Therapeutic Class Overview
Atypical (Second-Generation) Antipsychotics

Therapeutic Class

Overview/Summary: Antipsychotics are divided into three distinct classes based on their affinity for D_2 and other neuroreceptors: typical (conventional) antipsychotics, atypical antipsychotics, and D_2 partial agonists.[1] Typical antipsychotics are more commonly referred to as first generation antipsychotics (FGAs) and the atypical antipsychotics including the D_2 partial agonist (also considered an atypical) are also known as second generation antipsychotics (SGAs).[1,3] As a class, atypical antipsychotics are more selective than typical antipsychotics in targeting the intended mesolimbic D_2 pathway. They also block or partially block 5-HT_{2A} and 5-HT_{1A} serotonin receptors and have a greater affinity for 5-HT_2 receptors than for D_2 receptors.[1,5] These differences in neuropharmacologic activity are associated with a lower risk of EPS and tardive dyskinesia; the risks vary with the specificity of each agent for D_2 and serotonin receptors.[1,5] Another characteristic shared by atypical antipsychotics is a more favorable outcome in the treatment of the negative symptoms of schizophrenia.[1] The SGAs are comprised of nine separate chemical entities, each with a unique neuropharmacologic and adverse event profile, mechanism of action, and chemical structure. These SGAs are aripiprazole, asenapine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone. Currently, clozapine, olanzapine, quetiapine, risperidone and ziprasidone are available generically in at least one dosage form or strength. All atypical antipsychotics bear a warning that alerts prescribers and patients to the risk of hyperglycemia and other metabolic changes.[6-19,21-22] Ziprasidone also has a warning concerning QTc interval prolongation; however, all of the SGAs can increase the QTc interval to some degree.[6-19,21-22] Aripiprazole and quetiapine carry a black box warning regarding suicidality and antidepressant drugs.[6, 15-16] Olanzapine pamoate long-acting injectable product carries a black box warning regarding the risk of a post-injection delirium/sedation syndrome.[14] The current review addresses the safety and efficacy of atypical antipsychotics in children and adults for both FDA-approved and off-label indications.

In the United States, the frequency of prescribing an antipsychotic agent increased from 8.6 per 1000 children in 1996 to 39.4 per 1000 children in 2002.[108] Moreover, according to a survey of national trends in the outpatient use of antipsychotics in children and adolescents, only 14.2% of antipsychotic prescriptions in children were for patients diagnosed with psychotic disorders.[24] Indications commonly associated with antipsychotic prescribing in pediatric patients include psychosis, schizophrenia, bipolar disorder, aggressive and disruptive behavior, and tic disorders.[108] Additional off-label indications with available limited evidence for the use of atypical antipsychotics in children and adolescents include autistic spectrum disorders, major depressive disorder, anxiety disorders, and eating disorders. At this time, risperidone and aripiprazole are FDA approved for the management of children and adolescents with autism (aged 5-16 and 6-17 years, respectively). Moreover, the following agents are indicated for the treatment of schizophrenia in adolescents: aripiprazole, olanzapine, paliperidone, quetiapine, and risperidone. Aripiprazole, olanzapine, quetiapine and risperidone are also FDA approved for the treatment of manic or mixed bipolar I disorder in children and adolescents. None of the other available atypical antipsychotic agents are currently indicated for use in pediatric patients.[6-11,13-19,21-22]

Table 1. Current Medications Available in Therapeutic Class[1-3]

Generic Name (Trade name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Aripiprazole (Abilify®, Abilify Discmelt®)	Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults; acute or maintenance treatment of manic or mixed episodes associated with bipolar I disorder in children and adolescents aged 10-17 years; adjunctive therapy to	Injection: 7.5 mg/mL Orally	-

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Generic Name (Trade name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	either lithium or valproate for the acute treatment of manic and mixed episodes associated with Bipolar I Disorder with or without psychotic features in adults and in pediatric patients aged 10 to 17 years; maintenance treatment of manic or mixed episodes associated with bipolar I disorder in adults; treatment of agitation associated with bipolar I disorder, manic or mixed in adults; acute and maintenance treatment of schizophrenia in adults; treatment of agitation associated with schizophrenia in adults; treatment of schizophrenia in adolescents aged 13-17; treatment of schizophrenia in adults; adjunctive treatment to antidepressants for major depressive disorder in adults; irritability associated with autistic disorder in children and adolescents aged 6-17 years	disintegrating tablet: 10 mg 15 mg Oral solution: 1 mg/mL Tablet: 2 mg 5 mg 10 mg 15 mg 20 mg 30 mg	
Asenapine (Saphris®)	Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults; adjunctive therapy to either lithium or valproate for the acute treatment of manic and mixed episodes associated with Bipolar I Disorder; acute and maintenance treatment of schizophrenia in adults	Sublingual tablet: 5 mg 10 mg	-
Clozapine (Fazaclo ODT®, Clozaril®*)	Reduction in the risk of recurrent suicidal behavior in schizophrenia or schizoaffective disorder in adults; Treatment-resistant schizophrenia in adults	Orally disintegrating tablet: 12.5 mg 25 mg 100 mg Tablet: 12.5 mg 25 mg 50 mg 100 mg 200 mg	✔
Iloperidone (Fanapt®)	Treatment of schizophrenia in adults	Tablet: 1 mg 2 mg 4 mg 6 mg 8 mg 10 mg 12 mg	-
Lurasidone (Latuda®)	Treatment of schizophrenia in adults	Tablet: 20 mg 40 mg 80 mg	-
Olanzapine (Zyprexa®*, Zyprexa IM®*, Zyprexa Zydis®*, Zyprexa Relprevv®)	Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults; Acute or Maintenance treatment of manic or mixed episodes associated with bipolar I disorder in children and adolescents aged 10-17 years; Adjunctive therapy to either lithium or valproate for the acute treatment of manic and mixed episodes associated with Bipolar I	Injection: 10 mg vials Orally disintegrating tablet:	✔

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Generic Name (Trade name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	Disorder; Maintenance treatment of manic or mixed episodes associated with bipolar I disorder in adults; Treatment of agitation associated with bipolar I disorder, manic or mixed in adults; Treatment of agitation associated with bipolar I mania in adults; Treatment of depressive episodes associated with bipolar disorder in adults; Acute and maintenance treatment of schizophrenia in adults; Treatment of agitation associated with schizophrenia in adults; Treatment of schizophrenia in adolescents aged 13-17; Adjunctive treatment to antidepressants for major depressive disorder in adults	5 mg 10 mg 15 mg 20 mg Tablet: 2.5 mg 5 mg 7.5 mg 10 mg 15 mg 20 mg Long-acting Injection: 210 mg vial 300 mg vial 405 mg vial	
Paliperidone (Invega®; Invega Sustenna®)	Acute and maintenance treatment of schizophrenia in adults; Treatment of schizophrenia in adolescents aged 12-17; Treatment of schizoaffective disorder as monotherapy and as an adjunct to mood stabilizers and/or antidepressants in adults	Extended-release tablet: 1.5 mg 3 mg 6 mg 9 mg Suspension for IM injection: 39 mg 78 mg 117 mg 156 mg 234 mg	-
Quetiapine (Seroquel®*, Seroquel XR®)	Maintenance treatment of bipolar I disorder as adjunct therapy to lithium or divalproex in adults; Treatment of acute manic episodes associated with bipolar I disorder as either monotherapy or adjunct therapy to lithium or divalproex in adults; Treatment of acute manic episodes associated with bipolar I disorder as either monotherapy or adjunct therapy to lithium or divalproex in children and adolescents aged 10-17 years; Treatment of manic or mixed episodes associated with bipolar I disorder as either monotherapy or adjunct therapy to lithium or divalproex in adults; Treatment of depressive episodes associated with bipolar disorder in adults; Acute and maintenance treatment of schizophrenia in adults; Treatment of schizophrenia in adolescents aged 13-17; Treatment of schizophrenia in adults; Adjunctive treatment to antidepressants for major depressive disorder in adults	Extended-release tablet: 50 mg 150 mg 200 mg 300 mg 400 mg Tablet: 25 mg 50 mg 100 mg 200 mg 300 mg 400 mg	✔
Risperidone (Risperdal®*, Risperdal M-	Maintenance treatment of manic or mixed episodes associated with bipolar I disorder in adults; Maintenance treatment of bipolar I disorder as adjunct therapy to lithium or valproate in adults; Short-term	Injection: 12.5 mg 25 mg	✔

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Generic Name (Trade name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Tab®*, Risperdal Consta®)	treatment of acute manic or mixed episodes associated with bipolar I disorder in adults and in children and adolescents aged 10-17 years; Short-term treatment of acute mixed or manic episodes associated with bipolar I disorder in combination with lithium or valproate in adults; Acute and maintenance treatment of schizophrenia in adults; Treatment of schizophrenia in adolescents aged 13-17; Irritability associated with autistic disorder in children and adolescents aged 5-16 years	37.5 mg 50 mg Orally disintegrating tablet: 0.5 mg 1 mg 2 mg 3 mg 4 mg Oral solution: 1 mg/mL Tablet: 0.25 mg 0.5 mg 1 mg 2 mg 3 mg 4 mg	
Ziprasidone (Geodon®*)	Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults; Maintenance treatment of bipolar I disorder as adjunct therapy to lithium or valproate in adults; Treatment of acute manic or mixed episodes associated with bipolar disorder; Treatment of agitation associated with schizophrenia in adults; Treatment of schizophrenia in adults	Capsule: 20 mg 40 mg 60 mg 80 mg Injection: 20 mg/mL	✔

†Generic available in at least one dosage form and/or strength.

Evidence-based Medicine

- The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) was a large, multi-center study initiated by the National Institute of Mental Health to examine the effectiveness of SGAs compared with first generation antipsychotics (FGAs) in patients with chronic schizophrenia.[56-58] Among the unexpected outcomes was the finding that, with the exception of clozapine, the SGAs did not separate out as robustly from the FGAs with respect to overall efficacy and times to treatment discontinuation.
    - Due to relatively high discontinuation rates across all treatment arms, potential biases regarding optimal dosing of individual drugs, and clear differences in treatment-emergent side effect profiles, the implications of CATIE are subject to interpretation which may preclude definitive guidance in developing pharmacotherapy guidelines for patients with schizophrenia as a whole.
- The role of the second generation antipsychotics (SGA) has been clearly established in the treatment of bipolar disorder and schizophrenia (and, in the case of aripiprazole, quetiapine XR and olanzapine/fluoxetine combination therapy, as adjunctive treatment of major depressive disorder).
- Meta-analyses evaluating the roles of available atypical antipsychotics in the treatment of schizophrenia suggest that all agents are significantly more effective than placebo.[59-71, 81-85] The trends for respective efficacy suggest that clozapine is the most effective agent in the class, followed by olanzapine and risperidone. Aripiprazole tended to exhibit lower efficacy than the other agents.[59-71, 81-85]

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- A meta-analysis in adult patients with bipolar disorder found risperidone to be the most effective treatment option (taking into account both efficacy and tolerability).[81] The next best treatment options, in order of decreased efficacy, were olanzapine, haloperidol, quetiapine, carbamazepine, aripiprazole, valproate, lithium, and ziprasidone. Lamotrigine, topiramate and gabapentin were found to be less effective than placebo.
- In the management of major depressive disorder, aripiprazole, quetiapine, and risperidone augmentation therapies were associated with improved outcomes.[90]
- The efficacy of asenapine in the treatment of schizophrenia in adults has been evaluated in four, published, randomized, double-blind, placebo-controlled, and active-controlled (haloperidol, risperidone, and olanzapine) trials, ranging in duration from 6 weeks to 1 year[30-33]. The efficacy and safety of asenapine in the treatment of manic or mixed bipolar I disorder were evaluated in five placebo-controlled, and active-controlled (olanzapine) studies in adult patients, with or without psychotic features.[72-76]
    - In a direct-comparison study, asenapine was less effective than olanzapine in terms of changes from baseline in PANSS and CGI-S scores.[33] Study discontinuation due to inadequate efficacy was noted in 14% of patients receiving olanzapine compared with 25% of patients in the asenapine group. Mean weight gain was 0.9 kg with asenapine and 4.2 kg with olanzapine.[33] In another study, clinically significant weight gain was noted in 17% of patients receiving risperidone and 9% of patients in the asenapine group.[30]
    - In a pooled analysis of patients experiencing bipolar mania, asenapine and olanzapine were comparable in terms of reduction from baseline in YMRS scores at week-52 of therapy.[76]
    - A meta-analysis of various antimanic therapy options, found that asenapine was associated with a statistically significant improvement in YMRS scores from baseline compared to placebo (mean difference, -0.30; -0.53 to -0.07), though it was less effective compared to olanzapine (0.22; 0.08 to 0.37).[81]
- Iloperidone has been studied as monotherapy for the treatment of adult patients with an acute or subacute exacerbation of schizophrenia.
    - Three 6-week, randomized, double-blind, placebo- and active comparator (risperidone and haloperidol)-controlled studies found iloperidone to be significantly more effective than placebo.[35]
    - One 4-week, placebo- and active- comparator (ziprasidone)-controlled study found a significant improvement in PANSS scores with iloperidone therapy compared to placebo.[34]
- Lurasidone has been investigated for the treatment of adult patients with acute and chronic symptoms of schizophrenia in two 6-week, placebo-controlled studies and two 21-day studies directly comparing the safety and efficacy of lurasidone 120 mg once daily with ziprasidone 80 mg twice daily.[40-43]
    - Lurasidone and ziprasidone were comparable in terms of reduction in total PANSS, PANSS positive symptom, PANSS general symptom, CGI-S scores and several cognition scales.[41-42] In addition, both drugs were comparable in terms of rates of discontinuation for any reason rate and discontinuation due to adverse events.[41,42] Both therapies were associated with a small weight loss from baseline and neither therapy was associated with a clinically significant ECG abnormality.
    - Of note, lurasidone was more effective in improving negative symptom PANSS scores compared to ziprasidone (P=0.046).[42]
- Available evidence suggests that, except for clozapine, olanzapine is associated with greater weight gain compared to all other atypical antipsychotic agents. In contrast, ziprasidone is associated with a low incidence of weight gain.[227]
- Data from the FDA Adverse Reporting System (AERS) indicates that the risk of experiencing a diabetes-related adverse event is greatest with olanzapine, followed by risperidone, and least with ziprasidone and aripiprazole, across all age groups.[256]
- Risperidone is associated with the greatest risk of prolactin elevation-related adverse events.[59-71,81-85,273]
- Risperidone, aripiprazole and ziprasidone are associated with a high incidence of extrapyramidal adverse events.[235] Quetiapine is associated with the least risk of extrapyramidal adverse events.[235]

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- The incidence of sexual dysfunction was noted to be higher with the use of olanzapine, risperidone, and clozapine than with quetiapine, ziprasidone or aripiprazole.[239]
- The Agency of Healthcare Research and Quality (AHRQ) is the lead federal agency for research on healthcare quality, costs, outcomes and patient safety. In 2011, AHRQ had issued an update to a prior 2007 review of scientific evidence on the safety and effectiveness of atypical antipsychotics for off-labeled use.[91, 202]
    - Indications associated with moderate/high strength of evidence for the use of atypical antipsychotics included general anxiety disorder (quetiapine), dementia (aripiprazole, olanzapine, risperidone), depression (aripiprazole, quetiapine, risperidone), augmentation of SSRIs for obsessive compulsive disorder [OCD] (risperidone), and post-traumatic stress disorder [PTSD] (risperidone).[102] Refer to Appendices IIa and IIb for additional details.
- The AHRQ had conducted a systematic review of literature on the safety and efficacy of antipsychotics in children and adolescents.[108,109] For details, refer to Appendices IIIa and IIIB.
    - Indications associated with moderate strength evidence for the use of atypical antipsychotics included disruptive behavior disorder, bipolar disorder, schizophrenia, and Tourette's syndrome.
    - No significant differences between the different atypical antipsychotics were noted in the identified head-to-head comparisons.
    - The risks of weight gain (weight gain: 4.6 kg) and dyslipidemia were highest with olanzapine. Weight gain with ziprasidone was not significantly different from placebo. The other atypical antipsychotics were associated with intermediate weight gain.
    - Risperidone was associated with the greatest incidence of prolactin-related adverse events (consistent with adult data).
    - Extrapyramidal adverse events were significantly more common with risperidone and aripiprazole compared with placebo.
- According to a systematic review by Safer et al, weight gain secondary to atypical antipsychotics is greater in children and adolescents than in adults.[270]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - Antipsychotics are a mainstay in therapy for schizophrenia.[297-299,308]
    - Lithium, valproate and/or antipsychotics are recommended as initial therapy of bipolar disorder.[284-287,302-303]
    - The American Psychiatric Association guideline recommends the use of antipsychotics for the management of psychosis or agitation in patients with dementia.[288]
    - For the treatment of anxiety disorders, sertraline is recommended as a first-line pharmacotherapeutic agent.[283] Second-line treatment options include SNRIs or switching to alternative SSRIs. Augmentation therapy with antipsychotics is an option in treatment-refractory patients but the guidelines recommend that initiation of combination therapy be limited to specialists.
    - In MDD, first-line treatment options include SSRIs, SNRIs, bupropion or mirtazapine.[291-293] Antipsychotic augmentation therapy is an option for patients who have failed antidepressant monotherapy.
    - In OCD, SSRIs and cognitive behavioral therapy are recommended as first-line treatment options.[294] Patients who have failed an SSRI trial may be offered augmentation therapy with an antipsychotic or cognitive behavioral therapy. Similarly, SSRIs and SNRIs are considered to be first-line treatment options for the treatment of PTSD.[295]
    - Atypical antipsychotics may be used as adjunctive therapy for the management of treatment-refractory PTSD.
    - The ESSTS guideline recommends risperidone as a first-line agent for the treatment of tics.[309] Aripiprazole has a role in treatment-refractory patients.
    - The AACAP guideline acknowledges that atypical antipsychotics are the most commonly prescribed class of drugs for the treatment of maladaptive aggression, regardless of

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diagnosis; yet emphasize that pharmacotherapy should not be used as the only intervention in children with oppositional defiant disorder.[306]

- Although the antipsychotics are not addressed in national and international insomnia treatment guidelines, the National Institute of Health (NIH) Consensus and State-of-the-Science Statement on Manifestations and Management of Chronic Insomnia in Adults state that due to the lack of evidence supporting the short and long term efficacy of antipsychotics, in addition to their significant risks, their use in the treatment of chronic insomnia cannot be recommended.[311]
- In a practice guideline on the use of atypical antipsychotics in children and adolescents, issued by the AACAP in 2011, the panel recommends that prior to initiation of antipsychotic therapy patients should undergo a thorough diagnostic assessment, evaluation for comorbid medical conditions and concomitant medications.[310] Furthermore, a multidisciplinary plan that includes education and psychotherapy should be established. The prescriber should also have a thorough discussion of the risks and benefits of psychotropic medication.
- Of the atypical antipsychotics, risperidone is recognized as an agent with the most substantial amount of methodologically stringent evidence for use in pediatric patients.[310]
- There is almost no data to support the use of atypical antipsychotics in pre-school aged children.[310] The guideline recommends a marked amount of caution before using these agents in pre-schoolers.
- Given the risk of metabolic side-effects, pediatric patients receiving atypical antipsychotic therapy should be closely monitored for changes in weight, blood pressure, fasting plasma glucose and lipid profile.[310]

Table 2. Evidence for the Use of Atypical Antipsychotics in Pediatrics (2011 AACAP guideline)[310]

	Clozapine	Risperidone	Olanzapine	Quetiapine	Ziprasidone	Aripiprazole
Schizophrenia/ Psychosis	+++	+++*	++++*	++++*	+	++++*
Bipolar Disorder	++	+++*	+++*	++++*	+++	+++*
Disruptive behavior disorders/ Aggression	++	+++	+++	++	+	+
Autism/ PDD irritability	+	++++*	+++	+	+	++++*
Tourettes/ tics		++++	+		+++	
PTSD	+					
Eating Disorder			+			
Long-term safety studies		+		+		

- PDD=pervasive developmental disorder; PTSD=post-traumatic stress disorder
- ++++ Multiple randomized controlled studies
- +++ One randomized controlled study
- ++ Uncontrolled study
- + Case studies
- * FDA approved in children and/or adolescents

- Other Key Facts:
  - Paliperidone is an active metabolite of risperidone and therefore carries some similarity in chemical structure and pharmacologic effects with the parent drug.
  - The use of clozapine is limited due to a risk of agranulocytosis.
  - Clozapine, olanzapine, quetiapine, risperidone and ziprasidone are available generically.

Appendix I: Summary of the Strength of Evidence for Off-Label Efficacy Outcomes (adopted from 2011 AHRQ systematic review)[202]

Indication	Strength of Evidence	Findings	Conclusions
Dementia	**High**	The 2011 meta-analysis of PCTs, aripiprazole, olanzapine, and risperidone were superior to placebo as treatment of behavioral symptoms as measured by total scores on BEHAVE-AD, BPRS, and	Aripiprazole, olanzapine, and risperidone **have efficacy** as treatment for behavioral symptoms of dementia.

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		NPI. Effect sizes were generally considered to be "small" in magnitude. Psychosis –risperidone was superior to placebo, as measured by thepsychosis subscales of the BEHAVE-AD, BPRS, and NPI. Results for aripiprazole did not meet conventional levels of statistical significance. Agitation – Aripiprazole, olanzapine and risperidone were superior to placebo, as measured by the agitation subscales of the BEHAVE-AD, BPRS, NPI, and CMAI. Three head to head trials compared atypicals; none was found superior.	
Depression			
Augmentation of SSRI/SNRI	**Moderate** (risperidone, aripiprazole, quetiapine) **Low** (olanzapine, ziprasidone)	The meta-analysis used "response" to treatment and remission as outcome. Pooling trials that reported the HAM-D as outcome, the relative risk of responding for participants taking quetiapine or risperidone was significantly higher than for placebo. Other trials reported MADRS scores; the relative risk of responding for participants taking aripiprazole was significantly higher than those taking placebo. Risperidone was included in two trials. These reported the drug superior to placebo. The relative risk of responding for participants taking aripiprazole was significantly higher than those taking placebo. Olanzapine had only two trials, so pooling was not performed; the trials reported olanzapine superior to placebo. In one available ziprasidone trial, the drug was superior to placebo in terms of MADRS scores. One trial compared ziprasidone at differing levels augmenting sertraline to sertraline alone. This trial found a greater improvement in CGI-S and MADRS scores augmenting with ziprasidone at 160mg than either augmentation with ziprasidone at 80mg or sertraline alone. However, there was no significant difference in HAMD-17, CGI-I or HAM-A scores.	Aripiprazole, quetiapine, and risperidone **have efficacy** as augmentation to SSRIs/SNRIs for major depressive disorder. Olanzapine and ziprasidone **may also have efficacy.**
Monotherapy	**Moderate**	Olanzapine alone was no better than placebo in improving symptoms at 6 or 12 weeks in three trials. Outcomes were too heterogeneous to allow pooling. In five PCTs, quetiapine was superior according to relative risk of both responding and remitted as measured by MADRS.	Olanzapine **does not have efficacy** as monotherapy for major depressive disorder. Quetiapine **has efficacy** as monotherapy for major depressive disorder
Obsessive Compulsive Disorder (OCD)			
Augmentation of SSRIs	**Moderate** (risperidone) **Low** (olanzapine)	The 2006 meta-analysis pooled results of 9 trials of risperidone, olanzapine, or quetiapine as augmentation therapy in patients who were resistant to treatment with SSRI. Atypical antipsychotics had a clinically important benefit, (measured by	Risperidone **has efficacy** in improving OCD symptoms when used as an adjunct to SSRI in treatment refractory patients. Olanzapine **may have efficacy.**

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		the Yale-Brown Obsessive-Compulsive Scale (YBOCS), when used as augmentation therapy. Relative risk of "responding" significant for augmentation with quetiapine and risperidone. The updated 2011 meta-analysis found risperidone superior to placebo, as measured by changes in the Y-BOCS. There were too few studies (2) of olanzapine augmentation to permit separate pooling of this drug. Both trials reported olanzapine superior to placebo. One new head to head trial found no difference in effect between olanzapine and risperidone as SSRI augmentation. One new head to head trial found quetiapine more effective than ziprasidone as SSRI augmentation. In one new trial, quetiapine produced a significant reduction in Y-BOCS score, while clomipramine did not.	Quetiapine is more **efficacious** than ziprasidone and clomipramine.
Augmentation of citalopram	**Low** (quetiapine) **Very low** (risperidone)	One trial of risperidone reported no differences between groups in achieving a response to therapy, but patients maintained on risperidone had a significantly longer period of time to relapse compared with placebo (102 days vs. 85 days). Two trials found quetiapine superior to placebo as augmentation for citalopram, according to Y-BOCS and CGI-I scores.	Quetiapine and risperidone **may be efficacious** as augmentation to citalopram in OCD patients.
Post-Traumatic Stress Disorder	**Moderate** (risperidone) **Low** (Olanzapine) **Very Low** (Quetiapine)	Three trials enrolled men with combat-related PTSD; these showed a benefit in sleep quality, depression, anxiety, and overall symptoms when risperidone or olanzapine was used to augment therapy with antidepressants or other psychotropic medication. Three trials of olanzapine or risperidone as monotherapy for abused women with PTSD were inconclusive regarding efficacy. One trial found a 3-fold decline in PTSD Scale (CAPS) scores in patients treated with quetiapine monotherapy compared with placebo. There were too few olanzapine studies (two) to pool; one reported olanzapine superior to placebo, while one did not. A meta-analysis of risperidone, using CAPS scores as outcome, found risperidone to be superior to placebo. In a meta-analysis by condition, atypical antipsychotics were efficacious for combat-related PTSD but not PTSD in abused women.	Risperidone is **efficacious** in reducing combat-related PTSD symptoms when used as an adjunct to primary medication.
Personality Disorders			
Borderline	**Low**	Four trials provide evidence that	Olanzapine had **mixed results** in

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	(aripiprazole) **Very low** (quetiapine, olanzapine)	olanzapine is superior to placebo and may be superior to fluoxetine. The benefit of adding olanzapine to dialectical therapy in one trial was small. Two trials of olanzapine found no difference from placebo in any outcomes compared with placebo. Aripiprazole was superior to placebo in one small trial. Another trial found aripiprazole superior to placebo in improving SCL-90, HAM-D, and HAM-A scores at 8 months and less self-injury at 18 months. A trial of ziprasidone found no significant difference in CGI-BPD, depressive, anxiety, psychotic or impulsive symptoms compared with placebo at 12 weeks. One trial found quetiapine to be superior to placebo on BPRS and PANSS scales. Due to heterogeneity of outcomes, a meta-analysis could not be performed.	7 trials, aripiprazole was found **efficacious** in two trials, quetiapine was found **efficacious** in one trial, and ziprasidone was found **not efficacious** in one trial.
Schizotypal	**Low**	Risperidone was superior to placebo in one small trial. In another trial risperidone was found to be no different from placebo on a cognitive assessment battery.	Risperidone had **mixed results** when used to treat schizotypal personality disorder in two small trials.
Tourette's Syndrome	**Low**	Risperidone was superior to placebo in one small trial, and it was at least as effective as pimozide or clonidine for 8 to 12 weeks of therapy in the three other trials. One trial of ziprasidone showed variable efficacy compared with placebo.	Risperidone **is at least as efficacious as pimozide or clonidine** for Tourette's syndrome
Anxiety	**Moderate**	Three placebo-controlled trials of quetiapine as monotherapy for Generalized Anxiety Disorder (GAD) could be pooled; relative risk of responding on HAM-A favored the quetiapine group. One head to head trial showed no difference between risperidone and paroxetine on HAM-A score improvement. One trial each found quetiapine equally effective as paroxetine and escitalopram.	Quetiapine **has efficacy** as treatment for Generalized Anxiety Disorder
Attention Deficit/Hyperactivity Disorder			
No comorbidity	**Low**	One trial showed risperidone superior to placebo in reducing scores on the Children's Aggression Scale –Parent version (CAS-P).	Risperidone **may be efficacious** in treating children with ADHD with no serious co-occurring disorders.
Mental retardation	**Low**	One trial showed risperidone led to greater reduction in SNAP-IV (Swanson, Nolan, and Pelham teacher & parent rating scale) scores than methylphenidate.	Risperidone **may be superior to methylphenidate** in treating ADHD symptoms in mentally retarded children.
Bipolar	**Low**	Two trials of aripiprazole showed no effect on SNAP-IV (Swanson, Nolan, and Pelham teacher & parent rating scale) scores than placebo.	Aripiprazole is **inefficacious** in reducing ADHD symptoms in children with bipolar disorder.
Eating Disorders	**Moderate** (olanzapine) **Low**	In a pooled analysis of 3 trials, there was no difference in change in BMI at either one or three months with olanzapine compared with placebo.	Olanzapine and quetiapine **have no efficacy** in increasing body mass in eating disorder patients.

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	(quetiapine)	One trial of quetiapine reported no statistical difference from placebo in BMI increase at three months.	
Insomnia	**Very Low**	In one small trial (N=13) of quetiapine, sleep outcomes were not statistically different from placebo.	Quetiapine may be **inefficacious** in treating insomnia.
Substance Abuse			
Alcohol	**Moderate** (aripiprazole) **Low** (quetiapine)	Two trials of aripiprazole and one of quetiapine reported percentage of patients completely abstinent during follow-up. In a pooled analysis, the effect versus placebo was insignificant.	Aripiprazole is **inefficacious** in treating alcohol abuse/ dependence. Quetiapine may also be **inefficacious.**
Cocaine	**Low**	Two trials of olanzapine and one of risperidone reported there was no difference in efficacy versus placebo as measured by the Addiction Severity Index (ASI).	Olanzapine is **inefficacious** in treating cocaine abuse /dependence. Risperidone may also be **inefficacious.**
Methamphetamine	**Low**	One trial found aripiprazole inefficacious in reducing use of intravenous amphetamine, as measured by urinalysis. Another trial found aripiprazole inefficacious in reducing craving for methamphetamine.	Aripiprazole is **inefficacious** in treating methamphetamine abuse/ dependence.
Methadone	**Low**	One trial of methadone-treated patients found no difference between risperidone and placebo in reduction of cocaine or heroin use.	Risperidone is an **inefficacious** adjunct to methadone maintenance

ADHD=attention-deficit hyperactivity disorder; BEHAVE-AD=Behavioral Pathology in Alzheimer's Disease Scale; BPRS=Brief Psychiatric Rating Scale; CGI-BPD=Clinical Global Impression Scale for Borderline Personality Disorder; CGI-I=Clinical Global Impression Improvement; CGI-S=Clinical Global Impression-Severity; CMAI =Cohen-Mansfield Agitation Inventory; HAM-A = Hamilton Anxiety Scale; HAM-D=Hamilton Depression Rating Scale; MADRS=Montgomery-Asberg Depression Rating Scale; MDD=major depressive disorder; NPI=Neuropsychiatric Inventory; OCD=obsessive-compulsive disorder; PANSS=Positive and Negative Syndrome Scale; PCT=placebo-controlled trial; PTSD=post-traumatic stress disorder; SSRI=selective serotonin reuptake inhibitor; SNRI=serotonin-norepinephrine reuptake inhibitors; ZAN-BPD=Zanarini Rating Scale for Borderline Personality Disorder

Appendix II: Summary of Adverse Events of Atypical Antipsychotics for Off-Label Use (adopted from 2011 AHRQ systematic review)[202]

Adverse Event	Head-to-Head Studies	Active Comparator Studies	Placebo-Controlled Studies
Weight Gain			
Elderly	In one large trial (CATIE-AD) patients who were treated with olanzapine, quetiapine, or risperidone averaged a monthly gain of 1.0, 0.7, and 0.4 lbs respectively, compared with a monthly weight loss of 0.9 lbs for placebo patients.	More common in patients taking olanzapine than risperidone or conventional antipsychotics, particularly if their BMI was less than 25 at baseline, according to a large cohort study.	According to the meta-analysis, more common in patients taking olanzapine and risperidone than placebo.
Adults	More common in olanzapine patients than ziprasidone patients in one trial.	More common among patients taking olanzapine than patients taking conventional antipsychotics in three trials. More common in patients taking aripiprazole than patients taking conventional antipsychotics in one trial. More common among patients taking olanzapine than patients taking mood stabilizers in two trials.	According to the meta-analysis, more common in patients taking aripiprazole, olanzapine, quetiapine, and risperidone than placebo.
Children/Adolescents	No head to head studies	No difference between	More common in patients taking

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		clonidine and risperidone in one trial.	risperidone in two PCTs. No difference in one small PCT of ziprasidone.
Mortality-in the elderly	No difference between olanzapine and risperidone according to a meta-analysis of six trials of olanzapine published in 2006.	Six large cohort studies compared mortality in elderly patients taking atypical and conventional antipsychotics. Four of these studies found a significantly higher rate of death with conventional antipsychotics, while two found no statistical difference in mortality between the drug classes.	The difference in risk for death was small but statistically significant for atypicals, according to a 2006 meta-analysis which remains the best available estimate. Sensitivity analyses found no difference between drugs in the class. Patients taking atypicals had higher odds of mortality than those taking no antipsychotics in the two cohort studies that made that comparison. There are no trials or large observational studies of ziprasidone in this population.
Endocrine			
Elderly	No evidence reported	No evidence reported	No difference in endocrine events in risperidone patients in one PCT. Regarding diabetes, risk was elevated but not statistically significant in one industry-sponsored cohort study of olanzapine patients.
Adults	Diabetes more common in patients taking olanzapine than patients taking risperidone in one trial.	No evidence reported	Endocrine events more common in patients taking quetiapine, risperidone, and ziprasidone in one PCT each. More common in olanzapine in two pooled PCTs. Diabetes more common in patients taking quetiapine in six pooled PCTs; however, the pooled odds ratio was elevated at 1.47 but not statistically significant. More common in olanzapine patients in one PCT; the odds ratio of 5.14 was not statistically significant, with very wide confidence intervals (0.6 to 244). Lower odds of diabetes in risperidone patients in one large observational study.
Cerebrovascular Accident (CVA)	No evidence reported	Hospitalization for CVA was increased in the first week after initiation of typical antipsychotics, but not for initiation of atypicals in a large cohort study.	More common in risperidone patients than placebo according to four PCTs pooled by the manufacturer. In a meta-analysis of PCTs, risperidone was the only drug associated with an increase. More common in olanzapine than placebo according to five PCTs pooled by the manufacturer.
Extrapyramidal Symptoms (EPS)			
Elderly	More common in patients taking aripiprazole and risperidone patients than patients taking quetiapine in one large trial (CATIE-AD).	No evidence reported	More common in patients taking risperidone, according to the meta-analysis. Quetiapine and aripiprazole were not associated with an increase. More common in olanzapine in one PCT.
Adults	No evidence reported	Less likely in patients taking quetiapine than mood stabilizers in one small trial. Less likely in patients taking olanzapine or aripiprazole than patients taking conventional antipsychotics in one trial each.	More common in patients taking aripiprazole, quetiapine, and ziprasidone than placebo according to the meta-analysis.
Sedation			
Elderly	More common in elderly patients taking olanzapine or quetiapine than risperidone	No difference in one trial of olanzapine versus benzodiazepines. No difference in three trials	More common in patients taking aripiprazole, olanzapine, quetiapine, and risperidone than placebo according to the meta-analysis.

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	according to the meta-analysis, but not statistically significant.	of olanzapine and three of risperidone versus conventional antipsychotics.	
Adults	More common in patients taking quetiapine than risperidone in two trials. No difference in one trial of risperidone versus olanzapine.	Olanzapine patients had higher odds than mood stabilizer patients in two trials. More common in olanzapine and quetiapine patients than SSRIs patients in three and two trials respectively. Olanzapine patients had lower odds than patients taking conventional antipsychotics in the pooled analysis of three trials.	More common in patients taking aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone than placebo in the meta-analysis.
Children/Adolescents	No head-to-head trials	No difference in one small trial of clonidine versus risperidone. More patients on haloperidol than risperidone reported sleep problems in one trial.	Less common in aripiprazole patients than placebo patients in one PCT. No difference from placebo in one small PCT of ziprasidone.

