half the usual adult starting dose.⁶ • Risperidone has the best evidence for psychosis.⁵
	Olanzapine (<i>Zyprexa</i> , generics)	
Continued...	Risperidone (<i>Risperdal</i> ,	

More...

Use	Off-Label Medication ^a	Therapeutic Considerations
Dementia, continued	generics)	<ul style="list-style-type: none">• Reserve for agitation or distress with psychosis (delusions, hallucinations, paranoia), or for treatment-refractory agitation or aggression, in patients who are a danger to themselves or others.^{6,7,33}• Increased risk of metabolic syndrome. Increased risk of stroke and mortality in elderly dementia patients.^{6,23} There is one additional death for about every 50 to 100 dementia patients treated for 8-12 weeks.^{5,6,32} Discuss risks/benefits with patient/family.⁶• Try to taper and discontinue the drug every three to six months.⁶• Use caution in patients with cerebrovascular disease or hypovolemia.⁶• Patients with Parkinson's dementia and Lewy body dementia are extra-sensitive to antipsychotic extrapyramidal effects. Low-dose quetiapine is the antipsychotic of choice.⁸
	Quetiapine (<i>Seroquel</i>)	
Insomnia	Quetiapine (<i>Seroquel</i> , generics)	<ul style="list-style-type: none">• Quetiapine appears <u>ineffective</u> for primary insomnia.^{5,9,24}• Quetiapine has been abused/misused for its sedating and anxiolytic effects.¹⁰• Quetiapine and olanzapine have been used for treatment of insomnia secondary to specific causes (e.g., depression, drug withdrawal, Parkinson's disease, fibromyalgia). Data are extremely limited.^{5,24}• Avoid for primary insomnia.³³ See our <i>PL Charts, Comparison of Insomnia Treatments</i> (U.S. subscribers; Canadian subscribers), for insomnia treatment options.
Post-traumatic stress disorder, adjunct	Aripiprazole (<i>Abilify</i> , generics [U.S.]	<ul style="list-style-type: none">• Role is for augmentation of antidepressants to reduce hyperarousal and re-experiencing.¹¹• Risperidone and olanzapine have the best evidence.^{5,25,27}• Not all studies have been favorable.^{15,16,27}
	Risperidone (<i>Risperdal</i> , generics)	
	Olanzapine (<i>Zyprexa</i> , generics)	
	Quetiapine (<i>Seroquel</i> , generics)	
Obsessive-compulsive disorder, adjunct	Aripiprazole (<i>Abilify</i> , generics [U.S.]	<ul style="list-style-type: none">• Role is as adjunct to SSRI in treatment-resistant OCD.⁵• Risperidone and aripiprazole have the best evidence of efficacy.^{5,12,26}• Olanzapine, paliperidone, and quetiapine are not consistently better than placebo.^{12-14,26,27}
	Risperidone (<i>Risperdal</i> , generics)	
	Olanzapine (<i>Zyprexa</i> , generics)	
	Paliperidone (<i>Invega</i>)	
	Quetiapine (<i>Seroquel</i> , generics)	

Use	Off-Label Medication ^a	Therapeutic Considerations
Generalized anxiety disorder	Quetiapine (<i>Seroquel</i> , generics)	<ul style="list-style-type: none"> • SSRIs and SNRIs are first-line.²⁷ Second-line agents include buspirone or pregabalin.^{27,34} • Quetiapine has best evidence of efficacy.^{5,12,27,28} • Ziprasidone is not better than placebo.^{12,27}
	Risperidone (<i>Risperdal</i> , generics)	
	Olanzapine (<i>Zyprexa</i> , generics)	
	Aripiprazole (<i>Abilify</i> , generics [U.S.]	
	Ziprasidone (<i>Geodon</i> , <i>Zeldox</i> [Canada])	
Autism	Risperidone (<i>Risperdal</i> , generics)	<ul style="list-style-type: none"> • Aripiprazole and risperidone are FDA-approved for irritability associated with autism in pediatrics (up to age 17 years).^{2,29} • Adults have been included in some risperidone studies.³⁰ • Olanzapine and quetiapine have been studied in an open-label fashion in adults.³¹
	Olanzapine (<i>Zyprexa</i> , generics)	
	Quetiapine (<i>Seroquel</i> , generics)	
Delirium in hospitalized patients (treatment)	Olanzapine (<i>Zyprexa</i> , generics)	<ul style="list-style-type: none"> • Reserve for patients who are severely agitated or distressed.³⁶ • Olanzapine may be less effective in patients over 75 years of age.³⁵ • See our <i>PL Chart, Preventing and Treating Delirium in Inpatients</i>, for more information.
	Quetiapine (<i>Seroquel</i> , generics)	
	Risperidone (<i>Risperdal</i> , generics)	

Users of this PL Detail-Document are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and internet links in this article were current as of the date of publication.