BMI=body mass index; CATIE-AD=Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease; CVA=cerebrovascular accident; EPS=extrapyramidal symptoms; PCT=placebo-controlled trial; SSRI=serotonin selective reuptake inhibitor

Appendix III: Summary of the Strength of Evidence for Efficacy Outcomes in Children and Adolescents (adopted from the 2012 AHRQ systematic review)[109]

Outcome	Comparison (# of studies)	Strength of Evidence	Summary
Pervasive developmental disorder			
Autistic symptoms	FGA vs. SGA (2 RCTs)	Low	No significant difference
	SGA vs. placebo (7 RCTs)	Low	Significant effect in favor of SGA on ABC (MD = 218.3; 95% CI: 227.1 to 29.5; I2 = 79.6%); CARS (MD = 24.9; 95% CI: 28.5 to 21.4; I2 = 64%).
CGI	SGA vs. placebo (3 RCTs)	Low	No significant difference
OC symptoms	SGA vs. placebo (3 RCTs)	Low	Significant effect in favor of SGA (MD = 21.7; 95%CI: 23.2 to 20.3; I2 = 49%).
Medication adherence	SGA vs. placebo (2 RCTs)	Low	No significant difference
Disruptive behavior disorder			
Aggression	SGA vs. placebo (5 RCTs)	Low	No significant difference
Anxiety	SGA vs. placebo (4 RCTs)	Low	No significant difference
Behavior symptoms	SGA vs. placebo (7 RCTs)	Moderate	Significant effect in favor of SGA for ABC (MD = 221.0; 95% CI: 231.1 to 210.8; I2 = 62%); BPI (MD = 23.8; 95%CI: 26.2 to 21.4; I2 = 0%); NCBRF (MD = 26.9; 95% CI: 210.4 to 23.5; I2 = 62%).
CGI	SGA vs. placebo (7 RCTs)	Moderate	Significant effect in favor of SGA for CGI–I (MD = 21.0; 95% CI: 21.7 to 20.3; I2 = 45%); CGI–S (MD = 21.3; 95%CI: 22.2 to 20.5; I2 = 78%).
Medication adherence	SGA vs. placebo (5 RCTs)	Low	No significant difference
Bipolar Disorder			
CGI	SGA vs. placebo (7 RCTs)	Moderate	Significant effect in favor of SGA (MD = 20.7; 95% CI: 20.8 to 20.5; I2 = 36%).
Depression	SGA vs. placebo (7 RCTs)	Low	No significant difference
Manic Symptoms	SGA vs. placebo (7 RCTs)	Low	All except one study significantly favored SGA (studies not pooled due to high heterogeneity).

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Medication adherence	SGA vs. placebo (7 RCTs)	Low	Significant effect in favor of placebo (RR = 2.0; 95% CI: 1.0 to 4.0; I2 = 0%).
Suicide-related behavior	SGA vs. placebo (7 RCTs)	Moderate	No significant difference for suicide-related deaths, attempts, or ideation.
Schizophrenia			
CGI	FGA vs. SGA (3 RCTs)	Low	Significant effect in favor of SGA (MD = 20.8; 95% CI: 21.3 to 20.3; I2 = 0%).
	Clozapine vs. olanzapine (2 RCTs)	Low	No significant difference
	Olanzapine vs. risperidone (3 RCTs)	Low	No significant difference
	SGA vs. placebo (6 RCTs)	Moderate	Significant effect in favor of SGA (MD = 20.5; 95% CI: 20.7 to 20.3; I2 = 28%).
Positive and negative symptoms	FGA vs. SGA (3 RCTs)	Low	No significant difference
	Clozapine vs. olanzapine (2 RCTs, 1 PCS)	Low	No significant difference
	Olanzapine vs. risperidone (3 RCTs, 1 PCS)	Low	No significant difference
	SGA vs. placebo (6 RCTs)	Moderate	Significant effect in favor of SGA (MD = 28.7; 95% CI: 211.8 to 25.6; I2 = 38%).
Medication adherence	FGA vs. SGA (2 RCTs, 1 PCS)	Low	No significant difference
	Clozapine vs. quetiapine (2 RCTs)	Low	No significant difference
	Olanzapine vs. risperidone (4 RCTs, 1 PCS)	Low	No significant difference
	SGA vs. placebo (2 RCTs)	Low	No significant difference
Suicide-related behaviors	SGA vs. placebo (5 RCTs)	Low	No significant difference
Tourette syndrome			
Tics	SGA vs. placebo (2 RCTs)	Moderate	Significant effect in favor of SGA (MD = 27.0; 95% CI: 210.3 to 23.6; I2 = 0%)
Behavioral symptoms			
Autistic symptoms	Risperidone vs. placebo (2RCTs)	Low	Significant effect in favor of risperidone in one study; NR in second study

ABC=Aberrant Behavior Checklist, BPI=Behavior Problem Inventory, CARS=Childhood Autism Rating Scale, CGI–I=Clinical Global Impressions–Improvement, CGI–S=Clinical Global Impressions–Severity, NCBRF=Nisonger Child Behavior Rating Scale, NR=not reported, OC=obsessive-compulsive, PCS=prospective cohort study, RR=relative risk

Appendix IIIb: Summary of Evidence for Adverse Events in Children and Adolescents (adopted from 2012 AHRQ systematic review)[109]

Outcome	Strength of Evidence	SGA vs. SGA	Placebo-Controlled Studies
Dyslipidemia	Low	Aripiprazole was significantly favored over olanzapine (RR = 0.25; 95% CI: 0.08–0.8)[a] and 95% CI: 271.3 to 27.4).[a] No significant differences were observed for clozapine versus olanzapine, olanzapine versus quetiapine and quetiapine versus risperidone.	Significant effect in favor of placebo over aripiprazole (RR = 2.5; 95% CI: 1.4, 4.4)[a], olanzapine (RR = 2.4; 95% CI: 1.2–4.9; I^2 = 45%), and quetiapine (RR = 2.4; 95% CI: 1.1–5.4; I2 = 0%).
	Moderate	Significant effect in favor of risperidone compared with olanzapine for cholesterol (MD = 10.2 mg/dL; 95% CI: 3.1–17.2; I^2 = 0%) and triglycerides (MD = 17.3 mg/dL; 95% CI: 3.5–31.1; I2 = 0%).	NA
EPS	Low	No significant difference for clozapine	No significant differences for

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		versus olanzapine, clozapine versus risperidone, olanzapine versus quetiapine, olanzapine versus risperidone, quetiapine versus risperidone.	placebo compared with olanzapine or quetiapine.
	Moderate	NA	Significant effect in favor of placebo over aripiprazole (RR = 4.2; 95% CI: 2.4–7.2; I^2 = 0%) and risperidone (RR = 2.7; 95% CI: 1.4–4.9; I^2 = 0%).
Insulin Resistance	Low	No significant difference for olanzapine versus quetiapine, olanzapine versus risperidone or quetiapine versus risperidone.	No significant difference between aripiprazole and placebo or olanzapine and placebo.
Prolactin-related sexual side effects	Low	Significant effect in favor of clozapine over olanzapine (MD = 210.8 ng/dL; 95% CI: 216.7 to 24.8; I^2 = 21%). No significant difference for quetiapine versus risperidone.	Significant effect in favor of placebo over risperidone in 7 or 8 studies (not pooled due to heterogeneity). No significant difference for quetiapine compared with placebo.
	Moderate	Significant effect in favor of olanzapine over risperidone (RR = 0.4; 95% CI: 0.2–0.6; I^2 = 0%).	Significant effect in favor of aripiprazole over placebo (MD = 24.1 ng/mL; 95% CI: 26.3 to 21.8; I2 = 0%). Significant effect in favor of placebo over olanzapine (MD = 11.5 ng/mL; 95% CI: 8.8–14.1; I2 = 0%).
Sedation	Low	No significant differences for clozapine versus olanzapine, olanzapine versus quetiapine, olanzapine vs risperidone, quetiapine vs risperidone.	Significant effect in favor of placebo over aripiprazole (RR = 2.7; 95% CI: 1.1–6.5; I2 = 76%). No significant difference in placebo comparisons with olanzapine and quetiapine.
	Moderate	NA	Significant effect in favor of placebo over risperidone (RR = 2.9; 95% CI: 1.5–5.5; I^2 = 32%) and ziprasidone (RR = 3.0; 95%CI: 1.7–5.2; I^2 = 0%).
Weight gain	Low	Significant effect in favor of aripiprazole over olanzapine (MD = 24.1 kg; 95%CI: 25.5 to 22.7),a quetiapine(MD = 21.6 kg; 95% CI: 23.0 to 20.3)[a] and risperidone (MD = 22.3 kg; 95%CI: 23.9 to 20.7).a No significant difference for clozapine versus olanzapine, clozapine versus risperidone, and quetiapine versus risperidone.	No significant difference for ziprasidone compared with placebo.
	Moderate	Significant effect in favor of quetiapine over olanzapine (RR = 1.5; 95%CI: 1.1–2.0; I^2 = 0%) and risperidone over olanzapine (MD = 2.4 kg; 95%CI: 1.5–3.3; I^2 = 72%).	Significant effect in favor of placebo over aripiprazole (MD=0.8 kg; 95%CI: 0.4–1.2; I^2 = 13%), olanzapine (MD = 4.6 kg; 95% CI: 3.1–6.1; I2 = 70%), quetiapine (MD = 1.8 kg; 95% CI: 1.1–2.5; I^2= 49%), and risperidone (MD = 1.8 kg; 95% CI: 1.5–2.1; I^2 = 0%).

AE=adverse event; EPS=extrapyramidal symptom; RR=relative risk.
a=Only 1 study contributed to this estimate; therefore, an I^2 value could not be calculated.

References

Please refer to the full therapeutic class review on atypical antipsychotics for a list of references.

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Therapeutic Class Review
Atypical (Second-Generation) Antipsychotics

Overview/Summary

Antipsychotic medications have been used for over fifty years to treat schizophrenia and a variety of other psychiatric disorders.[1] Schizophrenia is believed to be caused by an increase in the cerebral activity of dopamine D_2 in the mesolimbic and/or mesocortical regions of the brain. Antipsychotic medications exert their effect in part by blocking D_2 receptors. It is the blockade of these receptors in the mesolimbic pathway that is believed to contribute to desired antipsychotic effects, especially improvement of positive symptoms associated with the disorder.[2] Antipsychotics are divided into three distinct classes based on their affinity for D_2 and other neuroreceptors: typical (conventional) antipsychotics, atypical antipsychotics, and D_2 partial agonists.[1] Typical antipsychotics are more commonly referred to as first generation antipsychotics (FGAs) and the atypical antipsychotics including the D_2 partial agonist (also considered an atypical) are also known as second generation antipsychotics (SGAs).[1,3]

In addition to blocking D_2 receptors in the mesolimbic pathway, FGAs also block D_2 receptors in the mesocortical, tuberoinfundibular, and nigrostriatal pathways.[2] D_2 blockade in these other pathways is thought to be responsible for the hyperprolactinemia and extrapyramidal symptoms (EPS) associated with this class.[4] FGAs may be characterized according to their affinity for the D_2 receptor. Low potency antipsychotics, such as chlorpromazine and thioridazine, are more sedating and associated with a higher incidence of anticholinergic side effects. Fluphenazine, haloperidol, pimozide, thiothixene, and trifluoperazine are high potency antipsychotics that are less sedating but associated with a higher incidence of EPS. The medium potency antipsychotics (loxapine, molindone, and perphenazine) possess a moderate risk of EPS and anticholinergic side effects.[5]

With the exception of pimozide, all FGAs are indicated for use in the treatment of schizophrenia. FGAs are effective in the treatment of positive symptoms of schizophrenia, which include agitation, aggression, delusions, and hallucinations. Negative symptoms of schizophrenia which include avolition, anhedonia, alogia, affective flattening, and social withdrawal, do not respond as well to this antipsychotic class.[4] Pimozide is indicated only for the suppression of motor and phonic tics in patients with Tourette's disorder.

Currently, the American Hospital Formulary Service (AHFS) employs the term atypical antipsychotic when referring to the SGAs.[3] The term "atypical antipsychotic" was introduced in 1989 when clozapine was approved for use by the Food and Drug Administration (FDA). Originally, this term referred to an antipsychotic with a low risk of EPS.[5] As a class, SGAs or atypical antipsychotics are more selective in targeting the intended mesolimbic D_2 pathway. They also block or partially block 5-HT_{2A} and 5-HT_{1A} serotonin receptors and have a greater affinity for 5-HT_2 receptors than for D_2 receptors.[1,5] These differences in neuropharmacologic activity are associated with a lower risk of EPS and tardive dyskinesia; the risks vary with the specificity of each agent for D_2 and serotonin receptors.[1,5] Another characteristic shared by atypical antipsychotics is a more favorable outcome in the treatment of the negative symptoms of schizophrenia.[1] The SGAs are comprised of nine separate chemical entities, each with a unique neuropharmacologic and adverse event profile, mechanism of action, and chemical structure. These SGAs are aripiprazole, asenapine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone.

The neuropharmacology of aripiprazole differs from other SGAs, as it is a partial D_2 and 5-HT_{1A} agonist and a 5-HT_{2A} and 5-HT_{2C} antagonist. It is referred to as a D_2-serotonin system stabilizer since the partial agonist activity allows for blockade of an overstimulated receptor and stimulation of a receptor when activity is needed.[2] EPS rates comparable to placebo may be attributable to the partial-agonist activity of this agent. Aripiprazole is chemically classified as a quinolinone derivative and is FDA approved for use in schizophrenia in adults and adolescents, acute manic and mixed episodes associated with bipolar disorder in adults and adolescents, agitation associated with schizophrenia or bipolar disorder in adults,

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irritability associated with autistic disorder in children and adolescents and major depressive disorder in adults.[6]

Asenapine is the first antipsychotic agent that is solely available in the United States as a sublingual tablet formulation. It is approved for the treatment of schizophrenia in adults and acute treatment of manic or mixed episodes associated with bipolar I disorder in adults, either as monotherapy or adjunctive therapy.[7] It has a distinctive receptor binding profile in that it displays high affinity binding and antagonistic activity at a wide range of dopamine, serotonin, norepinephrine, and histamine receptors (H_1).[7]

Clozapine is classified as a dibenzodiazepine derivative with a high affinity for 5-HT receptors and a lower, transient affinity for D_2 receptors. Its use is limited by its risk of agranulocytosis. In addition to a boxed warning for agranulocytosis, clozapine also carries a boxed warning for cardiac toxicity, seizures, orthostatic hypotension, and respiratory and cardiac arrest.[8-9] This medication is effective in patients who do not respond to conventional or other atypical antipsychotics. It is approved for use in severely ill patients with schizophrenia or those with schizophrenia or schizoaffective disorder at risk for suicidal behavior.[8-9]

Iloperidone is indicated for the acute treatment of adults with schizophrenia. Iloperidone is a piperidinyl-benzisoxazole derivative thought to exert its pharmacological effects via antagonism of the D_2 and 5-HT_2 receptors, with high affinity for 5-HT_{2A}, D_2 and D_3 receptors and low affinity for 5-HT_{1A}, D_1 and H_1 receptors. The product information warns the prescriber of the association between iloperidone and QTc prolongation. Of note, iloperidone must be titrated to an effective dose which may delay symptom control during the first 1 to 2 weeks of therapy; therefore, this must be considered when choosing an agent for the acute treatment of schizophrenia.[10]

Lurasidone is indicated for the treatment of adults with schizophrenia. It is a high affinity antagonist at D_2 receptors and 5-HT_{2A}/5-HT_7 receptors, a moderate affinity antagonist at alpha$_{2C}$ adrenergic receptors, a partial agonist at 5-HT_{1A} receptors and is an antagonist at alpha$_{2A}$ adrenergic receptors. Lurasidone has little to no affinity for histamine$_1$ and muscarinic receptors. In dose-ranging studies, the 120 mg dose has not been found to offer added efficacy over the 80 mg daily dose, while being associated with a greater frequency of adverse events. To insure optimal absorption and distribution, the drug should be taken with food (at least 350 calories). Moreover, lurasidone is primarily metabolized in the liver via the CYP3A4 enzyme. Consequently, coadministration with strong CYP3A4 inducers or inhibitors is contraindicated.[11,12]

Olanzapine is approved for use in the treatment of adults and adolescents with schizophrenia, manic or mixed episodes associated with bipolar I disorder in adults and adolescents, and agitation associated with schizophrenia or bipolar disorder. In addition, olanzapine, in a fixed combination with fluoxetine (Symbyax®), is indicated in adults with treatment-resistant depression or for the management of depressive episodes associated with bipolar I disorder.[13] The long-acting olanzapine formulation administered via a deep intramuscular gluteal injection is only approved for the treatment of schizophrenia in adults.[14] Olanzapine is a thienobenzodiazepine with a dose-dependent risk of EPS and hyperprolactinemia related to higher D_2 receptor occupancy.[2]

Quetiapine is another dibenzothiazepine derivative, approved for use in the treatment of adults and adolescents with schizophrenia, adults and adolescents with acute manic episodes, and adults with depressive episodes associated with bipolar disorders.[15-16] Likely due to its low and transient occupancy of D_2 receptors, quetiapine is associated with a low incidence of EPS and has not been shown to significantly elevate prolactin levels.

Risperidone, a benzisoxazole derivative, is approved by the FDA for the treatment of schizophrenia and acute manic or mixed episodes associated with bipolar disorder in adults and adolescents.[17-18] Risperidone is also indicated for the management of irritability associated with autism. In comparison to other SGAs, the use of risperidone results in a higher incidence of prolactin level elevation and EPS, particularly at doses of 6 mg per day and higher. Paliperidone, the active metabolite of risperidone, has

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also been approved by the FDA for the treatment of schizophrenia in adults and adolescents. Moreover, paliperidone is indicated for the treatment of schizoaffective disorder as an adjunct to mood stabilizers and/or antidepressants.This medication is available in an extended-release formulation and has been shown to have an incidence of EPS similar to placebo at daily doses up to 6 mg.[19-20] Paliperidone palmitate is a long-acting injectable formulation. Through once monthly intramuscular injections, it releases paliperidone as the active moiety over a sustained period of time. Prior to starting paliperidone palmitate IM, tolerability should be established either with oral paliperidone or oral risperidone.[21]

Ziprasidone, another benzisoxazole derivative, is indicated for the treatment of schizophrenia and manic or mixed episodes associated with bipolar disorder (with or without psychotic features).[19] Ziprasidone differs from other medications in its class as it has a high affinity for D_2 receptors but a greater affinity for 5-HT_2 receptors. The higher affinity for the 5-HT_2 receptors may reduce the incidence of EPS, but this risk is dose dependent.[2,5] It also possesses potent serotonin and norepinephrine reuptake blocking effects.

Although in some respects the SGAs are safer and better tolerated than the FGAs, they are still associated with a number of serious risks and side effects. For this reason, the FDA has required various warnings to be inserted in the manufacturers' product information for these agents. All bear a warning that alerts prescribers and patients to the risk of hyperglycemia and other metabolic changes.[6-19,21-22] Ziprasidone also has a warning concerning QTc interval prolongation; however, all of the SGAs can increase the QTc interval to some degree.[6-19,21-22] Aripiprazole and quetiapine carry a black box warning regarding suicidality and antidepressant drugs.[6, 15-16] Olanzapine pamoate long-acting injectable product carries a black box warning regarding the risk of a post-injection delirium/sedation syndrome.[14] All SGAs carry a black box warning noting that they are associated with an increased risk of death when used in the treatment of psychosis and behavioral problems in elderly patients with dementia. Most of the deaths that prompted the addition of the warning were due to cardiac-related events (e.g., heart failure or sudden death) or infection.[23] Of note, this last black box warning is directed at using antipsychotics in a manner that is not FDA approved.

Due to the potential side-effect risks associated with these medications, any off-label use deserves close attention. Data published in peer-reviewed journals and in national and international guidelines support the use of SGAs as a treatment option for certain off-label uses. In many of these scenarios, SGAs are reserved for patients who are refractory to other first-line treatment modalities, including both pharmacotherapy and psychotherapy, and used in adjunction to mainstream therapies, as part of a multimodal approach.

Over the past 20 years, the use of antipsychotics in children and adolescents has grown. In the United States, the frequency of prescribing an antipsychotic agent increased from 8.6 per 1000 children in 1996 to 39.4 per 1000 children in 2002.[108] Moreover, according to a survey of national trends in the outpatient use of antipsychotics in children and adolescents, only 14.2% of antipsychotic prescriptions in children were for patients diagnosed with psychotic disorders.[24] Indications commonly associated with antipsychotic prescribing in pediatric patients include psychosis, schizophrenia, bipolar disorder, aggressive and disruptive behavior, and tic disorders.[108] Additional off-label indications with available limited evidence for the use of atypical antipsychotics in children and adolescents include autistic spectrum disorders, major depressive disorder, anxiety disorders, and eating disorders. At this time, risperidone and aripiprazole are FDA approved for the management of children and adolescents with autism (aged 5-16 and 6-17 years, respectively). Moreover, the following agents are indicated for the treatment of schizophrenia in adolescents: aripiprazole, olanzapine, paliperidone, quetiapine, and risperidone. Aripiprazole, olanzapine, quetiapine and risperidone are also FDA approved for the treatment of manic or mixed bipolar I disorder in children and adolescents. None of the other available atypical antipsychotic agents are currently indicated for use in pediatric patients.[6-11,13-19,21-22]

Concerns have also been raised about the risks of combination therapy with the antipsychotics, which can multiply the risks of dangerous adverse events. The practice of polypharmacy is not supported by

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well-designed clinical trials published in the peer-reviewed literature. However, national and international consensus guidelines consider this approach in patients with treatment-refractory illness.

Medications

The second-generation antipsychotics that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. First-generation agents were excluded due to their widespread availability as generic products.

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Aripiprazole (Abilify®, Abilify Discmelt®)	Atypical antipsychotic	-
Asenapine (Saphris®)	Atypical antipsychotic	-
Clozapine (Fazaclo ODT®, Clozaril®*)	Atypical antipsychotic	✔
Iloperidone (Fanapt®)	Atypical antipsychotic	-
Lurasidone (Latuda®)	Atypical antipsychotic	-
Olanzapine (Zyprexa®*, Zyprexa IM®*, Zyprexa Zydis®*, Zyprexa Relprevv®)	Atypical antipsychotic	✔
Paliperidone (Invega®)	Atypical antipsychotic	-
Paliperidone palmitate (Invega Sustenna®)	Atypical antipsychotic	-
Quetiapine (Seroquel®*, Seroquel XR®)	Atypical antipsychotic	✔
Risperidone (Risperdal®*, Risperdal M-Tab®*, Risperdal Consta®)	Atypical antipsychotic	✔
Ziprasidone (Geodon®*)	Atypical antipsychotic	✔

IM=intramuscular, ODT=orally disentigrating tablet, XR=extended release
*Generic is available in at least one dosage form or strength.

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Indications

Table 2. Food and Drug Administration (FDA) Approved Indications[6-11,13-19,21-22]

Indications	Aripiprazole	Asenapine	Clozapine	Iloperidone	Lurasidone	Olanzapine	Paliperidone/ paliperidone palmitate	Quetiapine	Risperidone	Ziprasidone
Bipolar Disorders										
Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults	✔ *	✔				✔ *				✔ *
Acute or Maintenance treatment of manic or mixed episodes associated with bipolar I disorder in children and adolescents aged 10-17 years	✔ *					✔ *£				
Adjunctive therapy to either lithium or valproate for the acute treatment of manic and mixed episodes associated with Bipolar I Disorder with or without psychotic features in adults and in pediatric patients aged 10 to 17 years	✔ *									
Adjunctive therapy to either lithium or valproate for the acute treatment of manic and mixed episodes associated with Bipolar I Disorder		✔				✔ *				
Maintenance treatment of manic or mixed episodes associated with bipolar I disorder in adults	✔ *					✔ *			✔ †	
Maintenance treatment of bipolar I disorder as adjunct therapy to lithium or divalproex in adults								✔ *‖		
Maintenance treatment of bipolar I disorder as adjunct therapy to lithium or valproate in adults									✔ †	✔ *
Short-term treatment of acute manic or mixed episodes associated with bipolar I disorder in adults and in children and adolescents aged 10-17 years									✔ *	
Short-term treatment of acute mixed or manic episodes associated with bipolar I disorder in combination with lithium or valproate in adults									✔ *	
Treatment of acute manic or mixed episodes associated with bipolar disorder										✔ *
Treatment of acute manic episodes associated with bipolar I disorder as either monotherapy or adjunct therapy to lithium or divalproex in adults								✔ *		
Treatment of acute manic episodes associated with bipolar I disorder as either monotherapy or adjunct therapy to lithium or divalproex in children and adolescents aged 10-17 years								✔ *		
Treatment of manic or mixed episodes associated with bipolar I disorder as either monotherapy or adjunct therapy to lithium or divalproex in adults								✔ ‖		

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Indications	Aripiprazole	Asenapine	Clozapine	Iloperidone	Lurasidone	Olanzapine	Paliperidone/ paliperidone palmitate	Quetiapine	Risperidone	Ziprasidone
Treatment of agitation associated with bipolar I disorder, manic or mixed in adults	✔ †					✔ †				
Treatment of agitation associated with bipolar I mania in adults						✔ †				
Treatment of depressive episodes associated with bipolar disorder in adults						✔ €		✔ * ‖		
Schizophrenia										
Acute and maintenance treatment of schizophrenia in adults	✔ *	✔				✔ *†	✔ *†	✔ * ‖	✔ *	
Reduction in the risk of recurrent suicidal behavior in schizophrenia or schizoaffective disorder in adults			✔							
Treatment of agitation associated with schizophrenia in adults	✔ †					✔ †				✔ †
Treatment of schizophrenia in adolescents aged 13-17	✔ *					✔ *£		✔ *	✔ *	
Treatment of schizophrenia in adolescents aged 12-17							✔ *			
Treatment of schizophrenia in adults	✔ *			✔ §	✔			✔ *	✔ †	✔ *
Treatment-resistant schizophrenia in adults			✔							
Miscellaneous Disorders										
Adjunctive treatment to antidepressants for major depressive disorder in adults	✔ *					✔ ε€		✔ ‖		
Irritability associated with autistic disorder in children and adolescents aged 5-16 years									✔ *	
Irritability associated with autistic disorder in children and adolescents aged 6-17 years	✔ *									
Treatment of schizoaffective disorder as monotherapy and as an adjunct to mood stabilizers and/or antidepressants in adults							✔ *			

*****Oral dosage form.
†Intramuscular dosage form.
‡ Approved for acute treatment only.
§ In choosing among treatments, prescribers should consider the ability of Fanapt® to prolong the QT interval and the use of other drugs first. Prescribers should also consider the need to titrate Fanapt® slowly to avoid orthostatic hypotension, which may lead to delayed effectiveness compared to some other drugs titration.
‖ Oral extended-release dosage form.
€ Approved to be used in combination with fluoxetine
ε Indicated for the treatment depression in patients who do not respond to 2 separate trials of different antidepressants of adequate dose and duration in the current episode.
£ Medical treatment of both pediatric schizophrenia and bipolar I disorder should be part of a total treatment program that includes psychological, educational, and social interventions. The increased potential for weight gain and hyperlipidemia, in adolescents compared with adults, may lead clinicians to consider prescribing other drugs first in adolescents.

A number of the atypical antipsychotics have been studied and used off-label for a variety of treatments.

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Pharmacokinetics

Table 3. Pharmacokinetics[6-11,13-19,21-22, 25]

Drugs(s)	Bioavailability (%)	Protein Binding (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Aripiprazole	87*; 100†	>99	25	Dehydroaripiprazole	75-146
Asenapine	35 (<2 if swallowed)	95	50	None identified	24
Clozapine	50-60	97	50	Desmethyl metabolite, limited activity	8-12
Iloperidone	96	~95	58.2-45.1	Two predominant; P88 and P95	18 (iloperidone), 26 (P88) and 23 (P95) in extensive metabolizers 33 (iloperidone), 37 (P88) and 31 (P95) in poor metabolizers
Lurasidone	9-19	99	9	Two (ID-14283 and ID-14326)	18
Olanzapine	Well absorbed	93	57	Not reported	21-54
Paliperidone/ paliperidone palmitate	28	74	59	Not reported	23
Quetiapine	100	83	73	N-dealkylated quetiapine	7; 9-12‡
Risperidone	70	90	70	Not reported	20*
Ziprasidone	60*; 100†	>99	Not reported	Not reported	2-5

*Oral dosage form.
†Intramuscular dosage form.
‡Active metabolite.

Clinical Trials

Numerous clinical studies evaluating the efficacy of antipsychotic medications have been conducted for both Food and Drug Administration (FDA)-approved and nonapproved indications. The FDA-approved indications for the antipsychotics have been validated by extensive clinical trials and evidence-based guidelines. The role of the second generation antipsychotics (SGA) has been clearly established in the treatment of bipolar disorder and schizophrenia (and, in the case of aripiprazole, quetiapine XR and olanzapine/fluoxetine combination therapy, as adjunctive treatment of major depressive disorder). However, clinical consensus guidelines do not differentiate one agent from another, supporting the concept that all patients will require an individualized approach to treatment selection, taking into account the agent's side effect profile and patient's individual risk factors.[6-11,13-19,21-22, 25]

The goal of this review was to evaluate available published literature with atypical antipsychotics for FDA-approved as well as off-label indications in children, adolescents, and adults. All available clinical studies evaluating the roles of new atypical antipsychotic agents (FDA-approved since 2009) in the treatment of

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either off-label or FDA-approved indications were included in the review. These agents include asenapine, iloperidone, lurasidone, and olanzapine pamoate. However, in recognition of the vast number of published studies evaluating the safety and efficacy of older atypical antipsychotics in adults, only a selection of randomized controlled studies, systematic reviews and meta-analyses were included in the review. On the other hand, this review provides a comprehensive summary of available published literature on the safety and efficacy of atypical antipsychotic agents for both off-label and FDA-approved indications in children and adolescents.

The efficacy of asenapine in the treatment of schizophrenia in adults has been evaluated in four, published, randomized, double-blind, placebo-controlled, and active-controlled (haloperidol, risperidone, and olanzapine) trials, ranging in duration from 6 weeks to 1 year[30-33]. These studies are outlined below in Table 4. Asenapine was associated with statistically significant improvement in the Positive and Negative Syndrome Scale (PANSS) scores from baseline compared to placebo, starting from week-2 of therapy. Clinical Global Impression-Improvement (CGI-I) and Clinical Global Impression-Severity of Illness (CGI-S) scores were also significantly improved with asenapine therapy, compared to placebo. Moreover, an extension study demonstrated a reduced risk of relapse associated with continuation of asenapine therapy.[31] However, a direct-comparison study suggests that asenapine is less effective than olanzapine in terms of changes from baseline in PANSS and CGI-S scores.[33] Furthermore, study discontinuation due to inadequate efficacy was noted in only 14% of patients receiving olanzapine compared with 25% of patients in the asenapine group. Mean weight gain was 0.9 kg with asenapine and 4.2 kg with olanzapine.[33] In another study, while 17% of patients receiving risperidone experienced a weight gain of at least 7% from baseline, 9% of patients in the asenapine were noted to exhibit clinically significant weight gain.[30] The efficacy and safety of asenapine in the treatment of manic or mixed bipolar I disorder were evaluated in five placebo-controlled, and active-controlled (olanzapine) studies in adult patients, with or without psychotic features.[72-76] Asenapine 5-10 mg twice daily was statistically more effective than placebo on the Young Mania Rating Scale (YMRS) and the Clinical Global Impression–Bipolar Scale (CGI-BS) in all studies. In a pooled analysis of patients experiencing bipolar mania, asenapine and olanzapine were comparable in terms of reduction from baseline in YMRS scores at week-52 of therapy.[76] Likewise, another pooled analysis of patients experiencing bipolar depression episode found that olanzapine and asenapine were associated with comparable improvement in baseline Montgomery-Asberg Depression Rating Scale (MADRS) scores after 21 days of therapy.[74] A meta-analysis of various antimanic therapy options, found that asenapine was associated with a statistically significant improvement in YMRS scores from baseline compared to placebo (mean difference, -0.30; -0.53 to -0.07), though it was less effective compared to olanzapine (0.22; 0.08 to 0.37).[81] In addition, another meta-analysis calculated that 6 patients would be treated with asenapine for one to achieve a positive response, compared with placebo.[59] Most commonly reported adverse events reported with asenapine included sedation, dizziness, somnolence and weight gain.[75] Of note, it was calculated that for every 9 patients treated with olanzapine over asenapine, 1 would experience a clinically significant weight gain.[75]

Iloperidone has been studied as monotherapy for the treatment of adult patients with an acute or subacute exacerbation of schizophrenia. Three 6-week, randomized, double-blind, placebo- and active comparator (risperidone and haloperidol)-controlled studies found iloperidone to be significantly more effective than placebo.[35] Another 4-week, placebo- and active- comparator (ziprasidone)-controlled study found a significant improvement in PANSS scores with iloperidone therapy compared to placebo.[34] Two meta-analyses of these four studies corroborated earlier data, finding iloperidone more effective than placebo in terms of improvement from baseline in various subscales of the PANSS scale and BPRS scores.[36-27] The long-term efficacy and safety of iloperidone in the treatment of schizophrenia was evaluated in a meta-analysis that pooled the follow-up data (up to 52 weeks) from 3 prospective randomized clinical trials.[38] The meta-analysis found the long-term efficacy of Iloperidone, assessed via the time to relapse endpoint, to be comparable to haloperidol (*P*=0.85), with a more favorable long-term safety profile.[38] Moreover, another meta-analysis designed to evaluate the short-term safety of iloperidone found the following dose-related adverse effects: dry mouth, dizziness, somnolence and dyspepsia.[39] Extrapyramidal adverse events were noted in association with iloperidone but were more common with

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haloperidol and risperidone therapies. Iloperidone was also associated with QTc prolongation and weight gain (1.5 kg to 2.1 kg).[39] An in-depth review of these studies can be found in Table 4.

Lurasidone has been investigated for the treatment of adult patients with acute and chronic symptoms of schizophrenia in two 6-week, placebo-controlled studies and two 21-day studies directly comparing the safety and efficacy of lurasidone 120 mg once daily with ziprasidone 80 mg twice daily.[40-43] In placebo controlled studies, lurasidone, dosed 40 mg, 80 mg, or 120 mg once daily was associated with significant improvements from baseline in PANSS and the Brief Psychiatric Rating Scale (BPRSd) scores, compared to placebo.[40,43] The two direct-comparison studies demonstrated comparable improvements in the lurasidone and ziprasidone groups in terms of the reduction in total PANSS, PANSS positive symptom, PANSS general symptom, CGI-S scores and several cognition scales.[41-42] Likewise, the two groups were comparable in terms of rates of discontinuation for any reason rate and discontinuation due to adverse events.[41,42] Of note, lurasidone was more effective in improving negative symptoms PANSS scores compared to ziprasidone (P=0.046).[42] Both therapies were associated with a small weight loss from baseline and neither therapy was associated with a clinically significant ECG abnormality. Extrapyramidal adverse events were noted in 3.3% of patients in the ziprasidone group and in 3.3% of patients receiving lurasidone.[42] Please refer to Table 4 for additional details.

In addition to oral tablet dosage forms, several atypical antipsychotics are formulated as short- and long-acting injection, orally disintegrating tablet, and oral solution formulations.[6,9,13,14,17,18, 21] These alternative routes of administration may help patients with compliance issues, or certain medical conditions (i.e. feeding tube, swallowing disorder, etc.). Studies comparing the efficacy and side effect profiles of these alternative dosage forms are outlined in the tables below. Based on the overall results of these trials, no significant differences in efficacy and safety measures were consistently found between the different products.[44,53-54] Long-acting injection formulations were associated with a longer relapse-free periods compared to oral agents in several randomized controlled trials.[47,55]

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) was a large, multi-center study initiated by the National Institute of Mental Health to examine the effectiveness of SGAs compared with first generation antipsychotics (FGAs) in patients with chronic schizophrenia. It was intended to include patients treated in typical clinical settings and to reflect typical clinical practice in which individuals with schizophrenia may require multiple medication trials before finding one that is adequately both efficacious and tolerable. The study design allowed for patients who discontinued one study antipsychotic drug to enter subsequent phases of the study to receive additional antipsychotic medications.[56-58] Among the unexpected outcomes was the finding that, with the exception of clozapine, the SGAs did not separate out as robustly from the FGAs with respect to overall efficacy and times to treatment discontinuation. However, because of relatively high discontinuation rates across all treatment arms, potential biases regarding optimal dosing of individual drugs, and clear differences in treatment-emergent side effect profiles, the implications of CATIE are subject to interpretation which may preclude definitive guidance in developing pharmacotherapy guidelines for patients with schizophrenia as a whole. Summaries of the CATIE studies are presented in Table 4.

Although the adverse events associated with the antipsychotics are presented in the Adverse Drug Events and Contraindications/Precautions sections, Tables 8 and 9 are included to supplement this information with a more detailed discussion of some important studies conducted in adult and pediatric populations pertaining to the issue of safety. These studies have been conducted to further explore the safety concerns with these agents and to evaluate the possible clinical impact of these effects on the patient populations in which antipsychotics are commonly used. These tables do not present an exhaustive list of all relevant published literature, but it has been assembled to present a balanced, unbiased representation of the studies that are available.