Levels of Evidence

In accordance with the trend towards Evidence-Based Medicine, we are citing the **LEVEL OF EVIDENCE** for the statements we publish.

Level	Definition
A	High-quality randomized controlled trial (RCT) High-quality meta-analysis (quantitative systematic review)
B	Nonrandomized clinical trial Nonquantitative systematic review Lower quality RCT Clinical cohort study Case-control study Historical control Epidemiologic study
C	Consensus Expert opinion
D	Anecdotal evidence In vitro or animal study

Adapted from Siwek J, et al. How to write an evidence-based clinical review article. *Am Fam Physician* 2002;65:251-8.

Project Leader in preparation of this PL Detail-Document: Melanie Cupp, Pharm.D., BCPS

References

- Product information for *Zyprexa*. Lilly USA, LLC. Indianapolis, IN 46285. December 2014.
- Product information for *Abilify*. Bristol-Myers Squibb Company. Princeton, NJ 08543. July 2014.
- Product information for *Seroquel XR*. AstraZeneca Pharmaceuticals LP. Wilmington, DE 19850. October 2013.
- Product monograph for *Seroquel XR*. AstraZeneca Canada Inc. Mississauga, ON L4Y 1M4. April 2015.
- Maglione M, Ruelaz Maher A, Hu J, et al. Off-label use of atypical antipsychotics: an update. Comparative effectiveness review No. 43. Prepared by the Southern California Evidence-based Practice Center under contract no. HHS290-2007-10062-1. Rockville, MD: Agency for Healthcare Research and Quality. September 2011. <http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0016529/pdf/TOC.pdf>. (Accessed June 8, 2015).
- American Geriatrics Society. Guide to the management of psychotic disorders and neuropsychiatric symptoms of dementia in older adults. April 2011. [https://www.nhqualitycampaign.org/files/AGS%20Guidelines%20for%20CFMC%20\(2\).pdf](https://www.nhqualitycampaign.org/files/AGS%20Guidelines%20for%20CFMC%20(2).pdf). (Accessed June 6, 2015).
- Rabins PV, Rover BW, Rummans T, et al. Guideline watch (October 2014): practice guideline for the treatment of patients with Alzheimer's disease and other dementias 2nd edition. October 2007. http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/alzheimerwatch.pdf. (Accessed June 6, 2015).
- Weintraub D, Hurtig HI. Presentation and management of psychosis in Parkinson's disease and dementia with Lewy bodies. *Am J Psychiatry* 2007;164:1491-8.
- Wiegand MH, Landry F, Bruckner T, et al. Quetiapine in primary insomnia: a pilot study. *Psychopharmacology (Berl)* 2008;196:337-8.
- PL Detail-Document*, Drugs of Abuse. *Pharmacist's Letter/Prescriber's Letter*. December 2013.
- VA/DoD Clinical Practice Guideline. Management of post-traumatic stress. 2010. <http://www.healthquality.va.gov/PTSD-FULL-2010c.pdf>. (Accessed June 6, 2015).
- Maher AR, Maglione M, Bagley S, et al. Efficacy and comparative effectiveness of atypical antipsychotic medications for off-label uses in adults: a systematic review and meta-analysis. *JAMA* 2011;306:1359-69.
- Bystritsky A, Ackerman DL, Rosen RM, et al. Augmentation of serotonin reuptake inhibitors in refractory obsessive-compulsive disorder using adjunctive olanzapine: a placebo-controlled trial. *J Clin Psychiatry* 2004;65:565-8.
- Shapira NA, Ward HE, Mandoki M, et al. A double blind, placebo-controlled trial of olanzapine addition in fluoxetine-refractory obsessive-compulsive disorder. *Biol Psychiatry* 2004;55:553-5.
- Krystal JH, Rosenheck RA, Cramer JA, et al. Adjunctive risperidone treatment for antidepressant-resistant symptoms of chronic military service-related PTSD: a randomized trial. *JAMA* 2011;306:493-502.
- Butterfield MI, Becker ME, Connor KM, et al. Olanzapine in the treatment of post-traumatic stress disorder: a pilot study. *Int Clin Psychopharmacol* 2001;16:197-203.
- McDonagh MS, Peterson K, Carson S, et al. Drug class review: atypical antipsychotic drugs: final report update 3 [Internet]. Portland, OR: Oregon Health & Science University, June 2010. <http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0009352/pdf/TOC.pdf>. (Accessed May 31, 2015).
- Product monograph for *Abilify*. Bristol-Myers Squibb Canada. Montreal, QC H4S 0A4. May 2013.
- Spielmanns GI, Berman MI, Linardatos E, et al. Adjunctive atypical antipsychotic treatment for major depressive disorder: a meta-analysis of depression, quality of life, and safety outcomes. *PLoS Med* 2013;10:e10001403. doi: 10.1371/journal.pmed.1001403. Epub 2013 Mar 12.
- Papakostas GI, Vitolo OV, Ishak WW, et al. A 12-week, randomized, double-blind, placebo-controlled, sequential parallel comparison trial of ziprasidone as monotherapy for major depressive disorder. *J Clin Psychiatry* 2012;73:1541-7.
- Dunner DL, Amsterdam JD, Shelton RC, et al. Efficacy and tolerability of adjunctive ziprasidone in treatment-resistant depression: a randomized, open-label, pilot study. *J Clin Psychiatry* 2007;68:1071-7.
- Wright BM, Eiland EH, Lorenz R. Augmentation with atypical antipsychotics for depression: a review of

More . . .

- evidence-based support from the medical literature. *Pharmacotherapy* 2013;33:344-59.
23. Wells GA, Kelly S, Johnston A, et al. Atypical antipsychotics for the behavioural and psychological symptoms of dementia in the elderly. Systematic review and network meta-analysis. Ontario Drug Policy Research Network. May 29, 2015. http://odprn.ca/wp-content/uploads/2015/06/Antipsychotics--systematic-review-Final-Report_1.pdf. (Accessed June 5, 2015).
 24. Soeiro-De-Souza MG, Dias VV, Missio G, et al. Role of quetiapine beyond its clinical efficacy in bipolar disorder: from neuroprotection to the treatment of psychiatric disorders (Review). *Exp Ther Med* 2015;9:643-52.
 25. Liu XH, Xie XH, Wang KY, Cui H. Efficacy and acceptability of atypical antipsychotics for the treatment of post-traumatic stress disorder: a meta-analysis of randomized, double-blind, placebo-controlled clinical trials. *Psychiatry Res* 2014;219:543-9.
 26. Dold M, Aigner M, Lazenberger R, Kasper S. Antipsychotic augmentation of serotonin reuptake inhibitors in treatment-resistant obsessive-compulsive disorder: an update meta-analysis of double-blind, randomized, placebo-controlled trial. *Int J Neuropsychopharmacol* 2015 May 4. pii. pyv047. doi: 10.1093/ijnp/pyv047. [Epub ahead of print].
 27. Katzman MA, Bleau P, Blier P, et al. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. *BMC Psychiatry* 2014;14(Suppl 1):S1. Epub 2014 Jul 2.
 28. Merideth C, Cutler AJ, She F, Eriksson H. Efficacy and tolerability of extended-release quetiapine fumarate monotherapy in the acute treatment of generalized anxiety disorder: a randomized, placebo controlled and active-controlled study. *Int J Psychopharmacol* 2012;27:40-54.
 29. Product information for *Risperdal*. Janssen Pharmaceuticals, Inc. Titusville, NJ 08560. April 2014.
 30. Dove D, Warren Z, McPheeters ML, et al. Medications for adolescents and young adults with autism spectrum disorders: a systematic review. *Pediatrics* 2012;130:717-26.
 31. Stachnik JM, Nunn-Thompson C. Use of atypical antipsychotics in the treatment of autistic disorder. *Ann Pharmacother* 2007;41:626-34.
 32. Maust DT, Kim HM, Seyfried LS, et al. Antipsychotics, other psychotropics, and the risk of death in patients with dementia: number needed to harm. *JAMA Psychiatry* 2015;72:438-45.
 33. Choosing Wisely. Psychiatry. Five things physicians and patients should question. Updated April 22, 2015. <http://www.choosingwisely.org/societies/american-psychiatric-association/>. (Accessed June 10, 2015).
 34. Baldwin DS, Anderson IM, Nutt DJ, et al. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: a revision of the 2005 guidelines from the British Association for Psychopharmacology. *J Psychopharmacol* 2014;28:403-39.
 35. Yoon H, Park K, Choi W, et al. Efficacy and safety of haloperidol versus atypical antipsychotic medications in the treatment of delirium. *BMC Psychiatry* 2013;13:240.
 36. American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults. Clinical practice guideline for postoperative delirium in older adults. October 10, 2014. <https://www.archcare.org/static/files/pdf/ags-2014-clinical-practice-guideline-for-postop-delirium-in-older-adults.pdf>. (Accessed June 11, 2015).

Cite this document as follows: *PL Detail-Document, Off-Label Use of Atypical Antipsychotics in Adults. Pharmacist's Letter/Prescriber's Letter. July 2015.*



Evidence and Recommendations You Can Trust...



3120 West March Lane, Stockton, CA 95219 ~ TEL (209) 472-2240 ~ FAX (209) 472-2249
Copyright © 2015 by Therapeutic Research Center

Subscribers to the *Letter* can get *PL Detail-Documents*, like this one, on any topic covered in any issue by going to www.PharmacistsLetter.com, www.PrescribersLetter.com, or www.PharmacyTechniciansLetter.com