The Agency of Healthcare Research and Quality (AHRQ) is the lead federal agency for research on healthcare quality, costs, outcomes and patient safety. Under the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, the AHRQ is required to conduct and support research into

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the clinical effectiveness, comparative effectiveness, and appropriateness of pharmaceuticals, medical devices and healthcare services for the recipients of Medicare, Medicaid, and the State Children's Health Insurance Program.[202,108]

In 2011, AHRQ had issued an update to a prior 2007 review of scientific evidence on the safety and effectiveness of atypical antipsychotics for off-labeled use.[91, 202] Specifically, asenapine, aripiprazole, iloperidone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone were evaluated for off-labeled uses, such as anxiety disorders, attention deficit hyperactivity disorder (ADHD), dementia and severe geriatric agitation, depression, eating disorder, insomnia, obsessive-compulsive disorder, posttraumatic stress disorder, personality disorders, substance abuse, Tourette's syndrome and autism. Efficacy analyses included controlled trials of at least six weeks in duration. Results from efficacy studies judged clinically similar were pooled in a meta-analysis. For trials judged not clinically similar, a narrative synthesis was performed. Adverse events analysis included trials of any duration, case series or cohort studies with a comparison group of >1,000 patients. Following analysis and synthesis of data, the draft report was reviewed by a technical expert panel consisting of scientists and clinicians with expertise in psychiatric conditions. Of note, no pertinent studies with asenapine, iloperidone or paliperidone met the inclusion criteria and were thus not included in the final evaluation of results.

The overall strength of evidence was assessed using a grading method developed by the Grade Working Group. The classification criteria are as follows[202]:

- High= High confidence that the evidence reflects the true effect. Further research is very unlikely to change the confidence on the estimate of effect.
- Moderate= Moderate confidence that the evidence reflects the true effect. Further research may change the confidence in the estimate of effect and may change the estimate.
- Low= Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.

The AHRQ evidence grading system took into account the following factors: risk of bias, consistency, directness, precision, dose-response, potential confounders that would decrease the observed effect, strength of association, and publication bias. In summary, indications associated with moderate/high strength of evidence for the use of atypical antipsychotics included general anxiety disorder (quetiapine), dementia (aripiprazole, olanzapine, risperidone), depression (aripiprazole, quetiapine, risperidone), augmentation of SSRIs for obsessive compulsive disorder [OCD] (risperidone), and post-traumatic stress disorder [PTSD] (risperidone).[102] Table 7 summarizes the strength of evidence for each agent for the off-label indications investigated in this report. For additional details of the 2011 AHRQ efficacy and safety findings, please refer to Appendices Ia and Ib.

In addition, the AHRQ had conducted a systematic review of literature on the safety and efficacy of antipsychotics in children and adolescents.[108,109] The review included studies of atypical antipsychotics (aripiprazole, clozapine, olanzapine, quetiapine, risperidone, paliperidone, and ziprasidone), conducted in patients 24 years of age or younger, used for the following FDA-approved and off-label indications: pervasive developmental disorder, ADHD/disruptive behavior disorders, bipolar disorder, schizophrenia, psychosis, Tourette's syndrome, OCD, PTSD, anorexia nervosa, and miscellaneous behavioral issues. In summary, indications associated with moderate strength evidence for the use of atypical antipsychotics included disruptive behavior disorder, bipolar disorder, schizophrenia, and Tourette's syndrome. No significant differences between the different atypical antipsychotics were noted in the identified head-to-head comparisons. The risks of weight gain (weight gain: 4.6 kg) and dyslipidemia were highest with olanzapine. Weight gain with ziprasidone was not significantly different from placebo. The other atypical antipsychotics were associated with intermediate weight gain. Risperidone was associated with the greatest incidence of prolactin-related adverse events (consistent with adult data). Extrapyramidal adverse events were significantly more common with risperidone and aripiprazole compared with placebo. For details of these findings, refer to Table 6 and Appendices IIa and IIB.

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Table 4. Efficacy Clinical Trials Using the Antipsychotics

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Acute Psychotic Symptoms				
Hatta et al[27] Olanzapine orally disintegrating tablet 10 mg vs risperidone oral solution 3 mg	MC, OL Acutely agitated psychotic patients with a score ≥ 15 on the PANSS-EC when visiting or brought to the psychiatric emergency department	N=87 2 months	Primary: PANSS-EC, CGI-C, patient satisfaction, blood pressure, heart rate and EPS Secondary: Not reported	Primary: There were no significant main effects on treatment (*P*=0.09), and no significant interaction was seen between time course and treatment on PANSS-EC (*P*=0.41). There were no differences in patient satisfaction found between treatment groups (*P*=0.91). There were no significant differences in mean CGI-C scores between treatment groups (*P*=0.22). There were no significant differences in mean changes in systolic and diastolic blood pressure between groups (*P*=0.41 and *P*=0.71, respectively). Mean change in heart rate was significantly greater in the olanzapine orally disintegrating tablet group (–9.2 beats/minute) compared to the risperidone oral solution group (1.1 beats/minute; *P*=0.03). There were no significant differences between groups in percent of patients experiencing EPS (*P*=0.28). Secondary: Not reported

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Verma et al[27] Risperidone 2.2 mg/day (mean dose) vs olanzapine 13.2 mg/day (mean dose)	MC, OL, OS Male patients admitted to a veterans affairs medical center geropsychiatric inpatient unit for the treatment of behavioral disturbances, physical aggression, verbal threats, wandering, general confusion	N=34 21 months	Primary: Differences in effectiveness, side effect profiles, and cost between the two cohorts based on PANSS, CMAI, GAF, ESRS, and RSSE scores Secondary: Not reported	Primary: CMAI, GAF, and PANSS scoring showed that both groups performed significantly better following their stay in the veterans affairs medical center from baseline scoring at admission (*P*<0.001). There were no significant differences between risperidone and olanzapine on any measure, including CMAI and PANSS (*P* values not significant). Upon discharge, the mean ESRS score was 23.46 with risperidone-treated patients and 20.54 with olanzapine-treated patients (*P*=0.557). The RSSE was 8.14 with risperidone-treated patients and 7.71 with olanzapine-treated patients (*P*=0.557). Secondary: Not reported
Currier et al[28] Risperidone liquid concentrate 2 mg plus lorazepam oral 2 mg vs haloperidol intramuscular 5 mg plus lorazepam intramuscular 5 mg	PRO Psychotic patients aged 18 to 65 years who required emergency medication for the control of agitation and/or violence	N=60 3 months	Primary: PANSS, CGI scale, time to sleep, need for repeat doses, and adverse events Secondary: Not reported	Primary: Both treatments lead to significant improvements in PANSS measures (*P*<0.0001) and there were no differences found between treatment groups (*P*=0.42). Both treatment groups lead to significant improvements in CGI scores (*P*<0.0001) and there were no differences found between treatment groups (*P*=0.419). There were no significant differences between treatment groups regarding time to sleep (*P* value not reported). One patient in the risperidone group required subsequent treatment with haloperidol for ongoing agitation compared to none in the haloperidol group (*P* value not reported). One patient in the haloperidol group reported one adverse event (dystonia) compared to no reports of side effects in the risperidone group (*P* value not reported). Secondary: Not reported
Early Psychosis				

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Marshall et al[29] Atypical antipsychotics (olanzapine, risperidone) vs cognitive behavioral therapy vs specialized team providing needs-focused intervention vs adherence coping education vs. standard care (at community mental health center)	SR Patients in the prodromal phase of psychosis or experiencing first-episode psychosis	N=1,808 2 months to 2 years	Primary: Prevention of psychosis, discontinuation, PANSS scores Secondary: Not reported	Primary: Olanzapine used for the prevention of psychosis for people with prodromal symptoms was associated with a risk ratio for conversion to psychosis of 0.58 (95%CI, 0.3 to 1.2).Cognitive behavioural therapy was associated with a similar risk of conversion to psychosis (RR, 0.50; 95% CI, 0.2 to 1.7). Risperidone in addition to cognitive behavioral therapy and specialised team was associated with a benefit over specialist team alone at six months of therapy (RR conversion to psychosis, 0.27; 95%CI, 0.1 to 0.9; NNT, 4). However, the benefit of risperidone augmentation was not sustained at 12 months (RR, 0.54; 95%CI, 0.2 to 1.3). Omega 3 fatty acid was associated with a significant benefit over placebo in the risk of conversion to psychosis (RR, 0.13; 95%CI, 0.02 to 1.0; NNT, 6). In patients with first-episode psychosis, specialised team involvement was associated with a lower risk of discontinuation (NNT=9), improved compliance (NNT=9) and a fewer number of patients not living independently at 5 years (NNT=19), compared to standard of care. There were no significant differences between groups in the mean number of days spent in hospital at one year or number of patients who were not hospitalized by 5 years. There were no significant differences between the group that received phase-specific treatment brief intervention and antipsychotics compared with the treatment as usual group either in discontinuation rate or number of hospital admissions. There were no significant differences between the group that receivied adherence coping education in addition to antipsychotic therapy and the treatment as usual group either in discontinuation rate, change in PANSS scores or quality of life measures. Secondary: Not reported

Schizophrenia				
Potkin et al[30] Asenapine 5 mg sublingual twice daily vs risperidone 3 mg orally twice daily vs placebo	AC, DB, DD, FD, MC, PC, PG, RCT Patients ≥18 years of age with a DSM-IV diagnosis of schizophrenia with acute exacerbation of symptoms defined by a CGI-S score ≥4 (at least moderately ill) and a PANSS total score ≥60 (with baseline scores ≥4 required on ≥2 items of the PANSS positive subscale [delusions, conceptual disorganization, hallucinatory behavior, grandiosity, and suspiciousness / persecution]); patients who had previously taken an antipsychotic (other than clozapine) were required to have had a history of a clinically meaningful response to that agent; current	N=182 (174, ITT population) 6 weeks	Primary: Change from baseline in PANSS total score at end point Secondary: Changes in CGI-S score and PANSS positive, negative, and general psycho-pathology subscale scores; safety analyses (performed in those who received ≥1 dose of study medication)	Primary: Mean changes from baseline in PANSS total score were -15.9 with asenapine vs -5.3 with placebo (*P*<0.005); the change with risperidone (-10.9) was nonsignificant vs placebo (*P* value not reported). Asenapine produced significantly greater decreases in PANSS total scores from week 2 onward compared with placebo. Secondary: At end point, mean changes from baseline in CGI-S were -0.74 for asenapine vs -0.28 for placebo (*P*<0.01); the change with risperidone (-0.75) was also significant vs placebo (*P*<0.005). Both active treatments were associated with significantly greater decreases in CGI-S scores from week 4 onward compared with placebo. At end point, mean changes from baseline in PANSS positive subscale score were -5.5 for asenapine vs -2.5 for placebo (*P*=0.01); the change with risperidone (-5.1) was also significant vs placebo (*P*<0.05). Compared with placebo, there were significantly greater decreases in PANSS positive subscale scores with asenapine from week 3 onward, and with risperidone at weeks 1, 3, 5, and 6. At end point, mean changes from baseline in PANSS negative subscale score were -3.20 for asenapine vs -0.60 for placebo (*P*=0.01); the change with risperidone (-1.05) was nonsignificant vs placebo. Asenapine produced significantly greater decreases in PANSS negative subscale scores from week 3 onward compared with placebo. At end point, mean changes from baseline in PANSS general psychopathology subscale score were -7.2 for asenapine vs -2.2 for placebo (*P*<0.005); the change with risperidone (-4.8) was nonsignificant vs placebo. Asenapine produced significantly greater decreases in PANSS general psychopathology subscale scores from week 2 onward compared with placebo. The overall frequency of adverse events was comparable across both treatment groups and placebo. All patients with adverse events recovered without sequelae.

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	antipsychotic medication was discontinued ≥3 days before baseline, current mood stabilization therapy was discontinued ≥5 days before baseline			There were no significant between-group differences on the SAS, BAS, and AIMS scales, although risperidone-treated patients were more likely to use antiparkinsonian drugs. Incidence of clinically significant weight gain (≥7.0% increase from baseline) was 17.0% with risperidone vs 4.3% with asenapine and 1.9% with placebo. Proportion of patients with post-baseline prolactin levels at end point ≥2 times the laboratory upper limit of normal was higher in the risperidone group (79%) than in the asenapine (9%) or placebo (2%) groups. There were no clinically important between-group differences with respect to treatment effects on blood pressure or heart rate during the study; also, there were no reports of QT interval prolongation >500 ms in any treatment group.
Kane et al[31] Asenapine sublingual 5 mg to 10 mg twice daily continued therapy vs switching to placebo sublingual from asenapine Note: prior to double-blind phase, patients were stabilized on 26 weeks of open-label asenapine therapy	DB, PC, MC, RCT Patients, 18 years of age and older, diagnosed with schizophrenia, history of at least 1 prior acute schizo-phrenia episode in the past 3 years, and schizophrenia requiring continu-ous antipsychotic therapy for at least 1 year prior to study entry	N=700 28 weeks (DB phase); 28 weeks (OL phase)	Primary: Time to relapse/impending relapse Secondary: Time to discontinuation for any reason, changes from baseline in PANSS total, PANSS Marder factors, CGI-S, CGI-I, Calgary Depression Scale for Schizophrenia (CDSS) scores, adverse events	Primary: Asenapine continued therapy was associated with a significantly lower risk of/impending relapse compared to placebo (12.1% vs. 47.4%; *P*<0.001). The relative risk of relapse/relative relapse with asenapine versus placebo was 0.26 over 6 months. Secondary: Significantly less patients continuing asenapine therapy discontinued the drug early compared to those who switched to placebo (30.4% vs. 62.5%; RR, 0.47; *P*<0.0001). During the double-blind phase of the study, patients continuing asenapine therapy experienced significant improvements from baseline in the following efficacy measures: PANSS total score, Marder factors (positive, negative, disorganized thought, hostility/excitement, and anxiety/depression symptoms), CGI-S scores, and CDSS total scores (*P*<0.0001 for all, except CDSS, *P*=0.027). During the double-blind phase, the incidence of adverse events considered serious with asenapine and placebo was 3.1% and 9.9%, respectively. The incidence of extrapyramidal events with asenapine and

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				placebo was 3.1% and 4.7%, respectively. The most frequently reported adverse events with asenapine versus placebo were anxiety (8.2% vs. 10.9%), increased weight (6.7% vs. 3.6%), and insomnia (6.2% vs. 13.5%). The incidence of weight gain of at least 7% was 3.7% and 0.5% with asenapine and placebo, respectively.
Kane et al[32] Asenapine 5 mg twice daily vs asenapine 10 mg twice daily vs haloperidol 4 mg twice daily vs placebo	DB, MC, PC, RCT Adult patients, 18 years of age or older, diagnosed with schizophrenia with an acute exacerbation of psychotic symptoms at study entry	N=458 6 weeks	Primary: Change from baseline in the total PANSS score Secondary: PANSS Subscale scores, PANSS Marder factors, CGI-S, CDSS, percentage of PANSS responders, percentage of CGI-I responders	Primary: Asenapine 5 mg and haloperidol were both associated with a significant improvement in PANSS total score from baseline, compared to placebo (P<0.05). Asenapine 10 mg was not associated with a significant change from baseline in PANSS total scores. Secondary: At study endpoint, all treatment groups exhibited significant improvements from baseline compared to placebo in PANSS subscale scores (P<0.05). All treatment groups were more efficacious than placebo in terms of the positive Marder factor, but none showed advantage on the negative factor. Only haloperidol was more effective than placebo in improving Marder hostility/excitement factor and asenapine 5 mg was the only group who exhibited improvement in Marder anxiety/depression and disorganized thought factors. Significantly more patients in the asenapine 5 mg and 10 mg groups were classified as PANSS responders, compared to placebo (55% vs. 49% vs. 33%, respectively, P<0.05). Significantly more patients in the asenapine 5 mg group were classified as CGI-I responders, compared to placebo (48% vs. 34%, respectively, P<0.05). At study endpoint, asenapine 5 mg and haloperidol groups experienced significant improvement in CGI-S scores from baseline, compared to placebo (P<0.05). At study endpoint, asenapine 5 mg group experienced significant improvement in CDSS scores from baseline, compared to placebo (P<0.05).

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				Treatment-related adverse events were noted in 44%, 52%, 57%, and 41% of the asenapine 5 mg, 10 mg, haloperidol, and placebo groups, respectively. The incidence of extrapyramidal adverse events was 15%, 18%, 34%, and 10% in the asenapine 5 mg, 10 mg, haloperidol, and placebo groups, respectively. The incidence of clinically significant weight gain was 5%, 4%, 2%, and 4% in the asenapine 5 mg, 10 mg, haloperidol, and placebo groups, respectively. The mean weight gain in patients assigned to asenapine 5 mg, asenapine 10 mg, and placebo groups was 0.7 kg, 0.6 kg, and -0.4 kg, respectively.
Schoemaker et al[33] Asenapine 5 mg to 10 mg twice daily vs olanzapine 10 mg to 20 mg once daily	DB, DD, MC, RCT Adult patients, 18 years of age and older, diagnosed with schizophrenia or schizoaffective disorder, PANSS total score ≥60, including scores ≥4 on at least 2 of 5 items on the PANSS positive subscale, and a CGI-S score of ≥4	N=1,225 1 year	Primary: PANSS total score, PANSS Marder factors, CGI-S, discontinuation rate, adverse events Secondary: Not reported	Primary: In the last observation carried forward analysis, at 1 year, olanzapine was significantly more effective than asenapine in terms of the following outcome measures: PANSS total score, PANSS Marder factors, and CGI-S (P<0.001). However, there were no significant differences between groups when evaluated by an observed cases analysis. Study completion rates were 38% with asenapine and 57% with olanzapine. Discontinuation due to inadequate response occurred in 25% and 14% of patients receiving asenapine and olanzapine, respectively. The incidence of adverse events was comparable between the two groups (60% for asenapine and 61% for olanzapine). Mean weight gain was 0.9 kg with asenapine and 4.2 kg with olanzapine (P<0.0001). Extrapyramidal adverse events were reported by 18% of asenapine-treated patients compared with 8% of patients receiving olanzapine. Secondary: Not reported
Cutler et al[34] Iloperidone 24 mg daily vs ziprasidone 160 mg daily vs	AC, DB, MC, PC, PG, RCT Men and women 18 to 65 years of age diagnosed with acute exacerbations of schizophrenia by	N=593 4 weeks	Primary: Change from baseline in PANSS total scores Secondary: Change from baseline on the PANSS-derived BPRS, PANSS	Primary: The iloperidone and ziprasidone groups achieved significantly greater improvement in PANSS total scores vs those receiving placebo (iloperidone: -12.0, ziprasidone: -12.3, placebo -7.1; P<0.01 and P<0.05, respectively). Secondary: The iloperidone and ziprasidone groups showed significantly greater improvement from baseline to end of study vs placebo in BPRS, PANSS-

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placebo daily	DSM-IV criteria, had BMI 18-35 kg/m^2, CGI-S scores ≥4 at baseline, overall PANSS total scores ≥70 at screening and baseline, a rating of ≥4 (moderate) on at least 2 of the following PANSS Positive Subscale symptoms at screening and baseline: delusions, conceptual disorganization, hallucinations, suspiciousness / persecution		subscales (PANSS-P, PANSS-N, and PANSS-GP), Calgary Depression Scale for Schizophrenia (CDSS), CGI-S, and the Clinical Global Impression of Change Safety endpoints included: Incidence of treatment-emergent adverse events	P, and PANSS-N scores (*P*<0.05 for BPRS, PANSS-N; *P*<0.01 for PANSS-P); no significant difference was observed in reduction of PANSS-GP scores (*P* not reported). Significantly more patients receiving iloperidone (72% [143/200]) than placebo (52% [48/93]) experienced improvement (≥20% reduction from baseline) in PANSS-P scores (*P*=0.005). The iloperidone group showed a significantly greater reduction in CGI-S scores vs placebo (-0.65 and -0.39, respectively; *P*=0.007), as did the ziprasidone group (-0.67; *P*=0.013). Significantly more patients receiving iloperidone (65% [183/283]) than placebo (52% [73/140]) achieved CGI-C improvement (*P*<0.05). Both the iloperidone and the ziprasidone did not demonstrate any improvement in CDSS scores vs placebo. Safety: Most adverse events were mild to moderate. Compared with ziprasidone, iloperidone was associated with lower rates of sedation (13% vs 27%), somnolence (4% vs 6%), EPS (3% vs 9%), akathisia (1% vs 7%), agitation (3% vs 7%), and restlessness (4% vs 5%). However, iloperidone demonstrated higher rates of weight gain (11% vs 5%), tachycardia (9% vs 2%), orthostatic hypotension (7% vs 0), dizziness (17% vs 13%), and nasal congestion (8% vs 3%) compared to ziprasidone. The incidence of clinically relevant changes in laboratory parameters was comparable between iloperidone and ziprasidone including total cholesterol, triglycerides, glucose, and prolactin.
Potkin et al[35] Study 1: Iloperidone 4, 8 or 12 mg daily or haloperidol 15 mg daily vs	3 AC, DB, MC, PC, RCT, Adults aged 18 to 65 years with acute or subacute exacerbation of schizophrenia and PANSS total score	N=1943 6 weeks	Primary: Study 1: Change in PANSS total score Study 2 & 3: Change in BPRS scores Secondary:	Primary: Study 1: PANSS-T scores significantly improved from baseline with, iloperidone 12 mg daily and with haloperidol 15 mg(iloperidone 12 mg: -9.0, haloperidol 15 mg: -13.9; placebo: *P*=0.047 and *P*<0.001, respectively). However, in the iloperidone 4 mg daily, and the iloperidone 8 mg groups (4 mg: -9.0: 8 mg: -7.8, placebo -4.6; *P*=0.097 and *P*=0.047 respectively), PANSS improvements were not significantly different. Study 2: Significant improvement in BPRS scores were demonstrated in

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placebo daily Study 2: iloperidone 4 to 8 mg daily or iloperidone 10 to 16 mg daily or risperidone 4 to 8 mg daily vs placebo daily Study 3: iloperidone 12 to 16 mg daily or iloperidone 20 to 24 mg/day or risperidone 6 to 8 mg daily vs placebo daily	of ≥60 at screening and at baseline		PANSS-P scale, PANSS-N scale, PANSS-GP, BPRS and CGI-S (in studies 2 & 3)	all of iloperidone doses and with risperidone when compared to placebo. The decrease in BRPS-TS for the iloperidone 4 mg to 8 mg dose was -6.2 (*P*=0.012), iloperidone 10 mg/day to 16 mg/day dose was -7.2 (*P*=0.001) and risperidone 4 mg to 8 mg dose was -10.3 (*P*<0.001). Study 3: Significant improvement in BPRS scores were demonstrated with iloperidone 20 mg/day to 24 mg/day (-8.6; *P*=0.010) and risperidone 6 mg to 8 mg (-11.5; *P*<0.001) compared to placebo (-5.0). Improvement in BPRS score for the iloperidone 12 mg/day to 16 mg/day (-7.1; *P*=0.09) group was not significantly different compared to placebo. Secondary: Study 1: Iloperidone 12 mg along with haloperidol 15 mg was significantly more effective than placebo at improving BPRS scores (iloperidone: -6.8, haloperidol: -9.0, placebo: -3.6; *P*=0.042 and *P*<0.001 respectively). Iloperidone 4 mg and 8 mg were not statistically significant in reducing BPRS scores compared to placebo (4 mg: -6.4, 8 mg: -3.8; *P*=0.070 and *P*=0.095 respectively). Study 2: Iloperidone 4 mg to 8 mg significantly improved PANSS-T (-9.5 vs -3.5 with placebo; *P*=0.017), PANSS-P (-3.5 vs -1.6 with placebo; *P*=0.020), PANSS-GP (-4.2 vs -1.1 with placebo; *P*=0.017), and CGI-S (-0.6 vs -0.2 with placebo; *P*=0.003) scores. Iloperidone 10 mg to 16 mg significantly decreased PANSS-T (-11.1 vs -3.5 with placebo; *P*=0.002), PANSS-P (-4.1 vs -1.6 with placebo; *P*=0.002), PANSS-N (-2.4 vs -1.0 with placebo; *P*=0.021), PANSS-GP (-4.8 vs -1.1 with placebo; *P*=0.003), and CGI-S (-0.5 vs -0.2 with placebo; *P*=0.006) scores. Study 3: Iloperidone 12 mg to 16 mg significantly improved CGI-S (-0.6 vs -0.4 with placebo; *P*=0.028) scores, whereas iloperidone 20 mg to 24 mg significantly decreased PANSS-T (-14.0 vs -7.6 with placebo; *P*=0.005), PANSS-P (-5.1 vs -3.1 with placebo; *P*=0.008), PANSS-N (-2.8 vs -3.4 with placebo; *P*=0.023), PANSS-GP (-5.9 vs -2.8 with placebo; *P*=0.007), and CGI-S (-0.6 vs -0.4 with placebo; *P*=0.037) scores.
Citrome et al[36] Iloperidone 4 mg to 8 mg	MA, PH Patients, aged 18	N=3,580 4 to 6 weeks	Primary: PANSS subscales (excitement/hostility	Primary: Compared to placebo, iloperidone 10-16 mg and 20-24 mg groups exhibited improvement from baseline in excitement/hostility scores of the

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daily vs iloperidone 10 mg to 16 mg daily vs iloperidone 20 mg to 24 mg daily vs active controls (haloperidol 15 mg daily, risperidone 4 mg to 8 mg daily, or ziprasidone 160 mg daily) vs placebo	to 65 years, diagnosed with schizophrenia or schizoaffective disorder		, depression/ anxiety, cognition, positive and negative symptoms) Secondary: Not reported	PANSS subscale (*P*<0.001). Compared to placebo, iloperidone 10-16 mg and 20-24 mg groups exhibited improvement from baseline in depression/anxiety scores of the PANSS subscale (*P*<0.05). Compared to placebo, iloperidone 10-16 mg and 20-24 mg groups exhibited improvement from baseline in cognition scores of the PANSS subscale (*P*<0.05). Compared to placebo, iloperidone 10-16 mg and 20-24 mg groups exhibited improvement from baseline in terms of positive scores of the PANSS subscale (*P*<0.05). Compared to placebo, iloperidone 10-16 mg group exhibited a significant improvement from baseline in terms of negative scores of the PANSS subscale (*P*<0.05). Compared to placebo, risperidone group exhibited statistically significant improvements from baseline in all five PANSS subscales (*P*<0.05). Compared to placebo, ziprasidone group exhibited improvements from baseline in the cognition, excitement/hostility, and positive symptom PANSS subscales (*P*<0.05). Secondary: Not reported
Citrome et al[37] Iloperidone 4 mg to 8 mg daily vs iloperidone 10 mg to 16 mg daily vs	MA, PH Patients, aged 18 to 65 years, diagnosed with schizophrenia or schizoaffective disorder	N=2,401 4 to 6 weeks	Primary: Change from baseline in BPRS derived scores, total PANSS scores, PANSS positive, and PANSS negative scores Secondary:	Primary: Compared to placebo, iloperidone 10-16 mg and 20-24 mg groups exhibited improvement from baseline in BPRS derived scores, total PANSS scores, PANSS positive, and PANSS negative scores (*P*<0.05). Compared to placebo, haloperidol, risperidone and ziprasidone treatment groups exhibited improvements from baseline in BPRS derived scores, total PANSS scores, PANSS positive, and PANSS negative scores (*P*<0.05).

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iloperidone 20 mg to 24 mg daily vs active controls (haloperidol 15 mg daily, risperidone 4 mg to 8 mg daily, or ziprasidone 160 mg daily) vs placebo			Not reported	The most commonly reported adverse events with iloperidone which occurred more frequently than with placebo were dizziness, dry mouth, somnolence, nasal congestion, fatigue, sedation, and tachycardia. The NNH value for dizziness in patients receiving iloperidone was calculated as 8. The incidence of extrapyramidal adverse events was comparable to the placebo group. Secondary: Not reported
Kane et al[38] Iloperidone 4-16 mg daily vs haloperidol 5-20 mg daily	MA Adults 18 to 65 years of age diagnosed with schizophrenia or schizoaffective disorder based on DSM-IV criteria, a PANSS score of ≥60, normal vital signs, no contraindication to study medications and an available caregiver to support treatment adherence	N=489 52 weeks (6 week phase, followed by a 46-week phase)	Primary: Time to relapse during long-term phase Secondary: Change in PANSS total score, Brief Psychiatric Rating scale, CGI-C, adverse events, lab tests and 12-lead electrocardiogram	Primary: Relapse rates were similar between the groups with 43.5% in the iloperidone group and 41.2% in the haloperidol group (HR, 1.030; 95% CI, 0.743 to 1.428; *P*=0.8596). The mean time to relapse was not significant with 89.8 days in the iloperidone group compared to 101.8 days in the haloperidol group (*P*=0.8411). Secondary: There was no significant difference between treatment groups in mean change in PANSS total scores (–16.1 for iloperidone vs –17.4 for haloperidol; *P*=0.338). There was no significant difference between treatment groups in changes in Brief Psychiatric Rating scale (–9.0 for iloperidone vs –9.6 for haloperidol; *P*=0.390). Of the patients treated with iloperidone, 65.0% exhibited improvement in CGI-C scores compared to 66.0% treated with haloperidol (*P* value not reported). Overall, 73.3% of patients who received iloperidone experienced at least 1 adverse event compared to 68.6% of patients in the haloperidol group (*P* value not reported).

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				At study end, iloperidone demonstrated significant improvement in overall ratings of EPS (–1.6) compared to haloperidol, which worsened from baseline (0.6; *P*<0.001). Long-term treatment with iloperidone produced slight increases in total cholesterol (–0.26 to 0.89 mg/dL), triglycerides (0.31 to 6.82 mg/dL) and glucose levels (2.66 to 5.80 mg/dL; *P* values not reported). Haloperidol changes from baseline to endpoint were as follows: in total cholesterol (7.44 to 6.95 mg/dL), triglycerides (–0.11 to 12.08 mg/dL) and glucose levels (–0.41 to –0.49 mg/dL; *P* values not reported). Similar changes in QTc prolongation were noted between the groups (*P* value not reported).
Weiden et al[39] Study 1: Iloperidone 4, 8 or 12 mg/day or haloperidol 15 mg daily vs placebo daily Study 2: iloperidone 4 to 8 mg daily or iloperidone 10 to 16 mg daily or risperidone 4 to 8 mg daily vs placebo daily Study 3: iloperidone 12 to 16 mg daily or	MA Adults aged 18 to 65 years with acute or subacute exacerbation of schizophrenia and PANSS total score of ≥60 at screening and at baseline This trial reported the safety results for the trial by Potkin et al.	N=1553 6 weeks	Primary: Short term safety of iloperidone including dose related adverse events, QT prolongation, weight gain, and changes in laboratory values. Secondary: Not reported	Primary: Across all doses of iloperidone the most common dose related adverse events were dry mouth, dizziness, somnolence, and dyspepsia. Extrapyramidal disorders, tremor, akathisia, dystonia and somnolence also occurred with iloperidone; however, these symptoms occurred more often in the haloperidol group and the risperidone group. Other events that occurred more often in the risperidone group than the iloperidone groups included akathisia, tremor, and somnolence. QTc prolongation increased in all iloperidone groups. QTcF increased from baseline to 2.9 msec with iloperidone 4 mg/day to 8 mg/day, 3.9 msec with iloperidone 10 mg/day to 16 mg/day, and 9.1 msec with iloperidone 20 mg/day to 24 mg/day (all *P*<0.05). Patients in the haloperidol group also demonstrated a significant increase in QTcF from baseline of 5.0 msec (*P*<0.05); however, patients in the risperidone groups showed a non-significant increase from baseline in QTcF interval of 0.6 msec (*P*= not significant) Weight gain experienced with iloperidone was statistically significant compared to placebo with an average increase of 1.5 kg with 4 mg/day to 8 mg/d, 2.1 kg with 10 mg/day to 16 mg/day and 1.7 kg with 20 mg/day to 24 mg/day (all *P*<0.05). In the risperidone group, the average weight gain was 1.5 kg (*P*=0.05 vs. placebo). The only group that did not experience weight gain was haloperidol (-0.4 kg; *P* value not reported).

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iloperidone 20 to 24 mg daily or risperidone 6 to 8 mg daily vs placebo daily				Similar changes were seen in all treatment groups in blood glucose levels, total cholesterol, and triglycerides. In the iloperidone group prolactin levels were generally decreased after treatment; while the haloperidol and risperidone groups demonstrated significantly increased levels of prolactin. Secondary: Not reported
Nakamura et al[40] Lurasidone 80 mg QD in the morning with or immediately following breakfast vs placebo QD in the morning with or immediately following breakfast	DB, MC, PG, PC RCT Patients aged 18-64 years who were hospitalized for an acute exacerbation of schizophrenia, with a minimum illness duration of 1 year, Brief psychiatric Rating Scale (BPRSd) total score (extracted from the positive and negative syndrome scale (PANSS) of at least 42 with a score of at least 4 on 2 or more positive symptom items, a Clinical Global Impressions-Severity of Illness Scale (CGI-S) score ≥4, a Simpson-Angus	N=180 6 weeks (patients were hospitalized until at least day 28)	Primary: BPRSd extracted from the PANSS Secondary: PANSS total, PANSS positive symptoms, PANSS negative symptoms, PANSS general psychopathology, PANSS cognitive, CGI-S, Montgomery-Asberg Depression Rating Scale (MADRS), adverse events	Primary: Patients in the lurasidone group experienced a statistically significant improvement from baseline in the BPRSd score over the placebo group (8.9 vs. -4.2; *P*=0.0118). Secondary: Patients in the lurasidone group experienced a statistically significant improvement in total PANSS score over placebo (-14.1 vs. -5.5; *P*=0.0040). Patients in the lurasidone group experienced a statistically significant improvement in positive PANSS score over placebo (-4.3 vs. -1.7; *P*=0.0060). Patients in the lurasidone group experienced a statistically significant improvement in negative PANSS score over placebo (-2.9 vs. -1.3; *P*=0.0250). Patients in the lurasidone group experienced a statistically significant improvement in general psychopathology PANSS score over placebo (-7.0 vs. -2.7; *P*=0.0061). Patients in the lurasidone group experienced a statistically significant improvement in cognitive PANSS score over placebo (-2.1 vs. -0.5; *P*=0.0015). Patients in the lurasidone group experienced a statistically significant improvement in CGI-S score over placebo (-0.6 vs. -0.2; *P*=0.0072). Patients in the lurasidone group experienced a statistically significant

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	Scale (SAS) score of <2 and an Abnormal Involuntary Movement Scale (AIMS) score of <3			improvement in MADRS score over placebo (-2.9 vs. -0.1; *P*=0.0187). The change from baseline SAS score was not statistically different between the lurasidone and placebo groups (0.2 vs. 0.1; *P*=0.58). The change from baseline BAS score was statistically different between the lurasidone and placebo groups with more patients in the lurasidone group experiencing akathisia (0.2 vs. -0.1; *P*=0.03). The change from baseline AIMS score was not statistically different between the lurasidone and placebo groups (0.3 vs. 0.5; *P*=0.61). Treatment with lurasidone was not associated with any significant treatment-emergent ECG abnormalities. There were no clinically significant changes in heart rate of blood pressure. The incidence of clinically significant (>7% increase from baseline) weight gain was slightly lower in the lurasidone group versus placebo (6.7% vs. 7.8%, *P* value not reported). There were no significant differences between lurasidone and placebo with regard to cholesterol, triglycerides, high density lipoprotein, or fasting blood glucose (no *P* value given). There was a statistically significant increase in glycosylated hemoglobin A1C in the lurasidone group versus placebo (0.1% vs. 0.0%; *P*<0.05). Treatment with lurasidone was associated with a statistically significant increase in prolactin levels over placebo (2.4 vs.-0.3 ng/mL; *P*< 0.05).
Harvey et al[41] Lurasidone 120 mg once daily vs ziprasidone 80 mg twice daily	DB, RCT Patients, aged 18 to 70 years, with chronic schizophrenia or schizoaffective disorder, without hospitalization or	N=301 21 days	Primary: MATRICS Consensus Cognitive Battery (MCCB), Schizophrenia Cognition Rating Scale (SCoRS), Wechsler Memory	Primary: There was no statistically significant difference between treatment groups in changes from baseline on the composite MCCB score (*P*=0.73). There was no statistically significant difference between treatment groups in changes from baseline in SCoRS scores (*P*=0.056). Compared with baseline, lurasidone therapy was associated with significant improvements in MCCB scores, BACS Symbol Coding scores,

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	acute exacerbation of psychosis in the prior 3 months		Scale (WMS), Neuropsychological Assessment Battery (NAB) Secondary: Not reported	Trail Making Part A scores, and the WMS spatial span scores (P<0.05). Compared with baseline, ziprasidone therapy was associated with significant improvements in BACS Symbol Coding scores, animal naming, NAM Mazes, and Trail Making Part A scores (P<0.05). Secondary: Not reported
Potkin et al[42] Lurasidone 120 mg once daily vs ziprasidone 80 mg twice daily	DB, RCT Patients, aged 18 to 70 years, with chronic schizophrenia or schizoaffective disorder, without hospitalization or acute exacerbation of psychosis in the prior 3 months	N=301 21 days	Primary: PANSS negative, PANSS positive, PANSS total, PANSS general psychopathology, CGI scores Secondary: Not reported	Primary: Lurasidone was associated with significantly greater reduction in PANSS negative symptom scores compared to ziprasidone (-1.3 vs. -0.6; P=0.046). There were no statistically significant differences between the two groups in the reduction from baseline in PANSS total, PANSS positive symptom, PANSS general psychopathology, or CGI-S scores (P>0.05). The percentage of patients who discontinued from the study due to any reason was comparable between the lurasidone and ziprasidone groups (32.5% vs. 30.7%). The discontinuation rate due to adverse events was also similar in the lurasidone and ziprasidone groups (10.4% vs. 11.1%). Treatment with lurasidone and ziprasidone was associated with a small endpoint reduction in median weight (-0.65 kg vs. -0.35 kg) and median total cholesterol (-6.4 mg/dl vs. -44 mg/dl). Neither of the two groups experienced a change in median triglyceride levels. Likewise, neither of the two groups was associated with a clinically significant ECG abnormality. Extrapyramidal adverse events were noted in 3.3% of patients receiving lurasidone and 1.3% of patients in the ziprasidone group. Secondary: Not reported
Meltzer et al[43] Lurasidone 40 mg once daily vs	DB, MC, PC, RCT Patients aged 18-75 years who had	N=478 6 weeks	Primary: Change in PANSS total score at 6 weeks	Primary: All active treatment groups experienced a statistically significant improvement in the primary endpoint compared to the placebo group (P<0.05).

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lurasidone 120 mg once daily vs olanzapine 15 mg once daily vs placebo once daily	experienced an acute exacerbation of psychotic symptoms ≤2 months and had marked deterioration of function from baseline or patients who had been hospitalized for the treatment of an acute psychotic exacerbation for ≤2 weeks before screening, with a minimum illness duration of 1 year, PANSS total score of ≥80, with a score of at least 4 on 2 or more of select PANSS items, score of ≥4 on the SGI-S at screening		Secondary: PANSS positive symptoms, PANSS negative symptoms, PANSS, general psychopathology, CGI-S, MADRS, PANSS response rate (≥20% improvement from baseline) at week-6, adverse events	Secondary: All active treatment groups experienced a statistically significant improvement in PANSS positive symptoms compared to the placebo group (*P*<0.05). All active treatment groups experienced a statistically significant improvement in PANSS negative symptoms compared to the placebo group (*P*<0.05). All active treatment groups experienced a statistically significant improvement in PANSS general psychopathology symptoms, compared to the placebo group (*P*<0.05). All active treatment groups experienced a statistically significant improvement in CGI-S compared to the placebo group (*P*<0.05). Compared to placebo, only patients receiving olanzapine experienced a statistically significant improvement in MADRS (*P*=0.003). Compared to placebo, significantly more patients in the olanzapine group achieved PANSS response (*P*<0.001). While more patients in the lurasidone groups experienced response to therapy, statistically significant difference from placebo was not reached. The percentage of patients experiencing at least one treatment emergent adverse event was 78.9% with lurasidone, 82% with olanzapine and 72.4% with placebo. The most frequently reported adverse events associated with lurasidone therapy were headache, akathisia, somnolence, insomnia, and sedation. Change in EPS, measured by SAS, BAS, and AIMS was absent or mild in lurasidone-treated patients. ECG abnormalities were not observed.
Keks et al[44] Olanzapine oral tablet 5 mg once daily (titrated to optimal dose up to 20 mg daily) vs	FD, MC, OL, RCT, Schizophrenic or schizoaffective adult patients with a PANSS score ≥50 at	N=618 12 months Part 1: 13 weeks	Primary: Change in PANSS total score at 13 weeks to demonstrate non-inferiority	Primary: Changes in PANSS total scores at the end of 13 weeks were as follows: –16.9 (SD, 15.5) for risperidone and –17.8 (SD, 15.4) for the olanzapine group (95% CI, –2.7 to 3.0; *P*<0.0001). The upper limit of the PANSS 95% CI was 3.0, well below the non-inferiority margin of 8.0, demonstrating that risperidone was at least as effective as olanzapine.

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risperidone long-acting injection (25 or 50 mg every 2 weeks)	randomization, a BMI ≤40, hospitalized or required medical intervention for acute exacerbation of psychotic symptoms within 2 months of screening and who had at least 1 other exacerbation during the last 2 years prior to screening that required medical intervention and provided informed consent	Part 2: 40 weeks	Secondary: Change in PANSS total score at 12 months, changes in PANSS factor scores, changes in CGI-S scores and Wisconsin Quality of Life Index, clinical improvement (20% minimum reduction in PANSS), and time to significant deterioration in psychotic condition and adverse events	Secondary: Both treatment groups demonstrated significant improvements in PANSS total and factor scores at month 12 and at end-point (*P*<0.0001 for all measures). Patients in the risperidone group experienced a significantly greater improvement on one PANSS factor score (disorganized thoughts) compared to oral olanzapine (*P*<0.05); however, significantly greater improvement in anxiety/depression was seen in the olanzapine group (*P*<0.05). Both treatment groups demonstrated similar reductions in CGI-S scores (*P* value not reported). Both treatment groups demonstrated similar mean scores on the Wisconsin Quality of Life Index (*P* value not reported). Significantly more patients in the risperidone group achieved clinical improvement compared to the olanzapine group (91% vs 79%, respectively; *P*<0.001) at 12 months; however, at study endpoint, the treatment groups were not statistically different (79% vs 73%, respectively; *P*=0.057). Time to first deterioration was not significantly different (HR, 1.38; 95% CI, 0.82 to 2.33). Reports of EPS were more frequent in the risperidone group (25.0%) compared to the olanzapine group (15.0%; *P*<0.05). Weight gain was significantly higher in the olanzapine group compared to the risperidone group (4.0 kg vs 1.7 kg; *P*<0.05).
Lauriello et al[45] Olanzapine pamoate monohydrate (OPM) 210 mg every 2 weeks vs.	DB, MC, PC, PG, RCT Patients 18 to 75 years of age with acute schizophrenia, according to DSM-	N=404 (randomized to DB treatment) 8 weeks	Primary: Change from baseline to end point (based on the LOCF approach) in the PANSS total score after 8 weeks of treatment	Primary: At endpoint, improvement in total PANSS total scores for each of the active treatment groups was significantly greater than that for placebo (210 mg/2 weeks, -22.5 [SD 21.8], *P*<0.001; 300 mg/2 weeks, -26.3 [SD 24.9], *P*<0.001; 405 mg/4 weeks, -22.6 [SD 22.1], *P*<0.001). No statistically significant differences were observed among the 3 OPM treatment groups at end point.

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olanzapine pamoate monohydrate 300 mg every 2 weeks vs. olanzapine pamoate monohydrate 405 mg every 4 weeks vs. placebo every 2 weeks No oral antipsychotic supplementation was allowed throughout the trial	IV or DSM-IV-TR criteria, with a Positive and Negative Syndrome Scale (PANSS)-derived Brief Psychiatric Rating Scale (BPRS) total score ≥30 at baseline For patients treated previously with a depot antipsychotic, the last injection must have been received at least 2 weeks or 1 injection interval, whichever was longer, before DB treatment Patients who were randomly assigned to 405 mg/4 weeks OPM received a placebo injection at the 2-week interval between their active study drug injections, and patients randomly assigned to placebo received placebo injections every 2 weeks		Secondary: Change from baseline to end point (based on the LOCF approach) in the PANSS positive, negative, and general psycho- pathology subscales, PANSS-derived BPRS, and CGI-Severity of Illness scale (CGI-S) after 8 weeks of treatment, safety Response was defined as a ≥40% improve-ment in PANSS total score	Secondary: All 3 OPM treatment groups showed significantly greater decreases in PANSS positive, negative, and general psychopathology symptom subscales (all *P*<0.001), PANSS-derived BPRS total (all *P*<0.001), and CGI-S (all *P*<0.05) scores relative to placebo. The response rates were significantly higher for all 3 OPM dosage groups (210 mg/2 weeks, 47.2% [*P*<0.001]; 300 mg/2 weeks, 48.0% [*P*<0.001]; and 405 mg/4 weeks, 40.0% [*P*=0.003]) relative to placebo (20.4%). 19 patients (4.7%) experienced serious adverse events (210 mg/2 weeks, N=6; 300 mg/2 weeks, N=5; 405 mg/4 weeks, N=3; placebo, N=5); no deaths were reported. Sedation and increased appetite were more frequent in the 300 mg/2 weeks group than with placebo (*P*<0.05). Mean baseline-to-end point changes in fasting glucose did not differ significantly among study groups. Mean baseline-to-end point changes in fasting total cholesterol differed significantly among all groups (210 mg/2 weeks, 8.2 mg/dL, *P*=0.004; 300 mg/2 weeks, 5.5 mg/dL, *P*=0.015; 405 mg/4 weeks, 10.4 mg/dL, *P*<0.001 vs. placebo, -7.0 mg/dL). Mean baseline-to-end point changes in fasting triglycerides differed significantly among some groups (210 mg/2 weeks, 26.3 mg/dL, *P*=0.016; 405 mg/4 weeks, 30.3 mg/dL, *P*<0.016 vs. placebo, -9.4 mg/dL). A significantly greater percentage of patients in the 210 mg/2 weeks and 300 mg/2 weeks OPM groups experienced changes from normal to high levels of triglycerides relative to placebo (*P*<0.05). Mean baseline-to-end point weight gain was significantly greater for the OPM groups relative to placebo (3.2-4.8 kg vs. 0.3 kg; *P*≤0.001). The incidence of weight gain ≥7% of baseline was significantly greater in the OPM groups (210 mg/2 weeks, 23.6%, *P*=0.046; 300 mg/2 weeks,

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				35.4%, *P*<0.001; 405 mg/4 weeks, 27.0%, *P*=0.012) vs. placebo (12.4%). None of the baseline-to-end point changes in the scales used to measure treatment-emergent extrapyramidal symptoms were either clinically or statistically significant.
Ascher-Svanum et al[46] Olanzapine pamoate monohydrate (OPM) 210 mg every 2 weeks vs. olanzapine pamoate monohydrate 300 mg every 2 weeks vs. olanzapine pamoate monohydrate 405 mg every 4 weeks vs. placebo every 2 weeks No oral antipsychotic supplementation was allowed throughout the trial	PH of study by Lauriello et al Patients 18 to 75 years of age with acute schizophrenia, according to DSM-IV or DSM-IV-TR criteria, with a Positive and Negative Syndrome Scale (PANSS)-derived Brief Psychiatric Rating Scale (BPRS) total score ≥30 at baseline	N=233 8 weeks	Primary: Early responder (>30% improvement in PANSS total score at week-4), later responder (>40% improvement in PANSS total score at week-8), discontinuation rate, SF-36, Quality of Life Scale (QLS) Secondary: Not reported	Primary: At week-4, 59% of patients met the study criteria for early response, while, 41% were classified as early non-responders. Of the patients who were early non-responders at 4 weeks, 80% were classified as later non-responders at week-8, compared with 22% of patients previously categorized as early responders. Early responders exhibited significantly greater improvement in PANSS total score from baseline at every time point, compared to early non-responders (P<0.001). By week-8, early responders were associated with twice the reduction in PANSS scores compared to early non-responders. For all PANSS subscales, early responders exhibited significantly greater improvement from baseline compared to early non-responders (*P*<0.001). Response at week-4 predicted response at week-8, with a sensitivity of 84.9% and specificity of 72%. Rates of study discontinuation for any reason were higher for early non-responders compared to early responders (25% vs. 17.5%; *P*=0.007). Patients' sense of health status also improved significantly more in patients who were early responders verse early non-responders, as evidenced by the following SF-36 subscale scores: mental component summary (*P*=0.01), mental health (*P*=0.004), and social functioning (*P*=0.002). Early responders had significantly greater improvement than early non-responders in the total QLS score as well as all of its subscales (*P*<0.05). Secondary: Not reported
Kane et al[47] Olanzapine pamoate monohydrate (OPM) 405 mg every 4 weeks (medium dose group)	AC, DB, MC, PG, RCT Patients 18 to 75 years of age with a DSM-IV or DSM-IV-	N=1,065 (randomized to DB treatment) 24 weeks	Primary: Rate and time to psychotic exacerbation (defined as an increase in any	Primary: Time to exacerbation was longer for the OPM 150 mg/2 weeks, 405 mg/4 weeks and 300 mg/2 weeks groups relative to OPM 45 mg every 4 weeks group (*P*<0.01). There were no significant differences among the therapeutically dosed

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vs. olanzapine pamoate monohydrate 300 mg every 2 weeks (high dose group) vs. olanzapine pamoate monohydrate 150 mg every 2 weeks (low dose group) vs. olanzapine pamoate monohydrate 45 mg every 4 weeks (very low dose reference group) vs. olanzapine (oral) 10, 15, or 20 mg/day (assigned fixed dose was identical to that which achieved stabilization in a 4 to 8 week open-label period prior to randomization) No oral antipsychotic supplementation was allowed throughout the trial	TR diagnosis of schizophrenia, clinically stable (outpatient status for at least 4 weeks before study onset), with a Brief Psychiatric Rating Scale (BPRS) positive symptom subscale score ≤4 (range: 1-7) on each of the following items: conceptual disorganization, suspiciousness, hallucinatory behavior, unusual thought content After randomization, patients entered a 4-week open-label phase, switching from their previous antipsychotic to oral olanzapine monotherapy (10, 15, or 20 mg/day) and were required to demonstrate maintenance of clinical stability. For patients treated previously with a		BPRS positive symptom score >4, with an absolute increase ≥2 for a specific item or an absolute increase ≥4 on the positive symptom subscale), or hospitalization Secondary: Symptom severity, assessed by the PANSS, BPRS and CGI-S scores, safety	groups except for a shorter time to exacerbation in the “low dose” OPM group vs. the “high dose” (*P*=0.005) and oral olanzapine (*P*=0.004) groups. OPM 150 mg/2 weeks, 405 mg/4 weeks and 300 mg/2 weeks dose groups had demonstrated significantly greater decreases in time to exacerbation compared to the very low dose reference group (*P* value not reported) At 24 weeks, 93% of patients randomized to oral olanzapine therapy remained free of exacerbation, compared with 69%, 84%, 90%, and 95% of the groups receiving OPM 45 mg every 4 weeks, OPM 150 mg every 2 weeks, OPM 405 mg every 4 weeks and OPM 300 mg every 2 weeks, respectively (*P* value not reported). No significant differences in exacerbation rates were detected between the pooled 2-week (high and low doses combined) and therapeutic 4 week (medium dose) regimens, between the pooled 2-week regimen and the oral formulation, or between the therapeutic 4-week regimen and the oral formulation; all comparisons met criteria for noninferiority (*P*>0.05). Secondary: Patients randomized to the olanzapine pamoate monohydrate 150 mg/2 weeks, 405 mg/4 weeks and 300 mg/2 weeks dose groups experienced significantly improved PANSS scores from baseline compared to the very low dose reference group (*P*<0.001). Patients randomized to the OPM 150 mg/2 weeks, 405 mg/4 weeks and 300 mg/2 weeks dose groups experienced significantly improved PANSS scores, BPRS scores and CGI-S scores from baseline compared to the very low dose reference group (*P*<0.01). There were no statistically significant differences between the OPM 300 mg/2 weeks dose group and patients receiving oral olanzapine therapy in the total PANSS, BPRS and CGI-S total scores (*P*>0.05). OPM 150 mg/2 weeks, 405 mg/4 weeks and 300 mg/2 weeks groups achieved similar improvement in CGI-S total scores as the oral

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	depot antipsychotic, the last injection must have been received at least 2 weeks or 1 injection interval (4 weeks for injectable risperidone), whichever was longer, before DB treatment			olanzapine groups. The most common treatment-emergent adverse events were insomnia, weight gain, anxiety, and somnolence. The incidence of weight gain ≥7% from the time of randomization to endpoint in either the combined 2-week group (19%; *P*=0.42) or the medium 4-week dose group (15%; *P*=0.05) did not differ significantly from the oral olanzapine group (21%). The incidence of such weight gain was higher in the high dose (21%; *P*=0.004) and low dose (16%; *P*=0.05) groups relative to the very low dose reference group (8%). The very low dose reference group showed a greater mean decrease in total (-0.37 mmol/l [SD=0.80]) and low-density lipoprotein cholesterol (-0.32 mmol/l [SD=0.68]) relative to the other groups (all *P*<0.05). The high dose group exhibited a mean increase in prolactin (3.57 µg/l [SD=33.77]), whereas the other groups showed a decrease (all *P*<0.05). No significant between-group differences were observed for baseline-to-end point changes in fasting triglyceride levels, plasma glucose or EPS measurements.
Hill et al[48] Olanzapine pamoate monohydrate (OPM) 405 mg every 4 weeks (medium dose group) vs. olanzapine pamoate monohydrate 300 mg every 2 weeks (high dose group) vs. olanzapine pamoate	PH of the study by Kane et al Patients 18 to 75 years of age with a DSM-IV or DSM-IV-TR diagnosis of schizophrenia, clinically stable (outpatient status for at least 4 weeks before study onset), with a Brief Psychiatric Rating Scale (BPRS) positive symptom	N=599 24 weeks	Primary: PANSS total score, relapse rate, discontinuation rate, adverse events Secondary: Not reported	Primary: PANSS total scores were significantly improved from baseline with the high dose group compared to patients receiving low-dose OPM (ES, 0.356; *P*<0.01). Dose related effects were also seen in terms of relapse rate (low: 16%, medium: 10%, high: 5%). The high dose group was associated with a significantly smaller relapse rate compared to the low dose group (*P*=0.003; NNT=9). The following were all-cause discontinuation rates among the three groups (low: 36%, medium: 30%, high: 24%). The high dose group was associated with a significantly lower discontinuation rate compared to the low dose group (*P*=0.037; NNT= 9). Like-wise the rate of discontinuation due to efficacy-related reasons was dose-related (low: 20%, medium: 14%, high: 6%; *P*<0.001). Time to all-cause discontinuation (*P*=0.035)

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monohydrate 150 mg every 2 weeks (low dose group)	subscale score ≤4 (range: 1-7) on each of the following items: conceptual disorganization, suspiciousness, hallucinatory behavior, unusual thought content			and time to relapse (*P*=0.005) were also significantly related to dose. Weight gain was significantly related to dose (low: 0.67 kg, medium: 0.89 kg, high: 1.70 kg). The high dose group was associated with significantly greater weight gain compared to the low dose group (*P*=0.024). The following adverse events were also significantly related to dose: prolactin level, triglycerides, and high-density lipoprotein cholesterol level. For all of the above, the high dose group experienced significantly greater changes from baseline compared to the low dose group (*P*<0.05). Secondary: Not reported
Hough et al[49] Paliperidone palmitate 39 mg vs paliperidone palmitate 78 mg vs paliperidone palmitate 156 mg vs placebo The first two intramuscular injections on days 1 and 8 of the transition phase were 78 mg. Three adjustable doses of 39, 78, or 156 mg were administered every 4 weeks during the rest of the transition phase and the first	DB, MC, PC, PG, RCT Patients (18 to 65 years of age and BMI >15.0 kg/m^2) with schizophrenia according to DSM-IV-TR criteria for at least 1 year before screening and had a PANSS total score at screening and baseline of <120	N=410 9 weeks OL transition phase and 24 weeks OL maintenance phase and variable duration of DB recurrence prevention phase for patients who were clinically stable on a fixed dose for the last 12 weeks of the maintenance phase	Primary: Time between randomization to treatment in the DB recurrence prevention phase and the first documentation of a recurrence event during the DB phase (hospitalization, deliberate self-injury or violent behavior, suicidal or homicidal ideation, and certain predefined PANSS scores) Secondary: Adverse events, laboratory tests, investigators' evaluation of the	Primary: An independent Data Monitoring Committee recommended that the study be terminated early because of the significant (*P*<0.0001) interim efficacy results for time-to-recurrence per interim ITT analysis. Note: results were only graphically presented; no raw data reported. The results of the time-to-recurrence analysis based on the data at the conclusion of the DB phase were reportedly consistent with the results based on the interim data (details not reported). Secondary: The overall frequency of adverse events occurring in ≥5% of patients in any group was comparable across all treatment groups and placebo with the exception of weight increase (7% active drug overall vs 1% placebo). Local injection-site tolerability was good as reported by investigators. Patients' evaluations of injection site pain based on a visual analog scale showed a decrease in the intensity of pain at the injection site from DB baseline to endpoint for both active drug and placebo groups.

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12 weeks of the maintenance phase. The dose of paliperidone palmitate remained fixed for the last 12 weeks of the maintenance phase and the DB, PC recurrence prevention phase.			injection site, and patients' evaluations of pain at the injection site	
Kramer et al[50] paliperidone palmitate 78 mg vs paliperidone palmitate 156 mg vs placebo	DB, PC, RCT Patients, 18 to 65 years of age, with schizophrenia and PANSS scores between 60 and 120	N=197 9 weeks	Primary: Change in PANSS total score Secondary: PANSS Marder factors, 30% improvement in PANSS score, adverse events	Primary: Both paliperidone doses were associated with significant improvement in PANSS total scores compared to placebo ($P \leq 0.001$). Secondary: Both paliperidone doses were associated with significant improvement in all PANSS Marder factor subscale scores, except the uncontrolled hostility/excitement) compared to placebo ($P<0.05$). Only paliperidone 156 mg dose was associated with significant improvement from baseline in the hostility/excitement scores ($P=0.006$). At least 30% improvement from baseline in the PANSS total score was reached by 67% and 63% of patients receiving paliperidone 78 mg and 156 mg, respectively compared with 14% in the placebo group. Less than 30% improvement was experienced by 67%, 63%, and 86% of patients in the paliperidone 78 mg, 156 mg, and placebo groups ($P<0.01$). Fewer paliperidone-treated patients (2%) discontinued for treatment-emergent adverse events vs. placebo-treated (10%). Rates of treatment-emergent extrapyramidal syndrome-related adverse events were comparable between active treatment and placebo, with the exception of parkinsonism-related disorders (78 mg: 5%, 156 mg: 8%, placebo: 1%).
Nasrallah et al[51] Paliperidone palmitate 39 mg vs	DB, MC, PC, PG, RCT Patients (18 years of age and older	N=518 13 weeks	Primary: Change from baseline to end point based on the LOCF approach in	Primary: At endpoint (LOCF), improvement in total PANSS total scores for each of the active treatment groups was significantly greater than that for placebo (39 mg; $P=0.02$, 78 mg; $P=0.02$, 156 mg; $P<0.001$). Note: results were only graphically presented; no raw data reported.

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paliperidone palmitate 78 mg vs paliperidone palmitate 156 mg vs placebo Fixed doses or placebo were administered by intramuscular injection on days 1, 8, 36, and 64 of the DB treatment period.	and BMI >15.0 kg/m^2) with schizophrenia according to DSM-IV-TR criteria for at least 1 year before screening and had a PANSS total score at screening and baseline of 70 to 120 inclusive		the PANSS total score Secondary: PSP scale, CGI-S scales, safety assessments (adverse events, EPS rating scales [AIMS, BARS, and SAS]), clinical laboratory tests (including plasma prolactin levels), investigators' evaluation of the injection site, and patients' evaluations of pain at the injection site and of the injection	Secondary: Each active treatment group showed significant improvement (*P*<0.01) compared with placebo for change from baseline to end point (LOCF) in CGI-S score. Note: results were only graphically presented; no raw data reported. No outcomes on the PSP scale were reported. The overall frequency of adverse events occurring in at least 5% of patients in any group was comparable across all treatment groups and placebo with the following exceptions: weight increase (4% active drug overall vs 0% placebo), and somnolence (4% active drug overall vs 1% placebo). There were no clinically relevant differences between the active treatment groups and placebo in BARS, SAS, or AIMS scores. Parkinsonism was the most frequent category of EPS-related adverse events and reported at a similar rate for overall paliperidone palmitate groups (6%) and placebo (5%). Increases in prolactin levels were observed with greater frequency in patients who received active drug, compared with placebo, and in a dose-dependent manner (*P* not reported). Local injection-site tolerability was good as reported by investigators (no outcomes of patient-initiated evaluations were reported).
Pandina et al[52] Paliperidone palmitate 39 mg vs paliperidone palmitate 156 mg vs	DB, PC, PG, RCT Patients (18 years of age and older and BMI >17 and <40 kg/m^2) with schizophrenia according to DSM-IV criteria for at least 1 year before screening and had	N=652 13 weeks	Primary: Change from baseline to endpoint (day 92 or the last postbaseline assessment in the DB period) in PANSS total score Secondary:	Primary: Mean change from baseline in total PANSS total scores for each of the active treatment groups was significantly greater compared with placebo at endpoint; response was dose related. Estimated effect sizes (vs placebo) were: 0.26 (39 mg), 0.47 (156 mg), and 0.55 (234 mg; *P* not reported). Note: results were only graphically presented; no raw data reported. Secondary: PSP scores increased significantly compared with placebo from baseline

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paliperidone palmitate 234 mg vs placebo Subjects randomized to active treatment groups were given an initial loading dose of 234 mg paliperidone palmitate on day 1; subjects randomized to placebo received a placebo injection on day 1 (both injections administered in deltoid muscle).	a PANSS total score at screening of 70 to 120 (inclusive) and at DB baseline of 60 to 120 (inclusive); patients were hospitalized from days 1-8		Score changes in PSP scale, CGI-S scale, PANSS factor scores, PANSS subscales, and onset of effect, adverse events, EPS rating scales, clinical laboratory tests, and investigators' evaluation of the injection site	to endpoint in the 156 and 234 mg treatment groups (156 mg, +6.1; *P*<0.05, 234 mg, +8.3; *P*≤0.001). CGI-S scores decreased significantly compared with placebo from baseline to endpoint in the 156 and 234 mg treatment groups (156 mg, -1.0; *P*<0.05, 234 mg, -1.0; *P*≤0.001). PANSS scores decreased significantly compared with placebo from baseline to endpoint in the following groups and subscales: • Positive symptom subscale: 156 mg (-4.1; *P*≤0.001), 234 mg (-4.4; *P*≤0.001). • Negative symptom subscale: 156 mg (-1.9; *P*<0.05), 234 mg (-2.5; *P*≤0.001). • General psychopathology subscale: 39 mg (-4.6; *P*<0.05), 156 mg (-5.6; *P*≤0.001), 234 mg (-6.4; *P*≤0.001). The overall frequency of adverse events occurring in patients in any group was comparable across all active treatment (60%-63%) and placebo (65%) groups. Among the most common treatment-emergent adverse events that occurred >1% more frequently in all 3 active treatment groups combined than in the placebo group were: injection site pain (8% vs 4%), dizziness (2% vs 1%), sedation (2% vs 1%), pain in extremity (2% vs 0%), and myalgia (1% vs 0%). Akathisia was the most frequently reported EPS-related adverse event across all groups (placebo, 5%; 39 mg, 1%; 156 mg, 5%; 234 mg, 6%). Prolactin levels increased from baseline to endpoint in all 3 active treatment groups (specific data per group not reported); glucose, insulin, serum lipid, liver and renal function tests showed no clinically relevant changes. Injection site tolerability was good; induration, swelling, and redness occurred in ≤10% of patients across the 4 treatment groups and were generally considered mild.
Li et al[53]	OL, PG	N=452	Primary:	Primary:

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Paliperidone palmitate 150 mg on day-1, 100 mg on day-8, and 50 mg, 100 mg, or 150 mg once monthly injection vs risperidone 25 mg, 37.5 mg, or 50 mg biweekly injection	Patients, 18 years of age and older, diagnosed with schizophrenia, with PANSS total score between 60 and 120	13 weeks	Change from baseline in PANSS total scores Secondary: CGI-S, Personal and Social Performance Scale (PSP), PANSS subscales, PANSS Marder Factors	There was no significant difference between treatment groups in the change from baseline in mean PANSS total scores (difference, -2.3; 95%CI, -5.20 to 0.63). Secondary: There was no significant difference between treatment groups in the change from baseline in mean CGI-S scores (difference, -0.1; 95%CI, -0.33 to 0.10). There was no significant difference between treatment groups in the change from baseline in mean PSP scores (difference, 0.5; 95%CI, -2.14 to 3.12). There were no significant differences between treatment groups in the change from baseline in PANSS negative symptoms (difference, -0.0; 95%CI, --0.95 to 0.93) and general psychopathology subscale scores (difference, -0.9; 95%CI, -2.30 to 0.55). In addition, there were no significant differences between the groups in the PANSS Marder factor negative symptom, disorganized thoughts, and uncontrolled excitement/hostility scores. Risperidone was associated with significantly greater reduction in PANSS positive symptoms (difference, -1.2; 95%CI, -2.14 to -0.21), PANSS Marder positive symptoms (difference, -1.4; 95%CI, -2.61 to -0.24), and PANSS Marder anxiety/depression (difference, -0.1; 95%CI, -0.54 to -0.34) subscale scores compared to paliperidone. The incidence of treatment-emergent adverse events was comparable in the paliperidone and risperidone treatment groups (73.4% vs. 74.9%). Discontinuation rate due to adverse events was 3.5% with paliperidone and 4% with risperidone injection. A greater percentage of patients required the use of antiparkinson medication in the risperidone group (46.2%) compared to patients in the paliperidone group (31.4%). The incidence of prolactin-related adverse events was similar with paliperidone and risperidone (8.3% vs. 9%, respectively).

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				The two groups exhibited similar weight gain from baseline, 1.5 kg. There were no serious cardiac adverse events reported in the study.
Pandina et al[54] Paliperidone palmitate 150 mg on day-1, 100 mg on day-8, and 50 mg or 100 mg on day-36, and 25-150 mg injection on day-64 vs risperidone 25 mg on day-8 and -22, 25-37.5 mg on day-36 and -50, and 25-50 mg on day-64 and-78 long-acting injection	DB, DD, MC, PG, RCT Patients, aged 18 years and older, diagnosed with Schizophrenia, with PANSS score between 60 and120	N=1,220 13 weeks	Primary: Change from baseline in PANSS total score Secondary: CGI-S, PSP, PANSS subscale scores, Schedule for Deficit Syndrome (SDS), adverse events	Primary: The change in PANSS total scores favored paliperidone treatment over risperidone; however, the difference between the two groups was not statistically significant (difference, 1.2; 95%CI, -0.78 to 3.16). Secondary: There was no statistically significant difference between the two groups in the change in PSP scores from baseline (difference, 0.2; 95%CI, -1.22 to 1.69). There was no statistically significant difference between the two groups in the change in CGI-S scores from baseline (difference, 0.0; 95%CI, -0.07 to 0.17). There was no statistically significant difference between the two groups in the change in SDS scores from baseline (difference, 0.0; 95%CI, -0.35 to 0.95). There were no statistically significant differences between the two groups in the change in PANSS subscale scores from baseline (*P* value not reported). The frequency of discontinuation due to adverse events was low in both paliperidone and risperidone groups (3% vs. 1.6%). Treatment emergent adverse events reported at a greater frequency with paliperidone compared to risperidone included insomnia, injection site pain, and anxiety. Only constipation occurred at a greater frequency in the risperidone groups versus paliperidone. The incidence of extrapyramidal and cardiac adverse events was similar for both groups. There were no clinically relevant changes in ECG, fasting glucose or lipid levels.
Gaebel et al[55] Quetiapine vs	MC, OL, RCT Symptomatically stable patients with schizophrenia or a	N=710 2 years	Primary: Time to relapse Secondary: PANSS scores and	Primary: Patients treated with risperidone injection had significantly longer relapse-free periods compared to quetiapine (*P*<0.0001). Mean duration of treatment was 483.8±277.8 and 400.7±290.6 days, respectively.

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risperidone long-acting injection	related disorder who were on stable treatment with oral risperidone, olanzapine, or an oral conventional antipsychotic		adverse events	Secondary: Total PANSS scores improved significantly from baseline to endpoint for the risperidone group (*P*<0.001). The endpoint difference favors risperidone over quetiapine (*P*<0.001). Adverse events reported were similar between treatment groups (*P* value not reported).
Lieberman et al[56] CATIE Phase 1 Olanzapine 7.5-30 mg/day vs perphenazine 8-32 mg/day vs quetiapine 200-800 mg/day vs risperidone 1.5-6.0 mg/day vs ziprasidone 40-160 mg/day	DB, MC, RCT Patients 18 to 65 years old with a diagnosis of schizophrenia, a condition appropriate for treatment with an oral medication, and the decision-making capacity to make choices and provide informed consent	N=1,493 Up to 18 months	Primary: Discontinuation of treatment for any cause Secondary: Specific reasons for the discontinuation of treatment, and adverse effects	Primary: Overall, 74% of patients discontinued treatment before 18 months (olanzapine, 64%; risperidone, 74%; perphenazine, 75%; ziprasidone, 79%; quetiapine, 82%). Time to treatment discontinuation for any cause was significantly longer with olanzapine compared with quetiapine (*P*<0.001) and risperidone (*P*=0.002), but not compared with perphenazine (*P*=0.021)† or ziprasidone (*P*=0.028)†. Secondary: Treatment discontinuation due to lack of efficacy occurred in 28% of patients in the quetiapine group, 27% of the risperidone group, 25% of the perphenazine group, 24% of the ziprasidone group, and 15% of the olanzapine group. Time to discontinuation due to lack of efficacy was significantly longer with olanzapine than with all of the other groups (*P*<0.001) except ziprasidone (*P*=0.026)†. Treatment discontinuation due to intolerability occurred in 19% of patients who received olanzapine, 16% of the perphenazine group, 15% of both the quetiapine and ziprasidone groups, and 10% of the risperidone group. Time to discontinuation due to intolerability was similar among the groups (*P*≥0.027)†. Thirty-four percent of patients in the ziprasidone group, 33% of the quetiapine group, 30% of both the risperidone and perphenazine groups, and 24% of the olanzapine group decided to discontinue treatment. Time to treatment discontinuation was significantly longer with olanzapine than with quetiapine (*P*<0.001) and risperidone (*P*=0.008), but not compared with perphenazine (*P*=0.036)† or ziprasidone (*P*=0.018)†. Olanzapine was associated with the greatest discontinuation rates due to weight gain or metabolic effects, while perphenazine had the greatest

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				discontinuation rates due to EPS. Olanzapine also had the greatest adverse effects on hemoglobin A1c, total cholesterol, and triglycerides.
McEvoy et al[57] CATIE Phase 2 (efficacy) Clozapine 200-600 mg/day vs olanzapine 7.5-30.0 mg/day or quetiapine 200-800 mg/day or risperidone 1.5-6.0 mg/day	DB, MC, OL (clozapine), RCT Patients 18 to 65 years old with a diagnosis of schizophrenia, a condition appropriate for treatment with an oral medication, and the decision-making capacity to make choices and provide informed consent who had discontinued the second generation antipsychotic given in CATIE Phase 1 due to lack of efficacy	N=99 Up to 18 months	Primary: Time until discontinuation for any reason Secondary: Time to discontinuation for inadequate therapeutic benefit, intolerable side effects, or patient decision, psycho-pathology, and adverse events	Primary: Overall, 69% of patients discontinued treatment prior to study completion (clozapine, 56%; olanzapine, 71%; risperidone, 86%; quetiapine, 93%). Time to all-cause treatment discontinuation was significantly longer with clozapine (median 10.5 months) than with quetiapine (3.3 months; *P*=0.01), or risperidone (2.8 months; *P*<0.03), but not with olanzapine (2.7 months; *P*=0.12). Secondary: Discontinuation for inadequate therapeutic benefit occurred in 43% of patients in the quetiapine and risperidone groups, 35% of the olanzapine group, and 11% for the clozapine group. Time to discontinuation for inadequate therapeutic benefit was significantly longer for clozapine compared to the other three agents (*P*<0.02 for each comparison). There were no significant differences between treatments in time to discontinuation due to intolerable side effects or patient decision (*P* values not reported). Clozapine significantly reduced the PANSS total score (mean, -11.7) compared to quetiapine (2.5; *P*=0.02) and risperidone (4.1; *P*<0.03), but not compared with olanzapine (-3.2; *P*=0.22). Significant reductions in CGI scale scores at 3 months were seen with clozapine (mean, -0.7) compared to olanzapine (0.1; *P*<0.02) and quetiapine (0.2; *P*=0.003), but not compared to risperidone (0.0; *P*=6.18). Due to the small number of patients, adequate power was not reached to reasonably compare adverse events among the groups. Reported adverse events included anticholinergic events (highest with quetiapine, 47%), insomnia (risperidone, 31%), sialorrhea (clozapine, 33%), prolactin levels increased (risperidone, exposure-adjusted mean, 14.4 ng/mL).
Stroup et al[58] CATIE Phase 2 (tolerability) Ziprasidone 40-160 mg/day	DB, MC, RCT Patients 18 to 65 years old with a diagnosis of	N=444 Up to 18 months	Primary: Time until treatment discontinuation for any reason	Primary: Overall, 74% of patients discontinued treatment before completion of the study. Time to discontinuation for any reason was longer with olanzapine (median, 6.3 months) and risperidone (7.0 months) than with the quetiapine (4.0 months) and ziprasidone (2.8 months) groups (*P*=0.004

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vs olanzapine 7.5-30.0 mg/day or quetiapine 200-800 mg/day or risperidone 1.5-6.0 mg/day	schizophrenia, a condition appropriate for treatment with an oral medication, and have the decision-making capacity to make choices and provide informed consent who had discontinued the SGA given in CATIE Phase 1 due to intolerability		Secondary: Time to treatment discontinuation for inadequate therapeutic benefit, intolerable side effects, or patient decision, PANSS scores, CGI ratings, safety and tolerability outcomes	for overall group difference). Secondary: There were no differences among treatment groups regarding discontinuation due to lack of efficacy or intolerable side effects. In those patients who discontinued previous therapy due to inefficacy, olanzapine was more effective than quetiapine and ziprasidone, and risperidone was more effective than quetiapine (*P*=0.004 among groups). There were no significant differences between groups in those who discontinued previous treatment due to intolerability (*P* value not reported). There were significantly greater improvements in PANSS scores with olanzapine than with quetiapine (estimated mean difference, -6.8; *P*=0.005) and ziprasidone (estimated mean difference, -5.9; *P*=0.005), but not with risperidone. There were no differences in changes in CGI scores between treatment groups (*P* values not reported). Hospitalizations due to schizophrenia exacerbation were lower with olanzapine (0.28) than with risperidone (0.40), ziprasidone (0.48), and quetiapine (0.70). Common adverse events included sexual dysfunction (highest with risperidone, 29%), insomnia (ziprasidone, 31%), orthostatic faintness (quetiapine, 13%), weight gain (olanzapine, 1.3 lb/month), increases in total cholesterol (olanzapine, mean, -17.5 mg/dL), prolactin (risperidone, mean, 24.0 ng/mL), and triglycerides (mean, 94.1 mg/dL).
Stroup et al[58] CATIE Phase 3 Monotherapy with aripiprazole, clozapine, olanzapine, perphenazine, quetiapine, risperidone, or ziprasidone or	OL Patients 18 to 65 years old with a diagnosis of schizophrenia, a condition appropriate for treatment with an oral medication, and have the decision-making	N=270 Up to 18 months	Primary: Time until treatment discontinuation for any reason Secondary: Reason for treatment discontinuation, PANSS scores, CGI ratings, safety	Primary: Overall, 39% of patients discontinued treatment prior to study completion. A similar number of patients within the commonly selected regimens (second generation antipsychotics) discontinued therapy for any reason (33%-46%). There were no substantial differences between treatments in the proportion of possible treatment time that patients stayed on treatment (67%-80%). Secondary: A greater number of patients discontinued therapy with aripiprazole (18%), olanzapine (15%), and combination antipsychotic treatment (13%) for lack of efficacy compared to clozapine (5%), risperidone (3%),

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fluphenazine decanoate or combination of any two of these treatments	capacity to make choices and provide informed consent who had discontinued treatment in CATIE Phase 2		and tolerability outcomes	quetiapine (6%), and ziprasidone (8%). In terms of efficacy measures, there were no differences among mean changes of the PANSS scores or the CGI scale scores between the treatment groups. Side effects varied widely among the groups. Weight gain of at least 7 lb occurred most frequently with combination treatment (39%), clozapine (32%), and olanzapine (23%). Highest exposure-adjusted blood glucose increases were seen with aripiprazole, and risperidone caused substantial increases in prolactin levels.
Citrome et al[59] Asenapine 5 to 10 mg twice daily vs atypical antipsychotics (olanzapine 5 to 20 mg daily, risperidone 3 mg twice daily) vs placebo	SR Phase II or III clinical studies of asenapine in adult patients with schizophrenia and bipolar mania	Schizophrenia (N=1,778); Bipolar mania (N=473) 3 to 52 weeks	Primary: NNH, NNT Secondary: Not reported	Primary: The NNT for a positive response with asenapine (defined as a minimum of 20% decrease in the PANSS total scores) vs. placebo was 6. The NNT of 8 was calculated with asenapine vs. placebo for a 30% reduction from baseline in PANSS total scores. For the patients with schizophrenia, the NNH values for asenapine vs. placebo for commonly observed adverse reactions were 17 for somnolence, 34 for extrapyramidal symptoms, 34 for akathisia, and 25 for oral hypoesthesia. For patients with bipolar disorder, the NNH values for asenapine vs. placebo were 6 for somnolence, 13 for dizziness, 20 for extrapyramidal symptoms other than akathisia and 25 for increased weight. In schizophrenia trials, the NNH for weight gain of at least 7% from baseline were 35, 14, and 9 in asenapine, risperidone, and olanzapine groups, respectively. In schizophrenia trials, the NNH for fasting glucose level 1.5 times the upper limit of normal were 452, 188, and 174 in asenapine, risperidone, and olanzapine groups, respectively. In schizophrenia trials, the NNH for LDL cholesterol >50% upper limit of normal were 234 and 174 in asenapine and olanzapine groups, respectively.

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				The NNH for prolactin level over 4 times the upper limit of normal were 19, 4, and 33 in asenapine, risperidone, and olanzapine groups, respectively. Secondary: Not reported
Glick et al[60] Atypical antipsychotics (olanzapine, risperidone, quetiapine, aripiprazole, ziprasidone, clozapine) vs placebo	MA Randomized, double-blind studies with atypical antipsychotics in patients with schizophrenia or schizoaffective disorder	N=not reported at least 3 months	Primary: PANSS total score, relapse rate, discontinuation rate, adverse events Secondary: Not reported	Primary: Compared to placebo, olanzapine was associated with the greatest improvement in PANSS total scores from baseline, followed by risperidone (P>0.05), quetiapine (P=10^{-4}) and ziprasidone (P=0.004). Compared to olanzapine, the following risk ratios [RR] for relapse were determined: 0.87 for risperidone, 0.55 for ziprasidone and 0.39 for quetiapine (P value not reported). Compared to olanzapine, the following hazard ratios [HR] for relapse were determined: 0.84 for risperidone, 0.78 for ziprasidone and 0.60 for quetiapine (P value not reported). Compared to olanzapine, the following hazard ratios for all-cause discontinuations were determined: 0.77 for risperidone (P=0.005), 0.71 for quetiapine (P=0.02) and 0.68 for ziprasidone (P<0.001). Compared to olanzapine, the following hazard ratios for discontinuation due to poor efficacy were noted in the EUFEST study: 0.39 for ziprasidone (P<0.001) and 0.34 for quetiapine (P<0.001). Conclusion: Clozapine is the most effective atypical antipsychotic. Olanzapine is more effective than risperidone; though both are more effective compared to the other atypical antipsychotics. Extrapyramidal symptoms as measured by the use of antiparkinson drugs and compared with placebo were greatest in association with ziprasidone, followed by risperidone, olanzapine, aripiprazole and finally quetiapine (P value not reported). Akathisia as measured by the use of antiparkinson drugs and compared with olanzapine was most frequent in association with risperidone,

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				followed by aripiprazole, olanzapine, ziprasidone and finally quetiapine (*P* value not reported). Weight gain, compared with olanzapine, was greatest in association with clozapine and olanzapine (comparable), followed by risperidone and quetiapine (2-4 lb weight gain), and least with ziprasidone and aripiprazole (*P* value not reported). Aripiprazole and ziprasidone caused approximately 4 kg less weight gain compared with olanzapine. Risperidone and quetiapine caused approximately 2.5-3 kg less weight gain compared with olanzapine. Secondary: Not reported
Jones et al[61] Atypical antipsychotics (risperidone 4-8 mg daily, aripiprazole 10-30 mg daily, olanzapine 10-20 mg daily, quetiapine 150-750 mg daily, paliperidone ER 3-12 mg daily) vs placebo	SR Patients, mean age ranged from 37 to 39 years, diagnosed with schizophrenia	N=5,313 4 to 8 weeks	Primary: PANSS, CGI-S scores, discontinuation rate, adverse events Secondary: Not reported	Primary: All of the atypical antipsychotic drugs significantly improved total PANSS scores from baseline, compared to placebo (overall effect size -11.6; 95% CI, -13.3 to -10.0). Effect sizes (ES) for the individual agents ranged from -14.9 (95%CI, -17.6 to -12.3) for olanzapine to -9.5 (95%CI, -11.7 to -7.2) for aripiprazole. All of the atypical antipsychotic drugs were associated with a significant improvement in PANSS positive scores from baseline compared to placebo (overall ES, -3.7; 95%CI, -4.2 to -3.1). Effect sizes for individual agents ranged from -4.3 for risperidone and olanzapine (risperidone: 95%CI, -5.7 to -2.8 and olanzapine: 95%CI, -5.3 to -3.4) to -2.6 (95%CI, -3.4 to -1.7) for aripiprazole. All of the atypical antipsychotic drugs were associated with a significant improvement in PANSS negative scores compared to placebo (overall effect size, -2.4, 95%CI, -2.9 to -2.0). Effect sizes for individual agents ranged from -3.4 (95%CI, -4.2 to -2.7) for olanzapine to -1.3 (95%CI, -2.6 to -0.07) for quetiapine. Improvement on CGI-S score with atypical antipsychotic agents was -0.5 overall (95%CI, -0.6 to -0.4). Effect sizes for individual agents ranged from -0.8 (95%CI, -1.1 to -0.5) for risperidone to -0.3 (95%CI, -0.4 to -0.2) for aripiprazole.

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				Paliperidone ER, olanzapine and risperidone tended to have lower discontinuation rates due to lack of efficacy compared to all atypical antipsychotics combined. Whereas, discontinuation rates tended to be greater among patients receiving aripiprazole and quetiapine compared to the mean rate for the atypical antipsychotics (*P* value not reported). There was no significant difference in discontinuation rates due to adverse events for all the atypical antipsychotic agents combined compared to placebo. Results were similar for the individual agents except olanzapine, which had a higher discontinuation rate due to adverse effects. Atypical antipsychotics were associated with significant weight gain compared to placebo (OR, 2.84; 95%CI, 2.3 to 3.5). Odds of weight gain were lowest with paliperidone ER (OR, 1.75; 95%CI, 1.29 to 2.37) and highest with olanzapine (OR, 4.56; 95%CI, 3.46 to 6.01). Atypical antipsychotics were associated with increased odds of somnolence compared to placebo (OR, 1.7; 95%CI, 1.39 to 2.09). Odds of somnolence were lower than the mean with paliperidone ER and aripiprazole and higher than the mean with risperidone and olanzapine. Overall, there was no significant difference in agitation between atypical antipsychotics and placebo. Agitation tended to be lower than placebo for paliperidone ER and for quetiapine, but the significance of the result was uncertain. Secondary: Not reported
Klemp et al[62] Atypical antipsychotics (aripiprazole, clozapine, olanzapine, risperidone) vs haloperidol	MA Randomized controlled studies in patients with schizophrenia	N=7,743 2 to 52 weeks	Primary: Response (defined as at least 20%-30% reduction in PANSS, BPRS or CGI scores, adverse events Secondary:	Primary: Compared to placebo, clozapine was associated with the greatest response ratio (1.99; 95%CI, 1.76 to 2.26), followed by olanzapine (1.86; 95%CI, 1.70 to 2.06), risperidone (1.85; 95%CI, 1.69 to 2.01), aripiprazole (1.55; 95%CI, 1.36 to 1.76) and finally haloperidol (1.40; 95%CI, 1.25 to 1.57). The probabilities that clozapine, olanzapine, and risperidone are better than aripiprazole are 1, 1, and 0.99, respectively.

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vs placebo			Not reported	The probability that olanzapine is better than risperidone is 0.59. The probability that clozapine is better than olanzapine is 0.86. The probability that clozapine is better than risperidone is 0.88. Compared to placebo, olanzapine was associated with the greatest weight gain as seen with a response ratio of 12.21 (95%CI, 10.22 to 15.05), followed by clozapine (11.28; 95%CI, 6.89 to 17.77), risperidone (6.42; 95%CI, 4.81 to 8.61), haloperidol (5.27; 95%CI, 4.17 to 6.71) and finally aripiprazole (4.57; 95%CI, 3.07 to 6.54). The probability that olanzapine causes less weight gain than either risperidone, haloperidol or aripiprazole is 0. The probability that risperidone causes less weight gain than aripiprazole is 0.03. Compared to placebo, haloperidol was associated with the greatest risk of extrapyramidal adverse events as seen with a response ratio of 2.33 (95%CI, 2.03 to 2.49), followed by risperidone (1.41; 95%CI, 1.20 to 1.64), clozapine (1.34; 95%CI, 0.96 to 1.78) and aripiprazole (1.34; 95%CI, 1.06 to 1.65). Olanzapine was associated with a lower risk of extrapyramidal adverse events, compared to placebo, with a response ratio of 0.91 (95%CI, 0.77 to 1.05). The probability that risperidone causes less extrapyramidal adverse events than aripiprazole is 0.32. Secondary: Not reported
Leucht et al[63] Second generation antipsychotics (amisulpiride*, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, sertindole*, ziprasidone, zotepine*)	MA Patients with schizophrenia or related psychotic disorders	N=21,533 150 DB, randomized studies (OL studies excluded)	Primary: Overall efficacy Secondary: Positive, negative, and depressive symptoms, relapse, quality of life, EPS,	Primary: Four second-generation antipsychotic drugs were better than first-generation agents for overall efficacy, with small to medium effect sizes (amisulpiride, -0.31 [95% CI, -0.44 to -0.19; *P*<0.0001], clozapine, -0.52 [95% CI, -0.75 to -0.29; *P*<0.0001], olanzapine, -0.28 [95% CI, -0.38 to -0.18; *P*<0.0001], and risperidone, -0.13 [95% CI, -0.22 to -0.05; *P*=0.002]).

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vs first generation antipsychotics as comparator agents (including chlorpromazine, fluphenazine, haloperidol, perphenazine, thioridazine, thiothixene, trifluoperazine, plus others not available in the United States)		FD studies selected generally accepted optimal doses of each antipsychotic Duration of studies varied (from ≤12 weeks to >6 months)	weight gain and sedation	Secondary: Amisulpiride, clozapine, olanzapine, and risperidone were also more efficacious than first-generation agents for treatment of positive and negative symptoms. Aripiprazole, quetiapine, sertindole, ziprasidone, and zotepine were not more effective than first-generation agents for treatment of negative symptoms. Aripiprazole, quetiapine, sertindole, ziprasidone, and zotepine were no more efficacious than first-generation agents for positive symptoms (and quetiapine was less efficacious). Amisulpiride, aripiprazole, clozapine, olanzapine, and quetiapine were significantly better in treating depressive symptoms than first-generation agents, whereas risperidone was not. Olanzapine, risperidone, and sertindole were found to be significantly better than first-generation agents in preventing relapse; amisulpiride, aripiprazole, and clozapine showed no significant difference (no studies were available for the other second-generation agents). Only amisulpiride, clozapine, and sertindole were better than first-generation agents for improving quality of life (which was reported in only 17 studies). All second-generation antipsychotics were associated with much fewer EPS effects than haloperidol. Amisulpiride, clozapine, olanzapine, quetiapine, risperidone, sertindole, and zotepine were associated with significantly more weight gain than haloperidol, whereas aripiprazole and ziprasidone were not. Clozapine, quetiapine, and zotepine were significantly more sedating than was haloperidol, whereas aripiprazole was significantly less sedating.
Komossa et al[64] Aripiprazole, doses ranged	SR Randomized	N=1404 4 to 26 weeks	Primary: Leaving the study early, treatment	Primary: Based on data from two available studies, there was no significant difference between aripiprazole and olanzapine in terms of leaving the

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from 15 to 30 mg daily vs olanzapine, doses not reported vs risperidone, doses not reported	controlled trials evaluating patients with schizophrenia and other types of schizophrenia-like psychosis		response, PANSS scores, adverse events Secondary: Not reported	study early due to any reason (RR, 1.15; 95%CI, 0.92 to 1.45). Based on data from two available studies, there was no significant difference between aripiprazole and olanzapine in terms of proportion of patients experiencing treatment response (RR, 1.05; 95%CI, 0.95 to 1.17). Aripiprazole was less efficacious than olanzapine in terms of the general mental state, as measured by the PANSS total score (MD, 4.96; 95%CI, 1.85 to 8.06). Based on data from two available studies, there was no significant difference between aripiprazole and risperidone in terms of leaving the study early due to any reason (RR, 0.94; 95%CI, 0.71 to 1.26). Based on data from two available studies, there was no significant difference between aripiprazole and risperidone in terms of proportion of patients experiencing treatment response (RR, 1.14; 95%CI, 0.81 to 1.60). Based on data from two available studies, there was no significant difference between aripiprazole and risperidone PANSS total score changes from baseline (MD, 1.50; 95% CI, -2.96 to 5.96). Compared with olanzapine, aripiprazole was associated with fewer side-effects such as cholesterol increase (NNH=4), clinically significant weight gain (NNT=4), sedation (NNT=7) and prolactin associated side-effects (NNT=8). There was no significant difference between the groups in the risk of QTc prolongation. Compared with risperidone, dystonia, QTc abnormalities, prolactin and cholesterol increase were less frequent in the aripiprazole group. Tremor was more frequent with aripiprazole therapy compared with risperidone. There was no significant difference between risperidone and aripiprazole groups in weight gain of at least 7% from baseline. Secondary: Not reported

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Komossa et al[65] Olanzapine, doses ranged from 2.5 to 50 mg daily vs amisulpride*, doses ranged from 150 to 800 mg daily vs aripiprazole, doses ranged from 15 to 30 mg daily vs clozapine, doses ranged from 25 to 900 mg daily vs quetiapine, doses ranged from 50 to 826.67 mg daily vs risperidone, doses ranged from 0.5 to 16 mg daily vs ziprasidone, doses ranged from 40 to 160 mg daily	SR Randomised, at least single-blind design, comparing oral olanzapine with oral forms of amisulpride, aripiprazole, clozapine, quetiapine, risperidone, or ziprasidone in people with schizophrenia or schizophrenia-like psychosis	N=9476 (50 studies) 6 to 26 weeks	Primary: Leaving the study early, re-hospitalization, PANSS, adverse events Secondary: Not reported	Primary: Olanzapine improved the general mental state (assessed via the PANSS total score) more than aripiprazole (WMD, -4.96; 95%CI, -8.06 to -1.85), quetiapine (WMD, -3.66; 95%CI, -5.39 to -1.93), risperidone (WMD, -1.94; 95%CI, -3.31 to -0.58) and ziprasidone (WMD, -8.32; 95%CI, -10.99 to -5.64), but not more than amisulpride or clozapine. Fewer patients in the olanzapine group left the study early due to inefficacy of treatment compared to quetiapine (RR, 0.56; 95%CI, 0.44 to 0.70, NNT=11), risperidone (RR, 0.78; 95%CI, 0.62 to 0.98, NNT=50 and ziprasidone (RR, 0.64; 95%CI, 0.51 to 0.79, NNT=17). Significantly fewer patients left the study early due to adverse events in the olanzapine group compared with clozapine (RR, 0.62; 95%CI, 0.43 to 0.92, NNT=20). Fewer patients required re-hospitalization in the olanzapine group compared to quetiapine (RR, 0.56; 95%CI, 0.41 to 0.77; NNT=11) and ziprasidone (RR, 0.65; 95%CI, 0.45 to 0.93; NNT=17); whereas, more patients in the olanzapine group were re-hospitalized compared with the clozapine group (RR, 1.28; 95%CI, 1.02 to 1.61, NNH not estimable). Except for clozapine, all comparators caused less weight gain than olanzapine (vs. aripiprazole: WMD, 5.60kg, 95%CI, 2.15kg to 9.05kg; vs. quetiapine: WMD, 2.68kg, 95%CI, 1.10kg to 4.26kg; vs. risperidone: WMD, 2.61kg, 95%CI, 1.48kg to 3.74kg; vs.ziprasidone: WMD, 3.82kg, 95%CI, 2.96kg to 4.69kg). Metabolic side effects such as glucose and cholesterol level increases were also more frequent in the olanzapine group compared to most comparators. Olanzapine may be associated with more extrapyramidal side effects than quetiapine, assessed by the use of antiparkinson medication (RR, 2.05; 95%CI, 1.26 to 3.32, NNH=25), but less than risperidone (RR, 0.78; 95%CI, 0.65 to 0.95, NNH=17) and ziprasidone (RR, 0.70;95%CI, 0.50 to 0.97, NNH not estimable). Olanzapine may increase prolactin level to a greater degree than

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				aripiprazole, clozapine and quetiapine, but considerable less so than risperidone (WMD, -22.84; 95%CI, -27.98 to -17.69). There was no significant difference between olanzapine and aripiprazole, ziprasidone or risperidone groups in change in QTc interval from baseline. Quetiapine was associated with significantly increased QTc interval from baseline, compared to olanzapine. Secondary: Not reported
Komossa et al[66] Quetiapine, doses ranged from 50 to 800 mg daily vs. clozapine, doses not reported vs olanzapine, doses not reported vs risperidone, doses not reported vs ziprasidone, doses not reported	SR Randomised, at least single-blind design, comparing oral quetiapine with oral forms of clozapine, olanzapine, risperidone or ziprasidone in people with schizophrenia or schizophrenia-like psychosis	N=4101 (21 studies) 2 to 12 weeks	Primary: Leaving the study early, PANSS, adverse events Secondary: Not reported	Primary: Quetiapine was less effective in improving the general mental state (PANSS total score) compared to olanzapine (WMD, 3.66; 95%CI, 1.93 to 5.39) and risperidone (WMD, 3.09; 95%CI, 1.01 to 5.16). There were no significant differences in PANSS total scores between quetiapine and either clozapine or ziprasidone. Compared with olanzapine, quetiapine was associated with fewer movement disorders, assessed via the use of antiparkinson medication (RR, 0.49; 95%CI, 0.3 to 0.79, NNH=25 CI) and less weight gain (WMD, -2.81; 95%CI, -4.38 to -1.24) and glucose elevation (WMD, -9.32; 95%CI, -17.82 to -0.82), but more QTc prolongation (WMD, 4.81; 95%CI, 0.34 to 9.28). There was no significant difference in sedation between olanzapine and quetiapine. Likewise, cholesterol level changes from baseline were comparable between the groups. Compared with risperidone, quetiapine was associated with fewer movement disorders, assessed via the use of antiparkinson medication (RR, 0.5; 95%CI, 0.3 to 0.86; NNH=20), less prolactin increase (WMD, -35.28; 95%CI, -44.36 to -26.19) and some related adverse effects, but more cholesterol increase (WMD, 8.61; 95%CI, 4.66 to 12.56). Quetiapine was associated with significantly more sedation (RR, 1.21; 95%CI, 1.06 to 1.38; NNH=20), compared with risperidone. There was no significant difference in weight gain between the groups. Compared with ziprasidone, quetiapine was associated with fewer extrapyramidal adverse effects, assessed via the use of antiparkinson medication (RR, 0.43; 95%CI, 0.2 to 0.93, NNH not estimable) and

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				prolactin increase. However, quetiapine was associated with significantly more sedation (RR, 1.36; 95%CI, 1.04 to 1.77; NNH=14) and weight gain (RR, 2.22; 95%CI, 1.35 to 3.63; NNH=13) and cholesterol (WMD, 16.01; 95%CI, 8.57 to 23.46) compared to ziprasidone. There was no significant difference in QTc prolongation between the groups. Secondary: Not reported
Komossa et al[67] Risperidone, doses ranged from 0.5 to 12 mg daily vs amisulpride*, doses ranged from 100 to 1000 mg daily vs aripiprazole, doses ranged from 15 to 30 mg daily vs clozapine, doses ranged from 25 to 900 mg daily vs olanzapine, doses ranged from 2.5 to 40 mg daily vs quetiapine, doses ranged from 50 to 800 mg daily	SR Randomized, blinded studies comparing risperidone with oral forms of amisulpride, clozapine, olanzapine, quetiapine, or ziprasidone in patients with schizophrenia or schizophrenia-like psychosis	N=7,760 (45 studies) up to 12 weeks (31 studies); 13-26 weeks (6 studies); >26 weeks (8 studies)	Primary: Leaving the study early, CGI, PANSS, BPRS, Quality of Life Scale (QLS), adverse events Secondary: Not reported	Primary: Based on data from two studies, compared to aripiprazole, risperidone was not associated with a significant change in global state, measured on the CGI scale (RR, 0.88; 95%CI, 0.62 to 1.24). There was no significant difference between risperidone and aripiprazole groups in leaving the study early (35% vs. 34%; RR, 1.06; 95%CI, 0.79 to 1.41). Moreover, there was no significant difference between risperidone and aripiprazole groups in the mental state change from baseline, as measured on the PANSS total, negative and positive scales. Compared to clozapine, risperidone was not associated with a significant change in global state, measured on the CGI scale (RR, 1.07; 95%CI, 0.88 to 1.30). While the overall percentage of patients leaving the study early did not significantly differ between risperidone and clozapine groups (35% vs. 31%; RR, 1.10; 95%CI, 0.86 to 1.41), risperidone was associated with a significantly greater discontinuation rate due to inadequate efficacy (14% vs. 5%), but with a significantly lower rate of discontinuations due to side effects (7% vs. 12%), compared to clozapine. There were no significant differences between groups in the changes from baseline in PANSS total scores (a measure of mental state), BPRS scores, positive and negative PANSS subscale scores, GAF scores of general functioning, or cognitive functioning scores. Compared to olanzapine, risperidone was not associated with a significant change in global state, measured on the CGI scale (RR, 0.98; 95%CI, 0.88 to 1.09). Fewer patients receiving olanzapine left the study early than patients in the risperidone group (48% vs. 56%; RR, 1.14; 95%CI, 1.07 to 1.21; NNH=13). There was a trend in more patients leaving in the risperidone group due to inadequate efficacy. Olanzapine therapy was associated with significantly greater improvement in the

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vs ziprasidone, doses ranged from 40 to 160 mg daily				PANSS total scores (MD, 1.94; 95%CI, 0.58 to 3.31), negative symptoms as reflected by the SANS total scores (MD, 1.40; 95%CI, 0.37 to 2.43), and QLS total scores (MD, 5.10; 95%CI, 1.09 to 9.1). The percentage of patients leaving the study early did not significantly differ between risperidone and quetiapine groups (54% vs. 57%; RR, 0.94; 95%CI, 0.87 to 1.02). Risperidone was associated with greater efficacy in the following outcome measures: PANSS total score (MD, -3.09; 95%CI, -5.16 to -0.40), PANSS positive scores (MD, -1.82; 95%CI, -2.48 to -1.16), BPRS positive scores (MD, -1.10; 95%CI, -2.02 to -0.18) and BPRS negative scores (MD, -0.57; 95%CI, -0.97 to -0.17). Based on date from three studies, the percentage of patients leaving the study early did not significantly differ between risperidone and ziprasidone groups (58% vs. 65%; RR, 0.90; 95%CI, 0.83 to 0.98). Risperidone was associated with greater efficacy in the following outcome measures: PANSS total score (MD, -3.91; 95%CI, -7.55 to -0.27) and PANSS positive scores (MD, -2.50; 95%CI, -4.62 to -0.38). There were no significant differences between groups in the other efficacy endpoints. Risperidone produced more extrapyramidal side effects than a number of other atypical antipsychotics (use of antiparkinson medication vs. clozapine RR, 2.57, 95%CI, 1.47 to 4.48, NNH=6; vs. olanzapine RR, 1.28, 95%CI, 1.06 to 1.55, NNH=17; vs. quetiapine RR, 1.98, 95%CI, 1.16 to 3.39, NNH=20; vs. ziprasidone RR, 1.42; 95%CI, 1.03 to 1.96, NNH not estimable). Risperidone increased prolactin levels significantly more than all comparators (vs. aripiprazole, MD, 54.71, 95%CI, 49.36 to 60.06; vs. clozapine, MD, 38.50, 95%CI, 23.30 to 53.70; vs. olanzapine, MD,22.84; 95%CI, 17.69 to 27.98; vs. quetiapine, MD, 35.28; 95%CI, 26.19 to 44.36; vs. ziprasidone, MD, 21.97; 95%CI, 16.60 to 27.34). There were no significant differences between risperidone and aripiprazole in glucose level or ECG changes. There were no significant differences between risperidone and olanzapine in ECG changes, glucose level, or seizures. There was no significant difference between risperidone and ziprasidone in ECG changes from baseline.

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				Sedation (NNT=5) and seizures (NNT=14) occurred significantly less often with risperidone compared with clozapine. Sedation and somnolence occurred significantly less often with risperidone than with quetiapine (NNT=20 and NNT=13, respectively). Sedation was comparable between risperidone and the other drug comparisons. Risperidone was associated with significantly less weight gain compared with clozapine (MD, -3.30; 95%CI, -5.65 to -0.95) and olanzapine (MD, -0.61; 95%CI, -3.74 to -1.48). There were no significant differences in weight gain between risperidone and aripiprazole or quetiapine. Risperidone was associated with significantly more weight gain of >7% of total body weight compared to ziprasidone (RR, 2.03; 95%CI, 1.35 to 3.06; NNH=14). Risperidone was associated with greater increases in cholesterol levels compared with aripiprazole (MD, 22.30; 95%CI, 4.91 to 39.69) and ziprasidone (MD, 8.58; 95%CI,1.11 to 16.04), but less than olanzapine (MD -10.36; 95% CI -14.43 to -6.28) and quetiapine (MD, -8.49; 95%CI, -12.23 to -4.75). Secondary: Not reported
Komossa et al[68] Ziprasidone, doses ranged from 40 to 160 mg daily vs amisulpride*, doses not reported vs clozapine, doses not reported	SR Randomized, at least single-blind studies comparing ziprasidone with oral forms of amisulpride, clozapine, olanzapine, quetiapine, or risperidone in patients with schizophrenia or schizophrenia-like	N=3361 18 to 78 weeks	Primary: Leaving the study early, PANSS, BPRS, Quality of Life Scale (QLS), adverse events Secondary: Not reported	Primary: Based on one study comparing ziprasidone with clozapine, the two drugs were not shown to be significantly different in the number of patients leaving the study early due to any reason (RR, 1.0; 95%CI, 0.66 to 1.51). There was no significant difference between clozapine and ziprasidone in PANSS total score reduction from baseline (*P* value not reported). Ziprasidone was a less acceptable treatment than olanzapine based on leaving the study early for any reason (RR, 1.26; 95%CI, 1.18 to 1.35; NNH=7). There was no significant difference between the groups in leaving the study early due to adverse events (RR, 1.12; 95%CI, 0.77 to 1.61), while olanzapine was preferred over ziprasidone in terms of leaving the study early due to inadequate efficacy (RR, 1.57; 95%CI, 1.27 to 1.94). Ziprasidone was less efficacious than olanzapine in the PANSS total score reduction from baseline (MD, 8.32 CI 5.64 to 10.99) and the

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vs olanzapine, doses not reported vs quetiapine, doses not reported vs risperidone, doses not reported	psychosis			positive PANSS subscore (RR, 3.11; 95%CI, 1.93 to 4.30). There were no significant changes between ziprasidone and olanzapine groups in BPRS total score, negative PANSS subscore, or the QLS total score. Based on the data from two studies comparison ziprasidone with quetiapine, there were no statistically significant differences between the groups in leaving the study early for any reason, improvement in PANSS total score, changes in PANSS positive and negative subscales (*P* value not reported). Ziprasidone was a less acceptable treatment than risperidone based on leaving the study early for any reason (RR, 1.11; 95%CI, 1.02 to 1.20; NNH=14), but not different from the other atypical antipsychotic drugs. Ziprasidone was less efficacious compared to risperidone in terms of improvement in PANSS total score from baseline (MD, 3.91; 95%CI, 0.27 to 7.55). PANSS positive subscale scores were significantly improved with risperidone compared to ziprasidone (MD, 2.50; 95%CI, 0.38 to 4.62); though there was no significant difference between the groups in the PANSS negative subscale score changes from baseline (MD, 0.04; 95%CI, -1.12 to 1.20). Neither was there a significant difference between groups in the BPRS total score (MD, 0.70; 95%CI, -2.93 to 4.33). Based on limited data there were no significant differences in tolerability between ziprasidone and amisulpride or clozapine. There were no significant differences between ziprasidone and olanzapine in the risk of QTc interval prolongation (MD, 2.19; 95%CI, -0.58 to 4.96), prolactin level changes, or extrapyramidal side effects. Ziprasidone produced less clinically significant weight gain than olanzapine (MD, -3.82; 95CI,-4.69 to -2.96), quetiapine (RR, 0.45; 95% CI 0.28 to 0.74; NNT=13) or risperidone (3 RCTs, n=1063, RR 0.49 CI, 0.33 to 0.74). Ziprasidone was associated with significantly less sedation compared with quetiapine (RR, 0.73; 95%CI, 0.55 to 0.97; NNT=13). Sedation was comparable with ziprasidone, olanzapine, and risperidone therapies.

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				Ziprasidone was associated with less cholesterol increase than olanzapine, quetiapine and risperidone. Ziprasidone was associated with slightly more extrapyramidal side-effects than olanzapine (RR, 1.43; 95%CI, 1.03 to 1.99). Ziprasidone produced a greater increase of prolactin level compared to quetiapine (MD, 4.77; 95% CI, 1.37 to 8.16). Ziprasidone was associated with less movement disorders (RR, 0.70; 95% CI, 0.51 to 0.97) and less prolactin level increases (MD, -21.97; 95% CI -27.34 to -16.60) than risperidone. There were no significant differences between ziprasidone and risperidone in QTc interval prolongation. Secondary: Not reported
Leucht et al[69] Head-to-head comparisons of nine second-generation antipsychotic agents (amisulpiride*, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, sertindole*, ziprasidone, and zotepine*)	MA Patients with schizophrenia or other related psychotic disorders	N=13,558 78 DB studies Duration of trials not specified	Primary: PANSS total score Secondary: Positive and negative symptoms	Primary: Amisulpiride was found to have no significant differences with olanzapine, risperidone, and ziprasidone (*P* values not reported). Aripiprazole was found less efficacious than olanzapine in two studies sponsored by aripiprazole's manufacturer (N=794; WMD, 5.0; *P*=0.002); two further studies found no significant difference compared with risperidone (*P* values not reported). Clozapine was found to not be significantly different from olanzapine, quetiapine, risperidone, and ziprasidone (*P* values not reported). Olanzapine was found to be significantly more efficacious than aripiprazole (N=794; WMD, -5.0; *P*=0.002), quetiapine (N=1,449; WMD, -3.7; *P*<0.001), risperidone (N=2,404; WMD, -1.9; *P*=0.006), and ziprasidone (N=1,291; WMD, -8.3; *P*<0.001); and not significantly different than amisulpiride or clozapine. Quetiapine was found to be significantly less efficacious than olanzapine (N=1,449; WMD, 3.7; *P*<0.001) and risperidone (N=1,953; WMD, 3.2; *P*=0.003); and not significantly different than clozapine and ziprasidone.

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				Risperidone was found to be significantly more efficacious than quetiapine (N=1,953; WMD, -3.2; *P*=0.003) and ziprasidone (N=1,016; WMD, -4.6; *P*=0.002); less efficacious than olanzapine (N=2,404; WMD, 1.9; *P*=0.006); and not significantly different than amisulpiride, aripiprazole, clozapine, and sertindole (*P* values not reported). Sertindole was found to not be significantly different than risperidone in two studies sponsored by sertindole's manufacturer (*P* values not reported). Ziprasidone was found to be less efficacious than olanzapine (N=1,291; WMD, 8.3; *P*<0.001) and risperidone (N=1,016; WMD, 4.6; *P*=0.002); and not significantly different than amisulpiride, clozapine, and quetiapine (*P* values not reported). Zotepine was found to be less efficacious than clozapine (N=59; WMD, 6.0; *P*=0.002). Secondary: Results for positive symptoms paralleled those found for overall symptoms except that olanzapine was not significantly more efficacious than risperidone (*P* value not reported). No significant differences for negative symptoms were found, with the exception of a superiority of quetiapine compared with clozapine in two small studies of first-episode schizophrenia. The comparisons of quetiapine with risperidone and olanzapine with ziprasidone were heterogeneous, and the results did not change when outliers were excluded. The results were rather robust with regard to the effects of industry sponsorship, study quality, dosages, and trial duration.
Lobos et al[70] Clozapine 207 mg to 642 mg daily	SR Patients diagnosed with schizophrenia	N=3,099 2 to 26 weeks	Primary: Discontinuation rate, BPRS total score, PANSS total	Primary: Clozapine was associated with a higher discontinuation rate than olanzapine (RR, 1.60; 95%CI, 1.07 to 2.40; NNT=25) and risperidone (RR, 1.88; 95%CI, 1.11 to 3.21; NNT=16). Fewer participants in the

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vs olanzapine 16 mg to 30 mg daily vs quetiapine 362 mg to 536 mg daily vs risperidone 3.2 mg to 12 mg daily vs ziprasidone 130 mg daily	or schizoaffective disorder		score, negative symptoms, adverse events Secondary: Not reported	clozapine groups left the trials early due to inefficacy than risperidone (NNT=11). Clozapine was not significantly different from olanzapine, quetiapine, risperidone and ziprasidone in BPRS total score improvement from baseline (*P*>0.05). There was no significant difference between clozapine and olanzapine or risperidone in improvement of PANSS total score from baseline (*P*>0.05). According to two studies, quetiapine was more efficacious for negative symptoms compared to clozapine (MD, 2.23; 95%CI, 0.99 to 3.48). Clozapine was associated with less extrapyramidal side-effects, as estimated by the use of antiparkinson medication (RR, 0.39; 95%CI, 0.22 to 0.68; NNT=7) compared to risperidone. More participants in the clozapine group exhibited decreased white blood cells than those taking olanzapine, more hypersalivation and sedation than those on olanzapine, risperidone and quetiapine and more seizures than people on olanzapine and risperidone. In addition, clozapine was associated with a significant weight gain which was not observed with risperidone. Secondary: Not reported
Riedel et al[71] Atypical antipsychotics (aripiprazole, olanzapine, quetiapine, and risperidone)	MA Patients, 18 to 65 years of age, diagnosed with schizophrenia	N=129 8 weeks	Primary: Cognitive function, assessed via PANSS Secondary: Not reported	Primary: Compared to the other atypical antipsychotic, quetiapine was associated with the greatest cognitive improvement (*P*<0.005). Quetiapine was found to improve working memory, verbal memory, reaction quality and visual memory. Olanzapine was associated with a significant improvement from baseline in working memory, verbal memory and visual memory (*P* value not reported). Risperidone was associated with a significant improvement from baseline in reaction time (*P* value not reported).

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				Aripiprazole was associated with a significant improvement from baseline in reaction time and reaction quality (*P* value not reported). Secondary: Not reported
Bipolar Disorder				
McIntyre et al[72] Asenapine 5 mg to 10 mg twice daily vs olanzapine 15 mg on day 1, followed by 5 mg to 20 mg once daily vs placebo	DB, PC, RCT Adult patients, 18 years of age or older, diagnosed with bipolar I disorder, experiencing manic or mixed episodes	N=488 3 weeks (after 1 week placebo run-in period)	Primary: Change in YMRS total score from baseline Secondary: Change from baseline in Clinical Global Impression for Bipolar Disorder (CGI-BP), MADRS, percentage of responders (≥50% reduction in YMRS total score), percentage of remitters (YMRS total score ≤12 at endpoint), adverse events	Primary: Asenapine was associated with a statistically significant reduction in YMRS total score from baseline, compared to placebo (-10.8 vs. -5.5; *P*<0.0001). Statistically significant benefit with asenapine over placebo was noted as early as day-2 of therapy. Olanzapine was associated with a statistically significant reduction in YMRS total score from baseline, compared to placebo (-12.6 vs. -5.5; *P*<0.0001). Secondary: Asenapine was associated with a statistically significant reduction in CGI-BP score from baseline, compared to placebo (-1.2 vs. -0.7; *P*≤0.01). Olanzapine was associated with a statistically significant reduction in CGI-BP score from baseline, compared to placebo (-1.4 vs. -0.7; *P*≤0.0001). Asenapine was not associated with significant difference in MADRS reduction at endpoint compared to placebo (-3.2 vs. -1.8; *P*>0.05). Olanzapine was associated with a statistically significant reduction in MADRS score from baseline, compared to placebo (-4.2 vs. -1.8; *P*≤0.01). Significantly greater percentage of patients in the asenapine group experienced a response (42.3%) or remission (40.2%) compared to patients receiving placebo (25.2% and 22.3%, respectively; *P*<0.01 for both). The NNT values for YMRS response and remission were 6. Significantly greater percentage of patients in the olanzapine group

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				experienced a response (50%) or remission (39.4%) compared to patients receiving placebo (25.2% and 22.3%, respectively; *P*<0.005 for both). The NNT values for YMRS response and remission were 5 and 6, respectively. Treatment-related adverse events were reported by 60.8%, 52.9%, and 36.2% of asenapine-, olanzapine-, and placebo-treated patients. Most common adverse events with asenapine that occurred at more than twice the frequency of placebo included sedation (18.6% vs. 4.8%), dizziness (11.9% vs. 3.8%), somnolence (8.8% vs. 1.9%), fatigue (6.2% vs. 1.9%, and oral hypoasthenia (5.2% vs. 1%). Most common adverse events with olanzapine that occurred at more than twice the frequency of placebo included sedation (18.5%), dry mouth (14.3% vs. 1%), dizziness (8.5%), somnolence (7.4%), and increased weight (6.9% vs. 1%). The incidence of extrapyramidal events was 7.2% with asenapine, 7.9% with olanzapine and 2.9% with placebo. Asenapine, olanzapine, and placebo groups experienced the following weight gain: 1.6 kg, 1.9 kg, and 0.3 kg, respectively. NNH values versus placebo for the incidence of clinically significant weight gain were 17 and 8 in patients who received asenapine and olanzapine, respectively.
McIntyre et al[73] Asenapine 5 mg to 10 mg twice daily vs olanzapine 15 mg on day 1, followed by 5 mg to 20 mg once daily vs	DB, MC, PC, RCT Adult patients, 18 years of age or older, diagnosed with bipolar I disorder, experiencing manic or mixed episodes, with YMRS total score ≥20	N=480 3 weeks (after 1 week placebo run-in period)	Primary: Change in YMRS total score from baseline Secondary: Change from baseline in CGI-BP, MADRS, percentage of responders (≥50% reduction in YMRS total score),	Primary: Asenapine was associated with a statistically significant reduction in YMRS total score from baseline, compared to placebo (-11.5 vs. -7.8; *P*<0.007). Statistically significant benefit with asenapine over placebo was noted as early as day-2 of therapy. Olanzapine was associated with a statistically significant reduction in YMRS total score from baseline, compared to placebo (-14.6 vs. -7.8; *P*<0.0001). Secondary: Asenapine was associated with a statistically significant reduction in CGI-BP score from baseline, compared to placebo (-1.2 vs. -0.8; *P*≤0.05).

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placebo			percentage of remitters (YMRS total score ≤12 at endpoint), adverse events	Olanzapine was associated with a statistically significant reduction in CGI-BP score from baseline, compared to placebo (-1.5 vs. -0.8; $P \leq 0.0001$). Asenapine was not associated with a significant difference in MADRS reduction at endpoint compared to placebo (-3.0 vs. -1.9; $P > 0.05$). Olanzapine was associated with a statistically significant reduction in MADRS score from baseline, compared to placebo (-4.1 vs. -1.9; $P \leq 0.01$). The response (42.6% vs. 34%) and remission (35.5% vs. 30.9%) rates did not significantly differ between asenapine and placebo groups ($P > 0.05$). Significantly greater percentage of patients in the olanzapine group experienced a response (54.7%) or remission (46.3%) compared to patients receiving placebo (34% and 30.9%, respectively; $P < 0.05$ for both). The NNT values for YMRS response and remission were 5 and 7, respectively. Treatment-related adverse events were reported by 55.1%, 46.8%, and 27.6% of asenapine-, olanzapine-, and placebo-treated patients. Most common adverse events with asenapine that occurred at more than twice the frequency of placebo included sedation (8.6% vs. 3.1%), dizziness (10.3% vs. 2.0%), somnolence (11.9% vs. 3.1%), weight gain (6.5% vs. 0.0%, and vomiting (5.4% vs. 2%). Most common adverse events with olanzapine that occurred at more than twice the frequency of placebo included sedation (14.1%), dizziness (6.3%), somnolence (11.2%), increased appetite (6.3% vs. 1%) and increased weight (9.3%). The incidence of extrapyramidal events was 10.3% with asenapine, 6.8% with olanzapine and 3.1% with placebo.

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				Asenapine, olanzapine, and placebo groups experienced the following weight gain: 0.9 kg, 2.6 kg, and 0.1 kg, respectively. NNH values versus placebo for the incidence of clinically significant weight gain were 19 and 7 in patients who received asenapine and olanzapine, respectively.
Szegediet al[74] Asenapine 5 mg to 10 mg twice daily vs olanzapine 15 mg once daily on day 1, followed by 5 mg to 20 mg once daily vs placebo	MA, PH of 2 studies by McIntyre et al Adult patients, 18 years of age or older, diagnosed with bipolar I disorder, experiencing depressive symptoms, with YMRS total score ≥20 or CGI-BP-D score ≥4, or mixed symptoms	N=977 3 weeks (after 1 week placebo run-in period)	Primary: Change in MADRS, CGI-BP-D, and PANSS Marder anxiety/depression factor scores from baseline Secondary: Not reported	Primary: In patients with baseline MADRS scores ≥20, CGI-BP-D scores ≥4, or those experiencing a mixed episode, there was no statistically significant difference between asenapine and olanzapine (P>0.05) in terms of improvement in MADRS scores from baseline on day-21; though, asenapine was more effective than placebo (P<0.05). In patients with baseline MADRS scores ≥20, significantly more patients in the asenapine group experienced remission compared to placebo on day-21 (70% vs. 33%; P=0.012); though, asenapine was not associated with a significantly greater remission rate compared to olanzapine (70% vs. 48%; P=0.066). In patients with baseline CGI-BP-D severity scores ≥4 or those exhibiting a mixed episode more patients in the asenapine group experienced remission compared to placebo on day-21 (P≤0.05). In these patients, olanzapine was associated with significantly greater remission rate compared to placebo on day-21 (P<0.05). In patients with MADRS scores ≥20, CGI-BP-D severity scores ≥4 or those exhibiting a mixed episode at baseline, there was no statistically significant difference between asenapine and olanzapine in terms of CGI-BP-D score reduction from baseline on day-21 (P>0.05). In patients with either CGI-BP-D severity scores ≥4 or those exhibiting a mixed episode at baseline, there was no statistically significant difference between asenapine and olanzapine in terms of PANSS Marder anxiety/depression factor score reduction from baseline on day-21 (P>0.05). Patients with baseline MADRS scores ≥20 who received asenapine exhibited a statistically greater improvement in PANSS Marder anxiety/depression scores compared to olanzapine on day-7 (P=0.001). Secondary: Not reported

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McIntyre et al[75] Continuing asenapine 5 mg to 10 mg twice daily vs continuing olanzapine 5 mg to 20 mg once daily vs switching from placebo to asenapine in a blinded fashion	DB, ES Adult patients, 18 years of age or older, diagnosed with bipolar I disorder, experiencing manic or mixed episodes, with YMRS total score ≥20	N=480 9 weeks	Primary: Change in YMRS scores from baseline Secondary: YMRS response and remission rates, CGI-BP, PANSS, MADRS, adverse events	Primary: At day-84, there was no statistically significant difference between asenapine and olanzapine in the YMRS score reduction from baseline (-24.4 vs. -23.9; *P* value not reported). Secondary: At day-84, there were no statistically significant differences between asenapine and olanzapine in terms of YMRS response (77% vs. 82%) and remission rates (75% vs. 79%; *P*>0.05 for both). The relative NNT values for olanzapine relative to asenapine in terms of YMRS response and remission were 40 and 48. At day-84, there was no statistically significant difference between asenapine and olanzapine in the CGI-BP score reduction from baseline (*P*>0.05). At day-84, there were no statistically significant differences between asenapine and olanzapine in either the PANSS total score or MADRS score reduction from baseline (*P*>0.05). There were no marked differences in the incidence of treatment-emergent or treatment-related adverse events between asenapine and olanzapine groups (*P* value not reported). The most frequently reported adverse events were sedation, dizziness, and insomnia with asenapine and sedation, headache, somnolence and weight gain with olanzapine. The incidence of extrapyramidal adverse events was 10% with placebo/asenapine, 15% with asenapine and 13% with olanzapine. Mean weight gain after 12 weeks of therapy was 0.5 kg with placebo/asenapine, 1.9 kg with asenapine, and 4.1 kg with olanzapine. The percentage of patients with clinically significant weight gain was greater with olanzapine (31%) than with asenapine (19%) after 12 weeks of therapy. The estimated NNH for clinically significant weight gain for olanzapine relative to asenapine was 9.
McIntyre et al[76] Continuing asenapine 5 mg to 10 mg twice daily	DB, DD, MC, PG, ES of the 2 studies by McIntyre et al	N=218 40 weeks (in addition to	Primary: Adverse events Secondary:	Primary: The incidence of treatment-emergent adverse events was 71.9%, 86.1%, and 79.4% with placebo/asenapine, asenapine, and olanzapine, respectively.

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vs continuing olanzapine 5 mg to 20 mg once daily vs switching from placebo to asenapine in a blinded fashion	Adult patients, 18 years of age or older, diagnosed with bipolar I disorder, experiencing manic or mixed episodes, with YMRS total score ≥20	the 3 week RCT and 12 week prior ES)	YMRS response at 52 weeks, YMRS remission at 52 weeks, change in YMRS scores, CGI-BP scores, and MADRS scores	The most frequent treatment-emergent adverse events were headache and somnolence with placebo/asenapine, insomnia, sedation and depression with asenapine, and weight gain, somnolence and sedation with olanzapine. Prolactin levels >4 times the upper limit of normal occurred in 0%, 6.5%, and 2.9% of patients receiving placebo/asenapine, asenapine and olanzapine, respectively. Shifts from normal to high fasting glucose levels occurred in 10%, 26%, and 22.2% of patients receiving placebo/asenapine, asenapine and olanzapine, respectively. The NNH value for asenapine relative to olanzapine was 27. Clinically significant weight gain occurred in 21.9%, 39.2%, and 55.1% of patients receiving placebo/asenapine, asenapine and olanzapine, respectively. The NNH value for olanzapine relative to asenapine was 7. Secondary: At week-52, there was no statistically significant difference between asenapine and olanzapine in the YMRS score reduction from baseline (-28.6 vs. -28.2; *P* value not reported). At week-52, there was no statistically significant difference between asenapine and olanzapine in terms of YMRS remission and response rates (97.8% vs. 98.4%; *P* value not reported). At week-52, there was no statistically significant difference between asenapine and olanzapine in the CGI-BP mania severity score reduction from baseline (-3.5 vs. -3.2; *P* value not reported). At week-52, there was no statistically significant difference between asenapine and olanzapine in the MADRS score reduction from baseline (-4.8 vs. -4.4; *P* value not reported).
Calabrese et al[77] Quetiapine 300 mg/day	DB, MC, PC, PG, RCT	N=838 8 weeks	Primary: Mean change in MADRS total score	Primary: Quetiapine at either dose demonstrated statistically significant improvement in MADRS total scores compared with placebo from week 1

vs quetiapine 600 mg/day vs placebo	Patients 18 to 65 years of age diagnosed with bipolar I or bipolar II disorder who were experiencing an acute depressive episode		from baseline to week 8 Secondary: Changes in CGI-I, CGI-S and HAM-D scores from baseline to week 8, rates of and time to response (≥50% improvement in the total MADRS score from baseline) and remission (MADRS total score ≤12)	onward (*P*<0.001 for all assessments). Secondary: Quetiapine-treated patients experienced a statistically significant improvement (*P*<0.001) on the CGI-S as early as week 1 that was sustained till the end of the study for both doses; a larger percentage of patients improved on the CGI-I scale in the 600 mg/day (55.9%) and 300 mg/day (64.0%) quetiapine groups compared with the placebo group (34.3%) at the final assessment. The mean change from baseline in the HAM-D scores at week 8 was -13.84, -13.38, and -8.54 in the quetiapine 600 mg/day, quetiapine 300 mg/day, and placebo groups respectively (*P*<0.001 for both quetiapine doses vs placebo). The proportions of patients meeting response criteria at the final assessment were 58.2% in the quetiapine 600 mg/day group, 57.6% in the quetiapine 300 mg/day group, and 36.1% in the placebo group. The proportion of patients meeting remission criteria were 52.9% in the quetiapine 600 mg/day and 300 mg/day groups, and 28.4% in the placebo group. Treatment-emergent mania rates were low and similar for the quetiapine and placebo groups (3.2% and 3.9%, respectively).
Tohen et al[78] Olanzapine 5-20 mg/day vs olanzapine-fluoxetine 6/25 mg vs olanzapine-fluoxetine 6/50 mg	DB, MC, PC, PG, RCT Patients 18 years or older diagnosed with bipolar I disorder, depressed	N=833 8 weeks	Primary: Change in MADRS total score from baseline to week 8 Secondary: Changes in CGI-BP, YMRS and HAM-A scores from baseline to week 8, rates of and time to response (≥50% improvement in the	Primary: During all 8 study weeks, the olanzapine and olanzapine-fluoxetine groups showed statistically significant improvement in depressive symptoms compared with the placebo group (olanzapine, -15.0; *P*=0.002; olanzapine-fluoxetine, -18.5; *P*<0.001). The olanzapine-fluoxetine group showed statistically greater improvement than the olanzapine group at week 8 (*P*=0.01). Secondary: The olanzapine group showed greater mean improvement on the CGI-BP than the placebo group (*P*=0.004), and the olanzapine-fluoxetine group showed greater mean improvement than both the placebo (*P*<0.001) and olanzapine (*P*=0.16) groups.

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vs olanzapine-fluoxetine 12/50 mg vs placebo			total MADRS score from baseline) and remission (MADRS total score ≤12 at an end point and completion of ≥4 weeks of study)	Treatment-emergent mania (YMRS total score <15 at baseline and ≥15 subsequently) did not differ among groups (placebo, 6.7%; olanzapine, 5.7%; olanzapine-fluoxetine, 6.4%). Remission criteria were met by 24.5% (87/355) of the placebo group, 32.8% (115/351) of the olanzapine group, and 48.8% (40/82) of the olanzapine-fluoxetine group. Adverse events for the olanzapine-fluoxetine group were similar to those in the olanzapine group, but also included higher rates of nausea and diarrhea.
Perlis et al[79] Olanzapine 5-20 mg/day vs risperidone 1-6 mg/day	DB, MC, PG, RCT Hospitalized patients with bipolar I disorder, manic or mixed episode, without psychotic features	N=329 3 weeks	Primary: Mean change in YMRS score from baseline to 3 weeks Secondary: Changes in CGI-BP severity of illness scale, improvement in depression by HAM-D-21 and MADRS scales, safety (assessed by the evaluation of treatment-emergent adverse events, discontinuations due to adverse events, vital sign measurements, and clinical laboratory tests)	Primary: Changes in YMRS scores from baseline to week 3 were not significantly different between treatment groups (olanzapine, -15.03; risperidone, -16.62; *P*>0.05). Secondary: No significant differences between treatment groups for the HAM-D-21 (olanzapine, -6.06; risperidone, -5.20), MADRS (olanzapine, -6.22; risperidone, -5.40), or CGI-BP (olanzapine, -1.64; risperidone, -1.46) scores (all *P*>0.05). With a response definition of ≥50% reduction in the YMRS score at endpoint, 62.1% of olanzapine-treated patients responded compared with 59.5% of the risperidone-treated patients. Olanzapine-treated patients experienced greater elevations in liver function enzymes (*P*<0.05) and increase in weight (2.5 kg vs 1.6 kg; *P*=0.004); risperidone-treated patients were more likely to experience prolactin elevation (51.73 ng/mL vs 8.23 ng/mL; *P*<0.001) and sexual dysfunction (total score increase of 1.75 vs 0.64; *P*=0.049).
Yatham et al[80] Continuation of usual oral atypical antipsychotic (olanzapine, quetiapine, or	MC, OL, PRO, RCT Stable adults aged 18-65 years of age diagnosed with	N=49 6 months	Primary: Safety measures (adverse events, lab tests, vital signs, weight and	Primary: At least one treatment emergent adverse event was reported by 16 (70%) of patients in the injection group and 19 (73%) in the oral group (*P* value not reported).

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risperidone) vs switching to long-acting risperidone 25 mg injection every 2 weeks	Bipolar I or Bipolar II according to DSM-IV criteria and currently on one oral atypical antipsychotic agent in combination with a maximum of two of lithium, valproate or lamotrigine; and, if applicable, one antidepressant		movement disorders scales such as the BARS, SAS, and AIMS) and efficacy measures (CGI-S, YMRS, MADRS, HAM-A, EuroQol EQ-5D, VAS and time to intervention) Secondary: Not reported	There were no clinical significant changes in laboratory tests in either group (*P* value not reported). There were no significant changes in weight or heart rate within each group; however, diastolic blood pressure was significantly different at the study endpoint in the risperidone injection group (–5.2±11.0; *P*=0.033). There were significant between group differences in reduction of diastolic blood pressure favoring the injection group (*P*<0.05). There were no significant differences between groups for mean changes in AIMS (*P*=0.95), SAS (*P*=0.11) or BARS (*P*=0.52) scores. The differences in changes in CGI-S and YMRS scores between the two groups was not significant (*P*=0.67 and *P*=0.31, respectively). There were also no significant differences in changes in MADRS or HAM-A scores between the groups (*P* values not reported). There were no significant differences between the groups on changes in VAS, EuroQuol EQ-5D, or scores on the resource use questionnaire (*P* vales not reported). There were no significant differences between groups on the number of interventions or time to intervention (*P* value not reported). Secondary: Not reported
Cipriani et al[81] Atypical antipsychotics (aripiprazole, asenapine, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone) vs anticonvulsants (carbamazepine, valproate,	MA Patients, 18 years of age or older, with a diagnosis of bipolar disorder (manic or mixed episode)	N=16,073 3 weeks	Primary: Mean change in YMRS scores and dropout rates Secondary: Responder rate	Primary: Haloperidol (standardised mean difference [SMD] -0.56; 95%CI, -0.69 to -0.43), risperidone (-0.50; -0.63 to -0.38), olanzapine (-0.43; -0.54 to -0.32), lithium (-0.37; -0.63 to -0.11), quetiapine (-0.37; -0.51 to -0.23), aripiprazole (-0.37; -0.51 to -0.23), carbamazepine (-0·36; -0.60 to -0.11, asenapine (-0.30; -0.53 to -0.07), valproate (-0·20; -0.37 to -0.04), and ziprasidone (-0.20; -0.37 to -0.03) were significantly more effective than placebo in terms of mean change in YMRS scores from baseline. Gabapentin, lamotrigine, and topiramate were not significantly different from placebo in the mean change in YMRS scores from baseline (*P* value not reported).

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gabapentin, lamotrigine, topiramate) vs haloperidol vs lithium vs placebo				Risperidone was not significantly different from either olanzapine or quetiapine in the mean change in YMRS scores from baseline (*P* value not reported). Haloperidol had the highest number of significant differences and was significantly more effective than lithium (SMD, -0.19; 95% CI -0.36 to -0.01), quetiapine (-0.19; -0.37 to 0·01), aripiprazole (-0.19; -0.36 to -0.02), carbamazepine (-0.20; -0.36 to -0·01), asenapine (-0·26; -0·52 to 0·01), valproate (-0.36; -0.56 to -0.15), ziprasidone (-0.36; -0.56 to -0.15), lamotrigine (-0.48; -0.77 to -0·19), topiramate (-0.63; -0.84 to -0.43), and gabapentin (-0.88; -1.40 to -0.36). Risperidone and olanzapine exhibited a similar profile of comparative efficacy to haloperidol, being more effective than valproate, ziprasidone, lamotrigine, topiramate, and gabapentin. Topiramate and gabapentin were significantly less effective compared to all other antimanic drugs. Olanzapine was associated with significantly greater improvement in YMRS scores from baseline compared to asenapine (-.22; -0.37 to -0.08). Olanzapine, risperidone, and quetiapine were associated with significantly lower drop out rate compared to lithium, lamotrigine, placebo, topiramate, and gabapentin (*P* value not reported). Aripiprazole was not statistically different from olanzapine, risperidone, and quetiapine in terms of the likelihood of discontinuing therapy (*P* value not reported). When the evaluated antimanic drugs were ordered by their probability to be the best treatment in terms of both efficacy (improvement on the YMRS) and tolerability (assessed via drop out rates), risperidone was found to be the most effective treatment option. In order of decreased efficacy, the next best treatment options were olanzapine, haloperidol, quetiapine, carbamazepine, aripiprazole, valproate, lithium, ziprasidone and asenapine. Lamotrigine, topiramate and gabapentin were found to be less effective than placebo. Secondary: Compared to placebo, aripiprazole (Odds Ratio [OR], 0.50; 0.38 to 0.66), asenapine (0.49; 0.29 to 0.83), carbamazepine (0.40; 0.22 to 0.77),

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				valproate (0.50; 0.36 to 0.70), haloperidol (0.44; 0.33 to 0.58), lithium (0.55; 0.38 to 0.79), olanzapine (0.46; 0.36 to 0.58), quetiapine (0.50; 0.37 to 0.66), and risperidone (0.47; 0.35 to 0.61) were associated with better response rates. The difference in response rates between olanzapine and asenapine, olanzapine and risperidone, as well as quetiapine and risperidone were not statistically significant.
Perlis et al[82] Aripiprazole, olanzapine, quetiapine, risperidone or ziprasidone Monotherapy and adjunctive trial; no head-to-head comparative studies included.	MA of PC, randomized, trials Patients with a diagnosis of bipolar mania	N=4,304 12 placebo-controlled monotherapy trials; 6 placebo-controlled adjunctive or combination therapy trials Duration: 3-6 weeks	Primary: Change in YMRS score at day 21 or 28 and rates of response at endpoint (defined as ≥50% decrease in YMRS score) Secondary: Proportion of patients achieving response	Primary: For the monotherapy studies all of the agents demonstrated significant efficacy; no differences were detected among any of the second generation antipsychotics studied (the global F test for a main effect of drug was not significant [*P*=0.38], and no pairwise significant differences among drugs were found at the 0.05 level after adjustment for multiple comparisons using the Tukey HSD procedure). For the add-on therapy studies no differences in efficacy were detected among any of the drugs (the global F test for a main effect of drug was not significant [*P*=0.25], and no pairwise significant differences among drugs were found). Secondary: For the monotherapy trials overall response rates were 53% for second generation antipsychotics and 30% for placebo. For the add-on therapy studies only 3 trials reported data on response rates; the data set was too small to analyze.
Tarr et al[83] Atypical antipsychotics (olanzapine, quetiapine, aripiprazole, risperidone) vs mood stabilizers (valproic acid, lithium)	MA Patients with manic or mixed type Bipolar I disorder	N=1,631 3-4 weeks	Primary: Mean change from baseline in symptom severity, responder rate, drop-out rate Secondary: Not reported	Primary: Atypical antipsychotics were associated with significantly greater improvement in mania rating scales compared with mood stabilizers (SMD, -0.22; 95%CI, -0.33 to -0.11; *P*<0.0001). Responder rates were 7% higher with atypical antipsychotics compared with mood stabilizers (*P*=0.02; NNT=17). Drop-out rates were 5% lower with atypical antipsychotics compared with mood stabilizers (*P*=0.02).

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				Secondary: Not reported
Yildiz et al[84] Atypical antipsychotics (aripiprazole, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone) vs Mood stabilizers (carbamazepine, lithium, valproate) vs haloperidol vs tamoxifen vs placebo	MA Adult patients with manic or mixed Bipolar I disorder	N=13,093 Study duration not reported	Primary: Hedges' g scores, responder rate Secondary: Not reported	Primary: Compared to placebo, the following drugs were associated with a significant improvement from baseline in manic symptoms: aripiprazole, carbamazepine, haloperidol, lithium, olanzapine, paliperidone, quetiapine, risperidone, tamoxifen, valproate, and ziprasidone. The pooled effect size for these drugs was moderate (*P*<0.0001). For categorical responder rate, the pooled responder risk ratio was 1.52 (95%CI, 1.42 to 1.62; *P*<0.0001). The responder rate difference between these drugs and placebo was 17% (drug: 48% vs. placebo: 31%), with a NNT to produce a response of 6 (*P*<0.0001). Among the atypical antipsychotics, risperidone was associated with the fewest number of patients needed to be treated to produce a positive response to therapy (NNT=4.2), followed by olanzapine (NNT=5), quetiapine (NNT=5.6), ziprasidone (NNT=5.9), aripiprazole (NNT=8.3), and finally paliperidone (NNT=12.5). Risperidone, haloperidol and tamoxifen were associated with large effect sizes compared to placebo (Hedges's g, 0.26 to 0.46). Lamotrigine, topiramate and verapamil were not associated with significantly greater efficacy in terms of the Hedges's g scores compared to placebo (*P*=0.62). Compared to placebo, atypical antipsychotics as a class were associated with a larger Hedges' g effect size (0.40; *P*<0.0001) than the mood stabilizers (0.38; *P*<0.0001). Atypical antipsychotics were also associated with greater categorical responder rate than the mood stabilizers (*P*=0.006). Antipsychotics were comparable or faster acting than the mood stabilizers in 7 trials (*P*=0.01). Secondary: Not reported
Vieta et al[85] Atypical antipsychotics	MA Patients, 18 years	N=6,731 6 to 12 weeks	Primary: MADRS, HAM-D, response,	Primary: The greatest reduction in MADRS scores from baseline compared to placebo were noted with quetiapine 300 mg daily (-4.8; 95%CI, -6.18 to -

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(quetiapine, olanzapine, aripiprazole) alone or as combination therapy vs olanzapine/fluoxetine alone or as combination therapy vs paroxetine alone or as combination therapy vs mood stabilizers (lamotrigine, lithium, divalproex) alone or as combination therapy vs phenelzine alone or as combination therapy vs placebo	of age or older, with Bipolar I or II disorder and acute bipolar depression		remission Secondary: Not reported	3.49), quetiapine 600 mg (-4.8; 95%CI, -6.22 to -3.28) and olanzapine/fluoxetine combination therapy (-6.6; 95%CI, -9.59 to -3.61). Olanzapine was also associated with significant improvement in MADRS scores compared to placebo (*P*=0.004). The greatest reduction in HAM-D scores from baseline compared to placebo was noted with quetiapine (-4.0 points; 95%CI, -5.0 to -2.9; *P*=0.000). The other study drugs were not associated with a significant change in HAM-D scores compared to placebo. Quetiapine, lamotrigine, olanzapine, olanzapine/fluoxetine, imipramine, and divalproex were associated with a significantly greater response rate compared to placebo (*P*<0.05). Paroxetine, lithium, aripiprazole, and phenelzine were not associated with a significant difference in response rate compared with placebo. Quetiapine, olanzapine, olanzapine/fluoxetine were associated with significantly greater remission rates compared to placebo (*P*<0.05). The other study medications were no significantly difference from placebo in terms of remission rate. Secondary: Not reported
Treatment-Resistant Depression				
Papakostas et al[86] Aripiprazole 15 mg daily or 10 mg daily (if taken with fluoxetine or paroxetine) for 1 week, followed by upward titration up to 30 mg/day, clinical response or toxicity	OL, PRO Patients between the ages of 18 and 65 years, diagnosed to have MDD by the use of the Structured Clinical Interview	N=12 8 weeks	Primary: Clinical response (defined as a 50% or greater reduction in HAM-D-17 score from baseline), remission (defined as a final HAM-D-17 score of less	Primary: Using an ITT analysis, 58.3% of patients responded to therapy (*P* value not reported). A remission rate of 41.7% was observed in the study population (*P* value not reported). Secondary: There was a significant reduction in mean CGI score from baseline

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	for DSM-IV-Axis I disorders and with an initial 17-item HAM-D-17 score of 14 or greater; patients were required to have had an adequate trial of an SSRI (a minimum dose of 10 mg/day for escitalopram, 20 mg/day for fluoxetine, paroxetine, and citalopram, or 50 mg/day for sertraline, for at least 6 weeks)		than or equal to 7) Secondary: Reduction in CGI score, reduction in HAM-D-17 score, adverse effects	(*P*=0.0002). There was a significant reduction in mean HAM-D-17 score from baseline (*P*<0.0001). None of the evaluated patients experienced a severe side effect.
Papakostas et al[87] Ziprasidone 20 mg twice a day for 1 week, followed by an upward titration up to 80 mg/day, clinical response or toxicity	OL, PRO Patients between the ages of 18 and 65, diagnosed to have MDD by the use of the Structured Clinical Interview for DSM-IV-Axis I disorders and with an initial 17-item HAM-D-17 score of 14 or greater; patients were required to have had an adequate trial of an SSRI (a minimum dose of 10 mg/day	N=20 6 weeks	Primary: Clinical response (defined as a 50% or greater reduction in HAM-D-17 total score from baseline), remission (defined as a final HAM-D-17 score of less than or equal to 7) Secondary: Improvement in SQ-depression, -anxiety, -anger/hostility, somatic symptom, somatic well-being	Primary: Using an ITT analysis, 50.0% of patients responded to therapy (*P* value not reported). A remission rate of 38.5% was observed in the study population (*P* value not reported). Secondary: At the end of the study, a significant improvement was observed in SQ-depression scores (17.5 vs 12.5, respectively; *P*=0.001), SQ-anxiety scores (14.1 vs 11.8, respectively; *P*=0.002), and SQ-anger/hostility scores (10.4 vs 6.9, respectively; *P*=0.021). There was no significant improvement in SQ-somatic symptom scores (9.6 vs 10.6; *P*>0.05) or SQ-somatic well-being scores (1.5 vs 1.5, respectively; *P*>0.05). None of the evaluated patients experienced a severe side effect.

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	for escitalopram, 20 mg/day for fluoxetine, paroxetine, and citalopram, or 50 mg/day for sertraline, for at least 6 weeks)		scale, adverse effects	There was no change in QTc from baseline to week 6 of the study (*P*>0.05). In addition, cholesterol level decreased compared to baseline (*P*>0.05).
Barbee et al[88] Olanzapine, quetiapine, risperidone, ziprasidone started at a low dose and titrated up to the maximal tolerated dose	RETRO Patients with treatment-resistant, nonpsychotic MDD, diagnosed based on the DSM-IV criteria, with an adequate trial of an SSRI at the highest tolerated dose for a minimum of 6 weeks	N=49 (Duration varied from 9.40 to 35.86 weeks)	Primary: Clinical response assessed via a CGI scale Secondary: GAF score, rate of discontinuation	Primary: The overall response rate based on the CGI rating was 65%. Individual rates of response were 57% for olanzapine, 50% for risperidone, 33% for quetiapine and 10% for ziprasidone. While the response rates noted with olanzapine, risperidone and quetiapine were significantly different from zero (*P*<0.001); the observed response rate for ziprasidone was not different from zero (*P*=0.47). Secondary: There was an improvement in the GAF scores compared to baseline in the olanzapine (*P*<0.001) and risperidone (*P*=0.047) groups. There was no significant difference in the rate of discontinuation among patients receiving the four antipsychotic agents (*P*=0.13). Patients experienced only mild side effects with all of the evaluated antipsychotics.
Bauer et al[89] Quetiapine XR 150 mg daily, in addition to ongoing antidepressant therapy vs quetiapine XR 300 mg daily, in addition to ongoing antidepressant therapy vs	MA Patients, aged 18 to 65 years, diagnosed with MDD based on the DSM-IV criteria, with HAM-D total score ≥20 and a HAM-D Item 1 (depressed mood) score ≥2 after an adequate trial (>6 weeks of therapy at	N=939 6 weeks	Primary: Change in MADRS total score at week-6 Secondary: MADRS response rate, MADRS remission rate, HAM-D, HAM-A, Pittsburgh Sleep Quality Index (PSQI), CGI-S scores, adverse	Primary: Quetiapine XR 150 mg and 300 mg daily doses were associated with significant improvements in MADRS total scores from baseline, compared to placebo (-14.5 vs. -14.8 vs. -12.0, respectively; *P*<0.001 for both). Significant benefit of quetiapine XR over placebo was noted as early as week-1 and was sustained through week-6. Secondary: Quetiapine XR 300 mg daily was associated with significantly greater MADRS response rate compared to placebo (58.3% vs. 46.2%; *P*<0.01). Quetiapine XR 150 mg daily was associated with marginal benefit over placebo in terms of MADRS response rate, but the difference did not reach statistical significance (53.7% vs. 46.2%; *P*=0.063).

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placebo, in addition to ongoing antidepressant therapy	an adequate dose)of one of the following antidepressants: amitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline or venlafaxine		events	Quetiapine XR 150 mg and 300 mg daily doses were associated with significantly greater remission rates compared to placebo (35.6% vs. 36.5% vs. 24.1%, respectively; *P*<0.01 for both). Both quetiapine XR doses were associated with significant improvement from baseline, compared to placebo, in HAM-D, HAM-A, PSQI and CGI-S scores at week-6 of therapy (*P*<0.05). Significantly more patients in the quetiapine XR 150 mg and 300 mg groups discontinued the study due to adverse events compared to the placebo group (8.9% vs. 15.4% vs. 1.9%, respectively). In the quetiapine XR groups, the most common adverse events leading to discontinuation were somnolence and sedation. The incidence of adverse events potentially related to extrapyramidal side effects was 3.8%, 6.4% and 4.2% of patients in the quetiapine XR 150 mg, 300 mg, and placebo groups. The incidence of suicidality was 1.0%, 0.0% and 0.6% of patients in the quetiapine XR 150 mg, 300 mg, and placebo groups. Mean weight gain from baseline to week-6 in the quetiapine XR 150 mg, 300 mg, and placebo groups were 0.9 kg, 1.3 kg, and 0.2 kg, respectively. Secondary: Not reported
Komosa et al[90] Atypical antipsychotics (aripiprazole, amisulpride*, olanzapine, quetiapine, risperidone) as monotherapy or augmentation therapy to antidepressants vs	SR Patients with unipolar major depressive disorder or dysthymia	N=8,487 28 studies 12 to 52 weeks	Primary: Treatment response (reduction of ≥50% on the HAM-D or the MADRS or at least much improved score on the CGI scale) Secondary:	Primary: According to efficacy data from three available studies, aripiprazole augmentation therapy was associated with an odds ratio of a positive treatment response of 0.48 (95% CI, 0.37 to 0.63; *P* value not reported). There was no significant difference between olanzapine augmentation therapy and placebo in treatment response rate (*P* value not reported). According to efficacy data from three available studies, quetiapine monotherapy was associated with an odds ratio of a positive treatment response of 0.52 (95% CI, 0.41 to 0.66; *P* value not reported).

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placebo or antidepressants			MADRS scores, HAM-D scores, HAM-A scores, remission (HAM-D ≤7 or MADRS ≤10), adverse events	According to efficacy data from two available studies, quetiapine augmentation therapy was associated with an odds ratio of a positive treatment response of 0.68 (95% CI, 0.52 to 0.90; *P* value not reported). According to efficacy data from two available studies, risperidone augmentation therapy was associated with an odds ratio of a positive treatment response of 0.57 (95% CI, 0.36 to 0.89; *P* value not reported). Secondary: According to efficacy data from three available studies, aripiprazole augmentation therapy was associated with a reduction in MADRS scores from baseline, compared to placebo (Mean Difference [MD], -3.04; 95% CI, -4.09 to -2.00; *P* value not reported). According to efficacy data from one available study, aripiprazole augmentation therapy was associated with a significant improvement in CGI scores from baseline, compared to placebo (OR, 0.51; 95% CI, 0.34 to 0.78; *P* value not reported). Compared to placebo, aripiprazole augmentation therapy was also associated with a significantly greater odds ratio of achieving remission (OR, 0.48; 05%CI, 0.36 to 0.64). Olanzapine augmentation therapy was associated with a lower discontinuation rate due to inefficacy compared to placebo. There were no significant differences in efficacy endpoints between the olanzapine monotherapy group and either placebo or antidepressant comparator groups. However, olanzapine augmentation therapy was associated with a significant reduction in MADRS scores from baseline, compared to placebo (MD, -2.84; 95% CI, -5.48 to -0.20; *P* value not reported). Olanzapine augmentation therapy was likewise associated with a significant improvement from baseline, compared to placebo in anxiety symptoms, as measured by the HAM-A scale (MD, -1.44; 95%CI, -2.81 to -0.06). There was no significant difference between olanzapine augmentation therapy and placebo in HAM-D score reduction from baseline (MD, -7.90; 95%CI, -16.63 to 0.83). According to efficacy data from two available studies, quetiapine augmentation therapy was associated with a significant improvement in

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				CGI scores from baseline, compared to placebo (OR, 0.64; 95% CI, 0.49 to 0.84; *P* value not reported). Significantly more patients receiving quetiapine augmentation therapy, compared with placebo, experienced remission (OR, 0.52; 95%CI, 0.38 to 0.71). Likewise quetiapine augmentation therapy was associated with a significant improvement from baseline, compared to placebo in MADRS scores (OR, 6.80; 95%CI, 0.52 to 0.90) and HAM-A scores (OR, 0.23; 95%CI, 0.08 to 0.70). Significantly more patients receiving risperidone augmentation therapy, compared with placebo, experienced remission (OR, 0.39; 95%CI, 0.22 to 0.69). HAM-D scores were significantly improved from baseline, compared to placebo with risperidone augmentation therapy (OR, 0.60; 95%CI, 0.38 to 0.95). There was no significant difference between risperidone and placebo augmentation groups in MADRS scores at endpoint (MD, -1.85; 95%ci, -9.71 to 5.47). Compared to placebo, aripiprazole augmentation therapy was associated with an increased risk of weight gain, akathisia, and extrapyramidal symptoms. Aripiprazole was not associated with an increased incidence of sedation or tremor. Olanzapine augmentation was associated with an increased risk of sedation and weight gain. Risperidone was associated with an increased risk of weight gain and prolactin release. Risperidone therapy was not associated with an increased risk of extrapyramidal events or sedation. Quetiapine was associated with an increased risk of sedation and weight gain. Quetiapine was not associated with an increased risk of extrapyramidal events or prolactin levels.

* Agent is not available in the United States.
†Did not meet investigators' *a priori* standard of statistical significance, which adjusted for multiple comparisons.
Study design abbreviations: DB=double-blind, CI=confidence interval, DD=double dummy, ES=extension study, FD=fixed dose, HR=hazard ratio, LOCF=last observation carried forward, MA=meta analysis, MC=multicenter, NNH=number needed to harm, NNT=number needed to treat, OL=open-label, OR=odds ratio, OS=observational, PH=post-hoc analysis, PC=placebo controlled, PG=parallel group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=risk ratio, SMD=standardized mean difference, SR=systematic review
Other abbreviations: AIMS=Abnormal Involuntary Movement Scale, BARS=Barnes Akathisia Rating Scale, BMI=body mass index, CATIE=Clinical Antipsychotic Trials of Intervention Effectiveness, CGI=Clinical Global Impression, CGI-BP=Clinical Global Impressions-Bipolar Version, BPRS= Brief Psychiatric Rating Scale, CARS=Childhood Autism Rating Scale, CDSS=Calgary Depression Scale for Schizophrenia, CGAS=Children's Global Assessment Scale, CGI-C=Clinical Global Impression of Change, CGI-I=Clinical Global Impression-Improvement, CGI-S=Clinical Global Improvement-Severity of Illness, CI=confidence interval, CMAI=Cohen-Mansfield Agitation Inventory, CPRS=Children's Psychiatric Rating Scale, DSM-IV-TR=Diagnostic and Statistical Manual of Mental Disorders, 4th edition-text revision, EPS=extrapyramidal symptoms, ESRS=Extrapyramidal Symptom Rating Scale, GAF=Global Assessment of Functioning, HAM-A=Hamilton Rating Scale for Anxiety, HAM-D=Hamilton Rating Scale for Depression, ITT=intent-to-treat, LOCF=last observation carried forward, MADRS=Montgomery-Asberg Depression Rating Scale, MCCB=Matricus Consensus Cognitive Battery, MDD=major depressive disorder, NAB=Neuropsychological Assessment Battery, PANSS=Positive and Negative Syndrome Scale, PANSS EC=Positive and Negative Syndrome Scale Excited Component, PSP=Personal and Social Performance scale, PSQI=Pittsburgh Sleep Quality Index, QLS=quality of life scale, RSSE=Rating Scale for Side Effects, SAS=Simpson-Angus Scale, SCoRS=Schizophrenia Cognition Rating Scale, SD=standard deviation, SDS=Schedule for Deficit Syndrome, SGA=second-generation antipsychotic, SGOT=serum glutamic oxaloacetic transaminase, SGPT= serum glutamic pyruvic transaminase, SSRI=selective serotonin-reuptake inhibitor, VAS=visual analog scale, WMS=Wenchsler Memory Scale, WMD=weighted mean difference, YMRS=Young Mania Rating Scale

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Table 5. Off-Label Efficacy Clinical Trials Using the Antipsychotics for Adults

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
General				
Maher et al[91] (AHRQ Review) Atypical antipsychotic (risperidone, olanzapine, quetiapine, aripiprazole, ziprasidone, asenapine, iloperidone, paliperidone) vs atypical antipsychotic, placebo, or other pharmacotherapy Note: no relevant studies of asenapine, iloperidone, or paliperidone were identified	SR Controlled studies comparing atypical antipsychotics with another atypical antipsychotic, placebo or other pharmacotherapy in patients with anxiety disorder, ADHD, dementia and severe geriatric agitation, major depressive disorder, eating disorder, insomnia, OCD, PTSD, personality disorders, substance abuse, and Tourette's syndrome	N=not reported (169 trials) Study duration varied	Primary: Dementia (improvement in psychosis, agitation and total global score), anxiety (HAM-A response), OCD (proportion of patients responding using the YBOCS scale), adverse events Secondary: Not reported	Primary: *Psychosis, Agitation, Global Behavioral Symptoms in Dementia:* Compared with placebo, aripiprazole (difference, 0.20; 95%CI, 0.04 to 0.35), olanzapine (difference, 0.12; 95%CI, 0.00 to 0.25), and risperidone (difference, 0.19; 95%CI, 0.00 to 0.38) were associated with small but statistically significant improvement in global symptoms from baseline. The pooled effect size for quetiapine was similar, but not statistically significant compared to placebo (difference, 0.13; 95%CI, -0.02 to 0.28). For the outcome of psychosis, only risperidone was associated with a statistically significant improvement from baseline, compared to placebo (difference, 0.20; 95%CI, 0.05 to 0.36). The pooled effect sizes for aripiprazole (difference, 0.14; 95%CI, -0.02 to 0.29), olanzapine (difference, 0.05; 95%CI, -0.07 to 0.17), and quetiapine (difference, 0.04; 95%CI, -0.11 to 0.19) were not significantly different from placebo. Risperidone, aripiprazole, and olanzapine were all associated with statistically significant improvement in agitation compared to placebo. The pooled effect sizes ranged from 0.19 to 0.31. The pooled effect size for quetiapine was not significantly different from placebo (difference, 0.05; 95%CI, -0.14 to 0.25). There were no statistically significant differences between risperidone and olanzapine or risperidone and quetiapine (*P* value not reported). *Generalized Anxiety Disorder:* Significantly more patients in the quetiapine group experienced response to treatment, defined as at least a 50% improvement in HAMD-A scores from baseline, compared to placebo. The pooled result indicates a 26% increase in the risk of a positive response at 8 weeks of therapy (RR, 1.26; 95%CI, 1.02 to 1.56). Olanzapine (RR, 6.67; 95%CI, 0.93 to 47.59) and risperidone (RR, 0.99;

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				95%CI, 0.78 to 1.25) were not associated with a significantly increased risk of a positive treatment response, compared to placebo. In head-to-head studies, quetiapine was comparable to paroxetine and escitalopram at 8 weeks (*P* value not reported). *Obsessive Compulsive Disorder:* Significantly more patients in the risperidone group experienced a positive response to treatment, compared to placebo (RR, 3.92; 95%CI, 1.26 to 12.13). Risperidone was associated with a 3.9-fold greater probability of responding compared to placebo; the NNT was estimated as 5. Olanzapine (RR, 1.00; 95%CI, 0.49 to 2.03) and quetiapine (RR, 2.36; 95%CI, 0.85 to 6.57) were not associated with significantly greater response rates compared to placebo. *Other Conditions:* Available evidence (6 trials) indicated that atypical antipsychotics are not effective in causing significant weight gain in patients with eating disorders. The level of evidence is mixed regarding personality disorders and moderate for an association of risperidone with improving post-traumatic stress disorder. Evidence does not support efficacy of atypical antipsychotics for substance abuse. *Safety:* In the elderly patients, aripiprazole was associated with significantly increased odds of experiencing sedation. Olanzapine was associated with significantly increased odds of experiencing a cardiovascular event, increased appetite/weight gain, anticholinergic events, sedation, extrapyramidal symptoms (NNH=10), and urinary tract symptoms.

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Quetiapine was associated with significantly increased odds of experiencing sedation and urinary tract symptoms. Risperidone was associated with significantly increased odds of experiencing sedation, cardiovascular event, cerebrovascular event (for stroke, NNH=53), extrapyramidal symptoms (NNH=20) and urinary tract symptoms. In the non-elderly adult patients, aripiprazole was associated with significantly increased odds of experiencing increased appetite/weight gain, sedation, fatigue, akathisia, and extrapyramidal symptoms. Olanzapine was associated with significantly increased odds of experiencing sedation, increased appetite/weight gain, and fatigue. Quetiapine was associated with significantly increased odds of experiencing sedation, increased appetite/weight gain, fatigue, and extrapyramidal symptoms. Risperidone was associated with significantly increased odds of experiencing increased appetite/weight gain, sedation. Ziprasidone was associated with significantly increased odds of experiencing sedation and extrapyramidal symptoms. Secondary: Not reported
Anxiety Disorders				
Depping et al[92] Olanzapine, quetiapine, or risperidone as adjunctive therapy or monotherapy vs placebo vs antidepressants	SR Randomized controlled studies comparing olanzapine, quetiapine or risperidone with placebo, benzodiazepines, pregabalin or antidepressants in adult patients with generalized anxiety	N=4,144 (11 studies) up to 52 weeks	Primary: Treatment response (≥50% reduction in HAM-A scores), remission (HAM-A score ≤7), relapse (recurrence of anxiety symptoms), HAM-A, HAM-D, MADRS, CGI, BSPS Secondary:	Primary: Quetiapine was associated with a significantly greater response rate compared to placebo in patients with generalized anxiety disorder (OR, 2.21; 95%CI, 1.10 to 4.45; *P*=0.03). Compared to placebo, quetiapine therapy was associated with a greater remission rate (OR, 1.83; 95%CI, 1.07 to 3.12; *P*=0.03). Compared to quetiapine, more patients experienced a relapse with placebo (OR, 0.18; 95%CI, 0.10 to 0.30). There was no statistically significant difference between quetiapine and placebo groups in clinically meaningful change in CGI from baseline (OR, 2.28; 95%CI, 1.01 to 5.14). Moreover, HAM-A and MADRS scores were significantly improved in patients receiving quetiapine compared to placebo. Significantly more patients left the study early due to adverse events in the quetiapine group, compared to placebo (36.9% vs.5.4%). Compared to placebo, quetiapine therapy was associated with a

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	disorder , panic disorder, or phobias		Not reported	significantly increased risk of extrapyramidal adverse effects (2.5% vs. 4.4%), weight gain (MD, 0.63 kg), and sedation (6.7% vs. 24.5%). There was no statistically significant difference between quetiapine monotherapy and antidepressant groups in response rate, remission, global state (assessed via CGI scores), change in HAM-A scores, or change in MADRs scores (*P* value not reported). However, a larger percentage of patients in the quetiapine versus antidepressant groups left the study early due to adverse events (17.6% vs. 8.9%, respectively). Comparing quetiapine add-on therapy to antidepressants and placebo adjunctive therapy in patients with generalized anxiety disorder, there were no statistically significant differences between groups in response, remission, global state, change in HAM-A, MADRS scores or percentage of patients leaving the study early (*P* value not reported). Comparing quetiapine monotherapy and placebo in patients with social phobia, there were no statistically significant differences between groups in response rate or global state (*P* value not reported). However, patients in the quetiapine groups exhibited lower BSPS scores at endpoint, indicating an improvement in anxiety symptoms (MD, 31.10; 95%CI, -85.41 to 147.61). Comparing olanzapine monotherapy and placebo in patients with social phobia, there were no statistically significant differences between groups in response rate, global state or percentage of patients leaving the study early (*P* value not reported). However, patients in the quetiapine groups exhibited lower BSPS scores at endpoint, indicating an improvement in anxiety symptoms (MD, -22.50; 95%CI, -35.25 to -9.75). There were no significant differences between groups in weight gain. Comparing olanzapine add-on therapy to antidepressants and placebo adjunctive therapy in patients with generalized anxiety disorder, there were no statistically significant differences between groups in response, remission, or percentage of patients leaving the study early (*P* value not

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				reported). In contrast, olanzapine add-on therapy was associated with a significant improvement from baseline in anxiety symptoms (HAM-A scores) and depressive symptoms (HAM-D), compared to adjunctive placebo therapy. Significantly more patients in the olanzapine group experienced weight gain and sedation. Comparing risperidone add-on therapy to antidepressants and placebo adjunctive therapy in patients with generalized anxiety disorder, there were no statistically significant differences between groups in response, remission, CGI scores, MADRS scores, or percentage of patients leaving the study early (*P* value not reported). In contrast, risperidone add-on therapy was associated with a significant improvement from baseline in anxiety symptoms (HAM-A scores) compared to adjunctive placebo therapy. There were no significant differences between groups in weight gain, sedation or extrapyramidal adverse events from baseline. Secondary: Not reported
Lalonde et al[93] Atypical antipsychotics (olanzapine, quetiapine, risperidone), used as monotherapy in patients with uncomplicated GAD or as augmentation therapy for refractory GAD Refractory GAD was defined as moderate symptoms despite 4-10 weeks of prior therapy with an evidence-based drug	MA Adults over the age of 18 treated with an atypical antipsychotic for generalized anxiety disorder (GAD)	N=2,459 5 to 8 weeks	Primary:	Primary: Compared to placebo, augmentation with atypical antipsychotics was not associated with a significantly greater clinical response (RR, 1.14; 95%CI, 0.92 to 1.41; *P*=0.22). Patients receiving augmentation therapy with an antipsychotic were 43% more likely to discontinue therapy than those receiving placebo (RR, 1.43; 95%CI, 1.04 to 1.96; *P*=0.03). The NNH was 14. Compared to placebo, augmentation with atypical antipsychotics was not associated with a significantly greater remission rate (RR, 1.28; 95%CI, 0.96 to 1.71; *P*=0.09). Compared to placebo, augmentation with atypical antipsychotics was not associated with a significant change in HAM-A scores from baseline (mean difference, -2.69; 95%CI, -5.90 to 0.52).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Patients who received augmentation antipsychotic therapy did not experience a significantly greater weight gain than patients receiving placebo (*P* value not reported). Patients receiving quetiapine 150 mg monotherapy for the treatment of uncomplicated GAD were 31% more likely to experience a positive response than those receiving placebo (RR, 1.31; 95%CI, 1.20 to 1.44; *P*<0.00001). The NNT was 7. Patients receiving quetiapine 150 mg monotherapy for the treatment of uncomplicated GAD were 44% more likely to achieve remission than those receiving placebo (RR, 1.44; 95%CI, 1.23 to 1.68; *P*<0.00001). The NNT was 9. Patients receiving quetiapine 150 mg monotherapy experienced a significant 3.66 point reduction in HAM-A scores compared to placebo (95%CI, -5.13 to -2.19). Patients receiving quetiapine 150 mg monotherapy gained an average of 2.2 lbs (95%CI, 1.16 to 3.24) more than patients receiving placebo. Significantly more patients discontinued therapy in the quetiapine 150 mg monotherapy group compared with the placebo group (RR, 1.30; 95%CI, 1.09 to 1.54; *P*=0.004). Secondary: Not reported
Borderline Personality Disorder				
Lieb et al[94] Atypical antipsychotics, antidepressants, or mood stabilizers vs	SR Randomized controlled studies in adults patients with borderline personality disorder	N=1,714 5 to 24 weeks	Primary: Anger, impulsivity, psychotic symptoms, interpersonal problems, anxiety, depression	In one study (N=52), aripiprazole was found to have both significant effects on the reduction of the core symptoms of borderline personality (anger, impulsivity, psychotic symptoms, interpersonal problems) as well as in the treatment of comorbid conditions (depression, anxiety). Pooled data from placebo-controlled studies with olanzapine (N=631) demonstrate significant reduction of affective instability (SMC, -0.16;

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo			Secondary: Not reported	95%CI, -0.32 to -0.01), anger (SMC, -0.27; 95%CI, -0.43 to -0.12), and psychotic symptoms (SMC, -0.18; 95%CI, -0.34 to -0.03). Anxiety symptoms were also reduced in one study with olanzapine. Ziprasidone was not demonstrated to exert significant effects on any outcome measure. Among the mood stabilizers, beneficial effects were found with divalproex sodium, lamotrigine and topiramate. Carbamazepine was not associated with a benefit in patients with borderline personality disorder. There was little evidence of efficacy with antidepressants. Only amitriptyline was associated with a significant reduction in depressive symptoms from baseline. No significant effect was found with fluoxetine and fluvoxamine. Secondary: Not reported
Mercer et al[95] Antipsychotics, antidepressants, or mood stabilizers	MA Randomized, controlled, double-blind studies in patients with BPD	N=735 5 to 24 weeks	Primary: Anger, symptoms of depression Secondary: Not reported	Primary: Mood stabilizers, with the exception of divalproic acid, were found to have the largest effect size for anger (-1.75; 95%CI, -2.77 to -0.74; *P*<0.001). The effect on anger was seen with lamotrigine, topiramate, and carbamazepine when used for up to 10 weeks. Divalproic acid and carbamazepine had a moderate effect on depression (-0.63; 95%CI, -0.99 to -0.27; *P*<0.001). Antidepressants, with the exception of tricyclic antidepressants, had a moderate effect size for anger (-0.74; 95%CI, -1.27 to -0.21; *P*<0.001), but exhibited a small effect on depression (-0.37; 95%CI, -0.69 to -0.05; *P*<0.01). Antipsychotics had a moderate effect size for anger (-0.59; 95%CI, -1.04 to -0.15; *P*<0.01), with aripiprazole associated with the largest effect size compared with other antipsychotics. Antipsychotics did not have a significant effect size for depression (-0.46; 95%CI, -0.94 to 0.03;

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				P>0.05). Secondary: Not reported
Dementia				
Cheung et al[96] Quetiapine vs placebo	MA Patients receiving quetiapine or placebo for the treatment of behavioral and psychological symptoms of dementia	N=1,118 6 to 12 weeks	Primary: Neuropsychiatric Inventory (NPI), Clinical Global Impression of Change Scale (CGI-C) Secondary: Not reported	Primary: Quetiapine-recipients experienced a significant improvement from baseline, compared to placebo, in NPI scores, with a weighted mean difference of -3.05 (95%CI, -6.10 to -1.01; *P*=0.05). Quetiapine-recipients experienced a significant improvement from baseline, compared to placebo, in CGI-C scores, with a weighted mean difference of -0.31 (95%CI, -0.54 to -0.08; *P*=0.008). Secondary: Not reported
Brodaty et al[97] Risperidone vs placebo	DB, MC, PC, PG, RCT Patients residing in a nursing home aged ≥55 years with a diagnosis of dementia	N=345 12 weeks	Primary: CMAI total aggression score Secondary: CMAI total nonaggression score, CMAI individual subscale scores, BEHAVE-AD total score, psychotic symptom subtotal and global rating scores, and the CGI-S and CGI-C scores	Primary: There was a significantly greater improvement in CMAI rating scores in the risperidone group compared to the placebo group at each week of measure (*P*<0.01), except week 12 (*P*=0.058). The least-squares mean of the CMAI total aggression score decreased by 4.4 more in the risperidone group than the placebo group (-7.5 vs -3.1; 95% CI, -6.75 to -2.07; *P*<0.001), representing more than a 23% greater reduction in aggression in patients treated with risperidone. Both the differences in least-squares mean of the physical aggression and verbal aggression scores favored the risperidone group compared to placebo (-2.6; 95% CI, -4.45 to -0.67; *P*=0.008 and -1.8; 95% CI, -2.51 to -1.18; *P*<0.001, respectively). Secondary: The difference in least-squares mean between groups for the total nonaggression scale favored the risperidone group (-4.5; 95% CI, -7.39 to -1.70; *P*=0.002), with each of the subscale physical nonaggression and verbal nonaggression ratings also having a difference in least-squares

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				mean which favored the risperidone group compared to placebo (-1.8; 95% CI, -3.75 to 0.15; *P*=0.071 and -2.8; 95% CI, -4.16 to -1.37; *P*<0.001, respectively). Compared to baseline the least-squares mean scores for changes in BEHAVE-AD total and psychotic symptoms subscale were significantly more improved for the risperidone group at endpoint compared to placebo (-4.5; 95% CI, -6.45 to -2.46; *P*<0.001 and -1.4; 95% CI, -2.26 to -0.44; *P*=0.004, respectively). Each of the BEHAVE-AD subscale scores favored the risperidone group compared to placebo at endpoint compared to baseline, as illustrated in the differences in least-squares mean between the groups [paranoid and delusional ideation (-0.8; 95% CI, -1.38 to -0.15; *P*=0.015), hallucinations (-0.6; 95% CI, -1.04 to -0.14; *P*=0.010), activity disturbances (-0.4; 95% CI, -0.89 to 0.03; *P*=0.067), aggressiveness (-1.5; 95% CI, -2.08 to -0.95; *P*<0.001), diurnal rhythm disturbances (-0.2; 95% CI, -0.34 to 0.03; *P*=0.098), affective disturbance (-0.3; 95% CI, -0.57 to -0.02; *P*=0.034), and anxiety and phobias (-0.7; 95% CI, -1.12 to -0.21; *P*=0.004). Investigator and caregiver ratings of the CGI-S scale at endpoint showed statistically significant differences between the risperidone and placebo groups, with results favoring risperidone (*P*<0.001). Serious adverse events defined as life-threatening, requiring hospitalization, or causing significant disability or incapacity, occurred in 16.8% of risperidone-treated patient's vs 8.8% of placebo-treated patients. The most commonly encountered serious adverse events overall were injury, cerebrovascular disorders and pneumonia.
Brodaty et al[98] Risperidone	Post hoc analysis Patients with a diagnosis of	N=93 12 weeks	Primary: Change in BEHAVE-AD psychosis subscale	Primary: Mean change in BEHAVE-AD psychosis subscale score was more efficacious compared to placebo at endpoint (-5.2 vs -3.3; *P*=0.039; effect size, 0.31). After 2 weeks of treatment risperidone showed greater

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	Alzheimer's dementia or mixed Alzheimer's dementia with vascular dementia (analysis applied criteria for psychosis of Alzheimer's dementia to those with Alzheimer's dementia and mixed dementia) with a score of ≥2 on any of the 12 items of the BEHAVE-AD psychosis subscale (paranoia/delusions and hallucinations subscales) at both screening and baseline		and CGI-C at endpoint Secondary: Not reported	improvement in global functioning compared to placebo (28% vs 15%, respectively; *P*<0.05). Distribution of CGI-C favored risperidone at the endpoint (*P*<0.001). The number of patients classified as responders (defined as having a CGI-C of 'much' or 'very much' improved) was greater in the risperidone group (59%) than in the placebo group (26%). Secondary: Not reported
De Deyn et al[99] Risperidone vs placebo	MA Institutionalized adults ≥55 years of age diagnosed with dementia of the Alzheimer's type, vascular dementia, or a combination of the two	N=1,191 12 weeks	Primary: CMAI frequency rating scale to assess agitated and aggressive behaviors including the CMAI total, total (verbal and physical) aggression, and total (verbal and physical) nonaggression scores, the	Primary: Total mean CMAI score (change from baseline to endpoint) for the risperidone group showed greater improvement (5.4 points lower) than the placebo group (-11.8; 95% CI, -13.35 to -10.33 vs -6.4; 95% CI, -8.46 to -4.29; *P*<0.001). Risperidone-treated patients (N=713) compared to the placebo group (N=426) also showed greater mean improvement at endpoint for total aggression (-5.0; 95% CI, -5.83 to -4.19 vs -1.8; 95% CI, -3.02 to -0.65; *P*<0.001) and total nonaggression (-6.8; 95% CI, -7.78 to -5.88 vs -4.5; 95% CI, -5.79 to -3.29; *P*<0.001), with the differences between group means (3.2 and 2.3 points, respectively) favoring risperidone. The risperidone group had a significant mean improvement in total

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			BEHAVE-AD severity rating scale to assess behavioral symptom clusters including BEHAVE-AD total and psychotic-symptom subscale scores (paranoid/ delusional ideation and hallucinations) Secondary: CGI-C, CGI-S, safety assessments via adverse events, ESRS, MMSE, ECG and vital signs	BEHAVE-AD score compared to the placebo group at the endpoint (-6.1; 95% CI, -6.72 to -5.42 vs -3.6; 95% CI, -4.43 to -2.76; *P*<0.001). The total mean score for the psychotic-symptom subscale also favored the risperidone group compared to placebo at endpoint (-2.1; 95% CI, -2.40 to -1.79 vs -1.3; 95% CI, -1.68 to -0.81; *P*=0.003). The paranoid and delusional subset also had greater mean improvement (0.7 points lower) in the risperidone group than the placebo group (-1.7; 95% CI, -1.95 to -1.45 vs -1.0; 95% CI, -1.31 to -0.65; *P*=0.002) as did the hallucinations subset (-0.4; 95% CI, -0.53 to -0.27 vs -0.3; 95% CI, -0.45 to -0.09 respectively; *P*=0.191). Scores on the BEHAVE-AD total scale, at all evaluation points, were significantly more improved in risperidone-treated patients compared to the placebo. Secondary: Compared to baseline, there was a 17.7% increase in the number of risperidone-treated patients rated by investigators as “moderately ill or less” at endpoint versus an 8.3% increase in the placebo group (N=428) as measured with the CGI-S scale (*P*<0.001). At endpoint, caregivers rated 22.9% more risperidone-treated patients versus 12.8% of placebo patients as “moderately ill or less” utilizing the CGI-S scale (*P*<0.01). CGI-C scale ratings by investigators and caregivers also favored the risperidone group with significant results versus placebo at endpoint compared to baseline. Investigators at endpoint ranked 65.2% of risperidone and 45.2% of placebo-treated patients as improved, and fewer risperidone-treated patients were worse at endpoint compared to placebo (16.2% vs 25.1%, respectively; *P*<0.001, difference in distribution at endpoint). Caregivers rated 61.7% of risperidone patients as improved and 23.7% as worse versus 42.7% of placebo patients as improved and 33.3% as worse at endpoint compared to baseline (*P*<0.001, difference in distribution at endpoint). Risperidone-treated patients improved significantly more compared to

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				those on placebo on the mean CMAI total scores in both Alzheimer's disease and vascular dementia subgroups, but not in the mixed group (-12.4 vs -6.8; *P*<0.001; -9.8 vs -5.4; *P*=0.019; and -11.6 vs -5.8; *P*=0.36; respectively). Similarly, more patients treated with risperidone had significantly better improvement in mean BEHAVE-AD total scores in both Alzheimer's disease and vascular dementia subgroups, but not in the mixed group (-6.3 vs -3.9; *P*<0.001; -5.5 vs -3.2; *P*=0.020; and -5.3 vs -2.7; *P*=0.084, respectively). Significant differences in CMAI total and BEHAVE-AD total scores favored the risperidone group at endpoint regardless of severity of dementia. The incidence of adverse events was similar in the risperidone group (84.3%) and placebo group (83.9%) across risperidone dose groups. Most commonly reported adverse events were injury, fall, somnolence, purpura, and urinary tract infections all of which were comparable between groups (except somnolence). Somnolence occurred in 22.4% of risperidone patients and 13.9% of placebo patients. There was no significant increase in risk of death associated with risperidone (relative risk vs placebo, 1.17; 95% CI, 0.63 to -2.81).
Rocha et al[100] Ziprasidone 40 mg twice a day for 7 weeks (dose adjusted throughout study according to patient response and investigator judgment)	OL Adults ≥60 years, medically stable with diagnosis of dementia and a clinically significant level of behavioral or psychotic symptoms (score ≥3 on any of the agitation/ aggression, hallucinations, or delusions items of the NPI)	N=25 7 weeks	Primary: Mean change from baseline to endpoint in NPI total score Secondary: CGI-S measures	Primary: The mean total NPI score declined from 47.1±17.1 at baseline to 25.8±17.9 at day 49 (*P*<0.01). Additionally, the 12 NPI sub-item symptoms were reduced as follows: disinhibition, 76% reduction (3.16 to 0.76; *P*<0.01), aberrant motor behavior, 60% reduction (5.56 to 2.24; *P*<0.01), delusion, 53% reduction (4.88 to 2.28; *P*<0.01), agitation, 51% reduction (8.00 to 3.96; *P*<0.01), irritability, 56% reduction (5.6 to 2.44; *P*<0.01), sleep problems, 50% reduction (4.72 to 2.36; *P*=0.01), appetite problems, 38% reduction (1.36 to 0.84; *P*=0.28), depression, 30.2% reduction (3.84 to 2.68; *P*=0.14), hallucination, 27% reduction (2.52 to 1.84; *P*=0.19), anxiety, 19% reduction (4.00 to 3.24; *P*=0.38), apathy, 4% reduction (3.32 to 3.2; *P*=0.88), euphoria, 100% reduction (0.12 to 0; *P*=0.19). Secondary:

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				There was a 17% reduction in CGI-S severity score at day 49 compared to baseline (*P*<0.01) An adverse event was reported in 76% of patients overall, with the most frequent side effects being somnolence (52%), gastrointestinal symptoms (20%), parkinsonism (20%), agitation (8%), insomnia (8%), dizziness (8%), and lip edema (8%). Five patients developed EPS symptoms.
Schneider et al[101] Olanzapine vs quetiapine vs risperidone vs placebo Doses were initiated and adjusted as clinically needed based upon physician judgment.	DB, MC, PC, RCT Patients with dementia of the Alzheimer's type or probable Alzheimer's disease who were ambulatory and living at home or at an assisted-living facility; had delusions, hallucinations, aggression, or agitation that developed after dementia onset that was severe enough to disrupt their functioning; had signs and symptoms of psychosis, aggression, and agitation nearly daily the week prior to randomization or at least intermittently	N=421 36 weeks	Primary: Time until discontinuation of treatment for any reason in phase I of study Secondary: Attainment of minimal or greater improvement on the CGI-C scale, safety as assessed by the occurrence of adverse events	Primary: There were no significant overall differences between treatment groups regarding time to discontinuation of treatment for any reason. The median time to discontinuation for the olanzapine, quetiapine, risperidone, and placebo groups was 8.1 weeks, 5.3 weeks, 7.4 weeks, and 8.0 weeks, respectively. Secondary: The median time to discontinuation of treatment due to lack of efficacy was 22.1 weeks for olanzapine, 26.7 weeks for risperidone, 9.1 weeks for olanzapine and 9.0 weeks for placebo. The HR for the discontinuation of treatment because of lack of efficacy was 0.51 for olanzapine compared to placebo (*P*<0.001), and 0.61 for risperidone compared to placebo (*P*=0.01). Olanzapine and risperidone were equivalent to each other in time to discontinuation of treatment (HR, 0.84; 95% CI, 0.53 to 1.32) and olanzapine was more efficacious than quetiapine (HR, 0.63; 95% CI, 0.41 to 0.96; *P*=0.02). The time to discontinuation of treatment due to intolerance or death was favored by placebo with rates of discontinuation of 24%, 16%, 18%, and 5% for olanzapine, quetiapine, risperidone, and placebo, respectively (*P*=0.009 for overall comparison). At week 12, response rates (defined as a CGI-C score indicating at least minimal improvement with continued use of the study medication) were 32%, 26%, 29%, and 21% for olanzapine, quetiapine, risperidone, and placebo, respectively (*P*=0.22), with an overall rate of discontinuation of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	for 4 weeks			63% at 12 weeks. There were higher rates of parkinsonism or extrapyramidal signs in the olanzapine and risperidone groups (12% in each group) compared to the quetiapine group (2%) and placebo (1%; *P*<0.001). Sedation occurred more often with active drug treatment versus placebo (24%, 22%, 15% for the olanzapine, quetiapine, and risperidone groups versus 5% for the placebo group; *P*<0.001). Confusion or changes in mental status were more frequent in the olanzapine group (18%) and risperidone group (11%) than reported in the quetiapine group (6%) or placebo group (5%) (*P*=0.03).
Verhy et al[102] Olanzapine vs haloperidol	DB, MC, RCT Adults ≥60 years of age, diagnosed with dementia with a level of agitation clinically judged to represent a clinical problem requiring antipsychotic therapy, a score of ≥45 on the CMAI, and living in a nursing home or in their own homes	N=58 5 weeks	Primary: Reduction in the mean total sum score on the CMAI scale from baseline to endpoint Secondary: Improvement of scores on the NPI Dutch version, the CGI scale and MMSE, and the UKU side-effect rating scale, the AIMS and the SAS were used to measure side effects and EPS	Primary: The mean reduction in total CMAI score at endpoint compared to baseline for patients treated with olanzapine was -10.07 vs -16.57 in the haloperidol-treated group (*P*=0.338). Repeated analysis on CMAI scores illustrated that agitation levels decreased in both groups (*P*<0.001), but there were no statistically significant differences between the two groups (*P*=0.338). Secondary: The mean total NPI score showed an improvement for both the olanzapine and haloperidol groups (-11.09 vs -18.87; *P*=0.171) with the individual mean NPI scores for distress, psychosis, hyperactivity and mood also showing improvement at endpoint for the olanzapine and haloperidol groups (-3.4 vs -5.8; *P*=0.305; -1.0 vs -1.4; *P*=0.778; -6.9 vs -9.9; *P*=0.364; and -3.2 vs -2.7; *P*=0.823, respectively); however, none were able to reach a level of significance. The mean change at baseline on the CGI scale for the olanzapine group was -0.7 compared to -1.0 for the haloperidol group (*P*=0.917). Compared to baseline there were no statistically significant changes in EPS defined by the SAS and AIMS scales. The mean change in AIMS score for the olanzapine group and haloperidol group had a mean

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				increase by 0.42 (*P*=0.887). The mean change in SAS tended to show an improvement in the olanzapine group with a worsening trend in the haloperidol group (-1.44 vs 1.41; *P*=0.120). The mean change in MMSE score had a slight improvement in the olanzapine group but not in the haloperidol group (0.53 vs -0.13; *P*=0.481), while overall there were no statistically significant changes in the number of neurological side effects as shown by the mean change in UKU scores for the olanzapine and haloperidol groups (-0.7 vs -0.2; *P*=0.31).
Suh et al[103] Risperidone vs haloperidol	Post hoc analysis of DB, RCT, XO, head-to-head trial Adults ≥ 65 years with a diagnosis of dementia of the Alzheimer's type, vascular dementia, or a combination of the two per DSM-IV criteria	N=114 18 weeks	Primary: Korean version of BEHAVE-AD and CMAI scale Secondary: Not reported	Primary: Risperidone was more efficacious compared to haloperidol on various measures of the BEHAVE-AD-K scale, including: wandering (*P*=0.0496), agitation (*P*=0.0091), diurnal rhythm disturbances (*P*=0.0137), anxiety regarding upcoming events (*P*=0.0002) and other anxieties (*P*=0.0088). Risperidone was significantly more effective than haloperidol with various criteria of the CMAI-K scale including: physical sexual advances (*P*=0.0202), pacing and aimless wandering (*P*=0.0123), intentional falling (*P*=0.0398), hoarding (*P*=0.0499), performing repetitious mannerisms (*P*=0.0048), repetitive sentence or questions (*P*=0.0025), complaining (*P*=0.0101) and negativism (*P*=0.0027). A greater incidence of somnolence, insomnia and sialorrhea occurred in the haloperidol group compared to the risperidone group (*P*=0.0001). EPS symptoms were increased with haloperidol but were not increased with the risperidone group (*P*=0.0001). Secondary: Not reported
Fontaine et al[104] Olanzapine vs	DB Patients diagnosed with dementia (medically stable	N=39 14 days	Primary: NPI and CGI scales Secondary: Empirical BEHAVE-	Primary: The total NPI score for each group was significantly reduced at endpoint (*P*<0.0001), as were the subscale scores for depression/dysphoria (*P*=0.0277), anxiety (*P*=0.0016), the combined agitation, disinhibition, irritability, and aberrant motor behavior (*P*<0.0001), and

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
risperidone	and able to comply with oral medications), residing in an extended care facility, had a CGI score ≥4 and an Alzheimer's Disease Cooperative Study agitation screening scale score ≥ 25 with 6 points on the delusions, hallucinations, physical aggression, or verbal aggression subscales		AD, the PGDRS), the MOSES, the MMSE, and the QUALID; safety measures utilizing the AIMS scale, the BAS, and the SAS for EPS symptoms	delusions/hallucinations (*P*=0.0492). Significant reduction on the CGI scale at endpoint was seen in both groups (*P*<0.0001); however, there was no difference between the groups. Secondary: Global E-BEHAVE-AD scores at endpoint showed a significant reduction within each group (*P*=0.001), with a significant difference between groups for the sum of all subscale scores (*P*=0.021). Behavioral scores on the PGDRS scale were significantly reduced at endpoint for each group (*P*<0.001); however, there was no difference between the groups. There was no significant change in MOSES scores for either treatment group. QUALID scores were significantly improved for each group (*P*=0.03). SAS tended to rise over the course of the study, but did not reach statistical significance (*P*=0.08). Both groups had similar responses on the AIMS scale (*P*=0.52) when the none/normal categories were compared to the minimal and mild categories (no response were worse than "mild"). The BAS resulted in 15 of 18 patients in the olanzapine group and 16 of 18 patients in the risperidone group rated "absent" responses, with no responses rated worse than "mild".
Obsessive Compulsive Disorder (OCD)				
Komossa et al[105] Olanzapine, quetiapine, or risperidone as adjunctive	SR Randomized controlled studies	N=396 (11 studies) 6 to 16 weeks	Primary: Treatment response (≥25% reduction in Y-	Primary: There was no significant difference in response rates between olanzapine and placebo adjunctive therapies (OR, 0.28; 95%CI, 0.01 to 6.45). Moreover, there were no significant differences between groups in mental

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
therapy to antidepressants vs placebo, in addition to antidepressants	comparing adjunctive olanzapine, quetiapine or risperidone with placebo in adult patients with OCD		BOCS scores), Y-BOCS, HAM-A, HAM-D, MADRS, CGI Secondary: Not reported	state (assessed via Y-BOCS) scores, anxiety symptoms (assessed via HAM-A) or depressive symptoms (assessed via HAM-D). Fewer patients discontinued the study early due to inefficacy in the adjunctive olanzapine group, compared to placebo (OR, 0.10; 95%CI, 0.01 to 0.98; *P*=0.05). Olanzapine adjunctive therapy was associated with significantly greater weight gain compared with placebo (OR, 2.30; 95%CI, 0.80 to 3.80). There was no significant difference in response rates between quetiapine and placebo adjunctive therapies (OR, 0.53; 95%CI, 0.27 to 1.05). In addition, quetiapine was associated with greater improvement from baseline in Y-BOCS scores and HAM-A scores. There was no significant difference between the groups in depressive symptoms, assessed via MADRS and HAM-D. Significantly more patients discontinued from the study early due to adverse effects in the quetiapine group than in the placebo group (OR, 4.48; 95%CI, 1.43 to 14.04). Quetiapine therapy was associated with significantly more weight gain and sedation than placebo. Risperidone adjunctive therapy was associated with significantly greater response rate, improved global state (CGI) scores, reduction in anxiety (HAM-A) and depressive (HAM-D) symptoms compared with placebo. There was no significant difference in Y-BOCS scores between groups. Sedation occurred more frequently in the risperidone group. The other adverse events were comparable between groups. Secondary: Not reported
Post-Traumatic Stress Disorder				
Padala et al[106] Risperidone vs placebo	PC, PRO, RCT Females 19-64 years of age with Post-traumatic Stress Disorder	N=20 Duration not specified	Primary: Outcomes Post-traumatic Stress Disorder Scale-8 Secondary: HAM-D	Primary: Significant improvements from baseline were seen at visit 6 through visit 11 for the risperidone treated group (*P* value not reported). No significant changes were seen in the placebo group. Secondary: Scales showed results in line with the primary endpoint.
Pivac et al[107]	OL	N=55	Primary:	Primary:

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Olanzapine, 5-10 mg/day administered once or twice a day for 6 weeks vs fluphenazine, 5-10 mg/day administered once or twice a day for 6 weeks	Male war veterans, mean age 37.6 years, diagnosed with post-traumatic stress disorder, unresponsive to a 6-12 months trial of selective serotonin reuptake inhibitor	6 weeks	Arousal, trauma re-experiencing, avoidance, PANSS score, EPS, duration of therapy (3 weeks vs 6 weeks) Secondary: Not reported	There was no significant difference between the study drugs in alleviating the symptoms, both groups experienced an improvement in arousal, trauma re-experiencing and avoidance (P<0.001). Olanzapine was more effective in reducing symptoms in the PANSS negative, general psychopathology, supplementary items subscales, scores in CGI-S, CGI-I, and Patient Global Impression-Improvement scale (P<0.001). However, treatment for 3 or 6 weeks resulted in a similar decrease in the PANSS positive subscale scores (P>0.05). EPS was more common with fluphenazine therapy (P<0.001). Patients exhibited similar improvement in Post-traumatic Stress Disorder symptoms after 3 or 6 weeks of treatment (P value not reported). Secondary: Not reported

Study abbreviations: CI=confidence interval, DB=double-blind, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, PRO=prospective trial, R=randomized, RCT=randomized controlled trial, RETRO=retrospective, SR-systematic review, XO=cross-over
Miscellaneous abbreviations: AD=Alzheimer's Disease, ADHD=Attention Deficit Hyperactivity Disorder, AIMS=Abnormal Involuntary Movement Scale, BAS=Barnes Akathisia Scale, BEHAVE-AD=Behavioral Pathology in Alzheimer's Disease Rating Scale, BMI=body mass index, BPRS=Brief Psychiatric Rating Scale, CDRS=Children's Depression Rating Scale, CGAS=Children's Global Assessment Scale, CGI=Clinical Global Impressions Scale, CGI-C=Clinical Global Impression of Change, BSPS=Brief Social Phobia Scale, CGI-C=Clinical Global Impression of Change, CGI-I=Clinical Global Impression-Improvement, CGI-S=Clinical Global Impression Severity, CGI-SI=Clinical Global Impression—Severity of Illness, CMAI=Cohen-Mansfield Agitation Inventory, DOTES=Dosage Record Treatment Emergent Symptom Scale, DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th edition, ECG=electrocardiogram, EPS=extrapyramidal side effects, ESRS=Extrapyramidal Symptom Rating Scale, GAD=generalized anxiety disorder, HAM-A=Hamilton Rating Scale for Anxiety, HAM-D=Hamilton Rating Scale for Depression, MADRS=Montgomery-Asberg Depression Rating Scale, MDD=major depressive disorder, MMSE=Mini-Mental State Examination, MOSES=Multidimensional Observational Scale for Elderly Subjects, NNH=number needed to harm, NNT=number needed to treat, NPI=Neuropsychiatric Inventory, OCD=Obsessive Compulsive Disorder, OR=Odds Ratio, PANSS=Positive and Negative Syndrome Scale, PTSD=Post Traumatic Stress Disorder, QUALID=Quality of Life in Late Stage Dementia Scale, SANS=Scale for the Assessment of Negative Symptoms, SAPS=Scale for the Assessment of Positive Symptoms, SAS=Simpson-Angus Scale, SMC=standardized mean changes, PGDRS=Psychogeriatric Dependency Rating Scales, TSH=thyroid stimulating hormone, UKU=Udvalg for Kliniske Undersøgelser, YBOCS=Yale-Brown Obsessive Compulsive Scale, YMRS=Young Mania Rating Scale

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Table 6. Clinical Trials Using Antipsychotics for Children and Adolescents (FDA-Approved and Off-Label)

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
General				
Seida et al[108, 109] AHRQ Review Atypical (second-generation) antipsychotics (i.e. aripiprazole, clozapine, olanzapine, quetiapine, risperidone, paliperidone, ziprasidone) vs another atypical antipsychotic, first-generation antipsychotic (i.e. haloperidol), or placebo	SR Children and young adults 24 years of age or younger (mean age ranged from 4 to 21.5 years), diagnosed with pervasive developmental disorders, ADHD and disruptive behavior disorders, bipolar disorder, schizophrenia, or schizophrenia-related psychosis, Tourette syndrome, obsessive-compulsive disorder, post-traumatic stress disorder, anorexia nervosa, or behavioral issues;	N=not reported (140 studies) 2 weeks to 18 months	Primary: Efficacy (various measures), adverse events Secondary: Not reported	Primary: *Pervasive Developmental Disorders (PDD):* Compared with placebo, aripiprazole and risperidone were associated with significantly greater improvement from baseline in autistic symptoms and fewer obsessive compulsive symptoms associated with these disorders. However, no significant difference was found between either aripiprazole or risperidone and placebo in terms of the Clinical Global Impressions (CGI) scale and medication adherence. The overall strength of evidence score for use of these drugs for PDD was low. *Disruptive Behavioral Disorders:* Risperidone was associated with significantly greater improvement from baseline in various measures of behavior symptoms and on CGI compared to placebo. The overall strength of evidence of this outcome was moderate. Atypical antipsychotics and placebo were comparable in terms of effects on aggression, anxiety, or medication adherence. Compared to placebo, aripiprazole, olanzapine, quetiapine, and risperidone were associated with significant improvement from baseline in the CGI-Bipolar scale scores in patients who primarily had mania or mixed Bipolar disorder. There was no significant difference between atypical antipsychotics and placebo in suicide-related behaviors. The overall strength of evidence of these outcomes was moderate. The evidence comparing different atypical antipsychotics (olanzapine, quetiapine, risperidone, and ziprasidone) and low versus high doses of aripiprazole, quetiapine, risperidone, and ziprasidone was insufficient to form conclusions. Aripiprazole, olanzapine, and quetiapine were not significantly different from placebo for depressive symptoms. However, aripiprazole,

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	randomized controlled trials, nonrandomized controlled trials, and cohort studies were included			olanzapine, quetiapine, risperidone, and ziprasidone were associated with significantly greater effect on manic symptoms compared to placebo. Medication adherence was significantly better with placebo compared to antipsychotic therapy. The overall strength of evidence of these outcomes was low. *Schizophrenia:* Aripiprazole, olanzapine, paliperidone, quetiapine, and risperidone were associated with statistically significant improvements in CGI, positive and negative symptoms compared to placebo (strength of evidence: low). For both outcomes, risperidone was associated with greater efficacy over placebo compared to the other atypical antipsychotics. Clozapine, olanzapine, and risperidone were significantly more effective than haloperidol for CGI improvement. Medication adherence was comparable between patients who received olanzapine vs. quetiapine, olanzapine vs. risperidone, and atypical antipsychotics vs. placebo. There was no significant difference between atypical antipsychotics and placebo in terms of reduction of suicide-related behavior. The overall strength of evidence of these outcomes was low. *Behavioral Symptoms:* In two studies, patients receiving risperidone experienced greater improvement in Aberrant Behavior Checklist (ABC) scores compared to placebo (strength of evidence: low). *Adverse Events:* In head-to-head study comparison, risperidone caused less dyslipidemia vs. olanzapine; olanzapine caused fewer prolactin-related events vs. risperidone; quetiapine and risperidone caused less weight gain vs. olanzapine (strength of evidence: moderate). Furthermore, aripiprazole caused less dyslipidemia vs. olanzapine or quetiapine; aripiprazole caused less weight gain vs. olanzapine, quetiapine, or risperidone. There were no significant differences between atypical antipsychotics with respect to extrapyramidal symptoms, insulin resistance, and

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				sedation (strength of evidence: low). In placebo-controlled study comparison, risperidone caused less dyslipidemia vs. olanzapine; olanzapine caused fewer prolactin-related adverse events vs. risperidone; quetiapine and risperidone caused less weight gain vs. olanzapine (strength of evidence: moderate). Secondary: Not reported
Anorexia				
Leggero et al[110] Olanzapine 1.25 mg to 12.5 mg daily as part of multimodal treatment (included psychotherapy, psychoeducation, assisted feeding, and prolonged control of somatic conditions)	PRO Girls, aged 9.6 to 16.3 years, diagnosed with anorexia	N=13 6 months	Primary: Body Mass Index (BMI), Children's Global Assessment Scale (CGAS), Clinical Global Impressions-Severity (CGI-S), Child Behavior Checklist (CBCL), Eating Attitude Test (EAT), Eating Disorder Inventory (EDI-2), Structured Inventory for Anorexic and Bulimic Syndromes-Expert Form (Hyperactivity) (SIAB-EX) Secondary: Not reported	Primary: At 6 months, olanzapine therapy was associated with a statistically significant improvement from baseline in BMI (P<0.001). At 6 months, olanzapine therapy was associated with a statistically significant improvement from baseline in CGAS (P<0.001). At 6 months, olanzapine therapy was associated with a statistically significant improvement from baseline in CGI-S (P<0.001). At 6 months, olanzapine therapy was associated with a statistically significant improvement from baseline in total CBCL scores (P=0.044). At 6 months, olanzapine therapy was associated with a statistically significant improvement from baseline in CBCL internalizing scores (P=0.034). At 6 months, olanzapine therapy was associated with statistically significant improvements from baseline in EAT-26 Total, Dieting, Bulimic, and Oral control scores (P<0.05). An improvement in EAT-26 of at least 50% was achieved in 7 out of 13 patients (responders). At 6 months, olanzapine therapy was associated with statistically significant improvements from baseline in two areas of EDI-2: Interoceptive Awareness and Impulsivity (P<0.05 for both).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				At 6 months, olanzapine therapy was associated with a statistically significant improvement from baseline in SIAB-EX (*P*=0.005). Secondary: Not reported
Kafantaris et al[111] Olanzapine 2.5 mg to 10 mg once daily at bedtime, in adjunct to a comprehensive eating disorder treatment program vs placebo once daily at bedtime, in adjunct to a comprehensive eating disorder treatment program	DB, PC, RCT Girls, aged 12 to 21, with a primary diagnosis of anorexia	N=20 10 weeks	Primary: % of Median Body Weight (MBW) Secondary: Adverse events	Primary: Both olanzapine and placebo groups experienced statistically significant increase from baseline in %MBW (P=0.01); however there was no statistically significant difference between the two groups (*P*<0.05). Secondary: At week 10, the olanzapine group had significantly higher glucose levels and insulin levels compared to patients receiving placebo (*P*≤0.05). There were no statistically significant differences between the groups in metabolic parameters or ECG.
Hagman et al[112] Risperidone 0.5 mg up to a maximum of 4 mg daily vs placebo	DB, PC, RCT Girls, aged 12 to 21 years, with a primary diagnosis of anorexia, enrolled in an eating disorders programs	N=40 11 weeks	Primary: EDI-2 Drive for Thinness, EDI-2 Interpersonal Distrust, EDI-2 Body Dissatisfaction scores, Body Image Software (BIS), Color-A-Person Test (CAPT), Multidimensional Anxiety Scale for Children (MASC),	Primary: Compared to placebo, risperidone-treated patients exhibited statistically significant reduction over the first 7 weeks of the study in the EDI-2 Drive for Thinness (Effect Size [ES], 0.88; *P*=0.002). However, this difference was not sustained to week 11 (*P*=0.13). EDI-2 Drive for Thinness scores were not significantly decreased from baseline in the placebo group (*P*>0.05). Compared to placebo, risperidone-treated patients exhibited a statistically significant improvement from baseline in EDI-2 Interpersonal Distrust scores (ES, 0.60, *P*=0.03). There were no statistically significant changes between the risperidone and placebo groups in change over time for EDI-2 Body Dissatisfaction or body image distortion measurements, such as BIS and CAPT

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Resting Energy Expenditure (REE) Secondary: Change of IBW and BMI over time, number of weeks it took for patients to reach target weight and maintain it for 1 month, the number of weeks for patients to exhibit a worsening of anorexia symptoms and a 2-week weight loss, adverse events	(*P*>0.05). There were no statistically significant changes between the risperidone and placebo groups in change over time in anxiety scores, measured by MASC (*P*=0.44). Secondary: There were no statistically significant differences between groups in the change of IBW and BMI over time (P>0.05). Neither was there a significant difference between the groups in REE change from baseline (*P* value not reported). There were no significant differences between the groups in the number of weeks it took for patients to reach target weight and maintain it for 1 month (P=76), the number of weeks for patients to exhibit a worsening of anorexia symptoms and a 2-week weight loss (*P*=0.50). Likewise, there was no significant difference between the groups in the proportion of patients reaching these endpoints (*P* value not reported). There were no significant differences between the groups in orthostatic blood pressure, pulse, ECG changes, triglycerides, cholesterol, liver enzymes and glucose levels (*P*>0.05). Prolactin level was significantly increased from baseline in the risperidone group (*P*=0.001).
Bipolar Disorder				
et al[113] Aripiprazole 10 mg daily vs aripiprazole 30 mg daily vs	DB, MC, PC, RCT Children and adolescents, aged 10 to 17 years, diagnosed with bipolar I	N=296 4 weeks	Primary: Change from baseline in YMRS total score Secondary: Change from baseline in the Children's Global	Primary: At week-4, patients randomized to aripiprazole 10 mg daily therapy exhibited a statistically significant reduction from baseline on the YMRS total score, compared to placebo (14.2 vs. 8.2; *P*<0.0001). At week-4, patients randomized to aripiprazole 30 mg daily therapy exhibited a statistically significant reduction from baseline on the YMRS total score compared to placebo (16.5 vs. 8.2; *P*<0.0001).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo	disorder with current manic or mixed episodes, with or without psychotic features, and a Yong Mania Rating Scale (YMRS) total score ≥20 at baseline		Assessment Scale (CGAS), Clinical Global Impressions Scale-Bipolar Version (CGI-BP) severity of mania, depression, and overall bipolar illness, General Behavior Inquiry (GBI), CDRS-R. ADHD Rating Scale-Version IV (ADHD-RS-IV), response (defined as a reduction in baseline YMRS score of ≥50%), remission (defined as YMRS total score ≤12 and CGI-BP severity score ≤2), adverse events	Statistically significant improvements in the primary endpoint were observed in both aripiprazole dose groups compared to placebo as early as week-1 and were maintained throughout the study. Secondary: At week-4, patients randomized to aripiprazole 10 mg daily therapy exhibited a statistically significant improvement from baseline in CGAS scores, compared to placebo (*P*<0.0001). At week-4, patients randomized to aripiprazole 30 mg daily therapy exhibited a statistically significant improvement from baseline in the CGAS scores, compared to placebo (*P*<0.0001). At week-4, patients randomized to aripiprazole 10 mg daily therapy exhibited a statistically significant reduction from baseline in the CGI-BP severity of mania scores, compared to placebo (1.6 vs. 0.8; *P*<0.0001). At week-4, patients randomized to aripiprazole 30 mg daily therapy exhibited a statistically significant reduction from baseline in the CGI-BP severity of mania scores, compared to placebo (2.1 vs. 0.8; *P*<0.0001). At week-4, patients randomized to aripiprazole 10 mg daily therapy exhibited a statistically significant reduction from baseline in the CGI-BP overall bipolar illness scores, compared to placebo (1.6 vs. 0.8; *P*<0.0001). At week-4, patients randomized to aripiprazole 30 mg daily therapy exhibited a statistically significant reduction from baseline in the CGI-BP overall bipolar illness scores, compared to placebo (2.0 vs. 0.8; *P*<0.0001). Neither of the two aripiprazole treatment groups exhibited a statistically significant reduction from baseline in CGI-BP depression severity scores, compared to placebo (*P*>0.05). Changes from baseline in patient self-rated GBI-depression scores were likewise not significantly

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				different from placebo in the two aripiprazole groups (*P*>0.05). The change from baseline in parent/guardian-rated CGI-depression scores was marginally significant compared to placebo, but only in the aripiprazole 10 mg daily group (*P*=0.04). Neither of the two aripiprazole treatment groups exhibited a statistically significant reduction from baseline in CDRS-R scores, compared to placebo (*P*>0.05). At week-4, patients randomized to aripiprazole 15 mg and 30 mg daily therapy groups exhibited a statistically significant reduction from baseline in the ADHD-RS-IV total scores, compared to placebo (*P*<0.0001). Significantly more patients achieved treatment response after 4 weeks of therapy in the aripiprazole 10 mg (44.8%; *P*=0.0074) and 30 mg groups (63.6%; *P*<0.0001), compared to placebo (26.1%). Significantly more patients achieved disease remission after 4 weeks of therapy in the aripiprazole 10 mg (25%; *P*=0.0002) and 30 mg groups (47.5%; *P*<0.0001), compared to placebo (5.4%). At least one serious adverse event occurred in 5.1%, 2%, and 5.2% of patients receiving aripiprazole 10 mg, 30 mg, and placebo, respectively. No clinically significant trends in heart rate, blood pressure or ECG changes were observed among the groups. Mean weight gain from baseline was not statistically significant in the aripiprazole 10 mg daily (0.82 kg vs 0.56 kg; *P*=0.35) and aripiprazole 30 mg daily (1.08 kg vs 0.56 kg; *P*=0.13) groups, compared with placebo. There were no clinically significant changes from baseline in fasting serum glucose, total cholesterol, triglycerides, or HDL cholesterol (*P*

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				value not reported). Extrapyramidal events were reported by 23.5%, 39.4%, and 7.2% of the aripiprazole 10 mg daily, aripiprazole 30 mg daily, and placebo groups, respectively (*P* value not reported).
Tramontina et al[113] Aripiprazole 2-5 mg initially titrated up to 20 mg daily vs placebo	DB, PC, PG, RCT Children and adolescents, aged 8 to 17 years, with bipolar I or II disorder comorbid with ADHD, clear reports of ADHD symptom onset preceding mood symptoms, acutely manic or mixed state	N=710 6 weeks	Primary: Change from baseline in Young Mania Rating Scale (YMRS), the Swanson, Nolan, and Pelham Scale-Version IV (SNAP-IV), weight Secondary: Change from baseline in the Child Mania Rating Scale- Parent Version (CMRS-P), Clinical Global Impressions Severity of Illness scale (CGI-S), Children's Depression Rating Scale-Revised (CDRS-R), Kutcher Adolescent Depresssion Scale (KADS), adverse events	Primary: Aripiprazole-treated patients demonstrated a statistically significant reduction in YMRS scores from baseline compared to placebo (27.22 vs. 19.52; effect size=0.80; 95% CI, 015 to 1.41; *P*=0.02). Aripiprazole was associated with significantly higher response rates compared to placebo (88.9% vs. 52%; *P*=0.02; NNT=2.70). Aripiprazole was associated with significantly higher remission rates compared to placebo (72% vs. 32%; *P*=0.01; NNT=2.50). There was no statistically significant difference in the change in SNAP-IV scores from baseline between aripiprazole and placebo groups (*P*=0.19). Weight gain was not significantly different between aripiprazole and placebo groups (1.2 kg vs. 0.72 kg; *P*=0.25). Secondary: Aripiprazole-treated patients demonstrated a statistically significant reduction in CMRS-P scores from baseline compared to placebo (21.16 vs. 15.52; effect size=0.54; *P*=0.02). Aripiprazole-treated patients demonstrated a statistically significant reduction in CGI-S scores from baseline compared to placebo (2.05 vs. 1.64; effect size=0.28; *P*=0.04). There were no statistically significant differences in the change in CDRS-R and KADS scores from baseline between aripiprazole and placebo groups (*P*=0.59 and *P*=0.19, respectively).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				There were no statistically significant difference in the adverse event count between aripiprazole and placebo groups (3.76 vs. 4.83; *P*=0.99).
Biederman et al[114] Aripiprazole 5 to 40 mg daily Note: 39% of patients were receiving other antipsychotics concomitantly	SCR Children and adolescents, aged 4 to 17, diagnosed with manic, hypomanic, or mixed bipolar disorder	N=41 up to 84 weeks	Primary: Change from baseline in CGI-severity scores Secondary: Not reported	Primary: Patients receiving aripiprazole exhibited a reduction (improvement) in the mean mania CGI-severity score from 5.3 (marked/severe) to 3.4 (mild) (*P*<0.001). Of the patients receiving aripiprazole, 15% were minimally improved, 15% exhibited no change, 27% were very much improved, and 43% were much improved from baseline. Aripiprazole therapy was not associated with serious adverse events. Common side effects included nausea, insomnia, vomiting, and agitation. Weight gain was not noted to occur. Secondary: Not reported
Frazier et al[115] Olanzapine 2.5 mg/day to 20 mg/day, average 9.6 mg/day	OL, PRO Males and females, age 5-14 years, with bipolar (manic, mixed or hypomanic), with Young Mania Rating Scale (YMRS) total score ≥15	N=23 8 weeks	Primary: YMRS, Clinical Global Impression Severity (CGI-S), Brief Psychiatric Rating Scale (BPRS) Secondary: Adverse events, laboratory values, EPS (monitored by Simpson-Angus Scale, Barnes Akathisia Scale, Abnormal Involuntary	Primary: Compared to baseline a statistically significant improvement in symptoms of mania, and all items on the YMRS scale was seen (*P*<0.001). Compared to baseline a significant improvement was seen in: elevated mood, increased motor activity-energy, sleep, irritability, speech, language-thought disorder, thought content and disruptive-aggressive behavior (*P*<0.001 for all). Compared to baseline CGI-S scores improved significantly (*P*<0.001); however, there was no significant difference in the treatment response between bipolar youths with or without psychosis (*P* value not given). Secondary: No significant changes in Simpson-Angus, Barnes Akathisia or AIMS scores were reported.

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Movement Scale [AIMS])	From baseline the average weight gain was 5.0 +/- 2.3 kg, mean change in BMI was 2.4 +/- 1.3 kg/m^2 (*P*<0.001). Prolactin levels changed significantly from baseline to endpoint (*P*<0.002); at endpoint 6 subjects had values above normal, 1 of which was twice the upper limit. However no subjects had signs or symptoms associated with elevated prolactin. Pulse rates were significantly different at endpoint as compared to baseline for: supine pulse rate (*P*<0.004), standing pulse rate (*P*<0.001), and heart rate per EKG (*P*<0.002).
Shaw et al[116] Quetiapine 50 mg/day to 800 mg/day in divided doses, average dose was 467 mg/day	OL Patients 13-17 years of age with a psychotic disorder (schizophrenia, schizoaffective disorder, bipolar disorder, major depressive disorder with psychotic features, psychosis not otherwise specified)	N=15 8 weeks	Primary: YMRS (Young Mania Rating Scale), BPRS (Brief Psychiatric Rating Scale), PANSS (Positive and Negative Syndrome Scale), CGI-SI (Clinical Global Impression - Severity of Illness), SAS (Simpson-Angus Scale), AIMS (Abnormal Involuntary Movement Scale) BAS (Barnes Akathisia Scale) Secondary: Adverse events	Primary: Significant improvement from baseline was seen in: BPRS, PANSS, positive symptoms, negative symptoms, YMRS, and CGI-SI scores (*P*<0.001 for all). No significant change from baseline was seen for AIMS, BAS and SAS scores (*P* values not given). Secondary: Most frequently noticed adverse events were somnolence, headaches, and agitation. Total white blood cell count was less at the endpoint than discharge (*P*<0.05). No significant change in TSH or T4 was seen (*P*<0.008), or in total cholesterol or prolactin levels (*P* values not given). Significant changes in weight were observed from baseline to endpoint (*P*<0.001).

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Marchand et al[117] Quetiapine 100-1,000 mg/day, average 400 mg/day	RETRO Patients 4-17 years of age with diagnosis of bipolar I, bipolar II, cyclothymia or bipolar disorder	N=32 Chart review of patients from February 2000-April 2003 (length of treatment ranged from 1-32 months)	Primary: CGI-I, CGI-S Secondary: Body mass index (BMI)	Primary: 24 patients (80%) were responders with CGI-I ≤2. For patients receiving quetiapine as monotherapy (14 patients), 78.6% were responders. CGI-S score significantly improved from baseline (4.5) to endpoint (2.8) (*P*<0.001). Secondary: 19/32 patient weights were available. Change in BMI from baseline (20.9) to endpoint (21.7) was not significant (*P*<0.115).
DelBello et al[118] Quetiapine 25 mg twice daily up to a maximum of 150 mg three times daily, in addition to divalproex 20 mg/kg initially and titrated up to a therapeutic level of 80-130 mg/dL (quetiapine group) vs placebo, in addition to divalproex 20 mg/kg initially and titrated up to a therapeutic level of 80-130 mg/dL (placebo group)	DB, PC, PG, RCT Adolescents, aged 12 to 18 years, with bipolar I disorder currently mixed or manic, YMRS score ≥20	N=30 8 weeks	Primary: Change in Young Mania Rating Scale (YMRS) at 8 weeks Secondary: Change in PANSS-P, CDRS, CGAS, adverse events	Primary: At week-6, both quetiapine and placebo groups exhibited statistically significant reductions in the YMRS scores from baseline (*P*<0.05). However, quetiapine-treated patients exhibited a significantly greater reduction of YMRS scores from baseline compared to the group treated with divalproex alone (*P*=0.03). In addition, a significantly greater percentage of patients experienced treatment response, based on YMRS scores, in the quetiapine than in the placebo group (87% vs. 53%; *P*=0.05). Secondary: CDRS scores were significantly improved from baseline in both treatment groups (*P*≤0.01). However, there were no significant differences between groups in the change from baseline in CGAS scores (*P*=1.0) PANSS-P scores were significantly improved from baseline in both treatment groups (*P*<0.01). However, there were no significant differences between groups in the change from baseline in CGAS scores (*P*=0.8) CGAS scores were significantly improved from baseline in both treatment groups (*P*<0.01). However, there were no significant differences between groups in the change from baseline in CGAS

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				scores (*P*=0.2) Patients randomized to the quetiapine group experienced a significantly greater reduction over time in YMRS scores compared to patients in the placebo group (*P*<0.01). There were no significant differences between treatment groups in the reduction over time in CDRS or PANSS-P scores (*P*>0.05). The most common adverse events were sedation, nausea, headache, and gastrointestinal irritation. Sedation was significantly more common in patients receiving adjunctive quetiapine than placebo (*P*=0.03). There were no significant differences between the groups in change from baseline in QTc interval, platelet count, prolactin level, weight, extrapyramidal side effects, or liver function tests.
DelBello et al[119] Quetiapine 300 to 600 mg daily vs placebo	DB, MC, PC, RCT Adolescents, aged 12 to 18 years, with a depressive episode associated with bipolar I disorder	N=32 8 weeks	Primary: Change in Children's Depression Rating Scale-Revised Version (CDRS-R) at 8 weeks Secondary: Change in CDRS-R over the study period, change in Hamilton Anxiety Rating Scale (HAM-A), Young Mania Rating Scale (YMRS), Clinical Global Impression-Bipolar Version Severity (CGI-BP-	Primary: At week-6, both quetiapine and placebo groups exhibited statistically significant reductions in the CDRS-R scores from baseline (P<0.001). However, the difference between the quetiapine and placebo groups in the reduction of CDRS-R from baseline was not statistically significant (19 vs. 20; *P*=0.89). Secondary: There was no statistically significant difference between the groups in the average rate of change in CDRS-R scores over the eight weeks of the study (*P*=0.11). Response rates were 67% and 71% in the placebo and quetiapine groups, respectively (*P*=1.0). Remission rates were 40% and 35% in the placebo and quetiapine groups, respectively (*P*=1.0). At week-6, both quetiapine and placebo groups exhibited statistically

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			S), response, remission rate, adverse events	significant reductions in the HAM-A scores from baseline ($P \leq 0.05$). However, the difference between the quetiapine and placebo groups in the reduction of HAM-A from baseline was not statistically significant ($P=0.74$). Quetiapine was associated with a statistically significant reduction from baseline in the YMRS scores ($P=0.03$), while the change from baseline in the placebo group was not statistically significant ($P=0.09$). There was no statistically significant difference in the change in YMRS scores from baseline between quetiapine and placebo ($P=0.76$). At week-6, both quetiapine and placebo groups exhibited statistically significant reductions in the CGI-BP-S scores from baseline ($P<0.005$). However, the difference between the quetiapine and placebo groups in the reduction of CGI-BP-S from baseline was not statistically significant ($P=0.9$). The most commonly reported adverse events in the quetiapine group were gastrointestinal upset (65%), sedation (59%), and dizziness (41%). The only one of the above side effects that occurred at a significantly greater frequency in quetiapine-treated patients versus placebo was dizziness ($P=0.04$). Quetiapine-treated patients experienced significantly more frequent elevations in systolic, diastolic blood pressures, pulse and triglyceride level compared to placebo ($P<0.05$). Significant differences in QTc interval between groups were not observed ($P=0.8$). Quetiapine-treated patients gained an average of 2.3 kg while those receiving placebo gained 0.9 kg ($P=0.12$). Note: high placebo response rate was one of the limitations of this study.
Delbello et al[120]	DB, RCT	N=50	Primary:	Primary:

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Quetiapine 400 mg to 600 mg daily vs divalproex, dose was titrated up to serum level of 60 to 120 mcg/ml	Adolescents, aged 12 to 18 years, with bipolar I disorder (manic or mixed) and YMRS score of ≥20	28 days	Change from baseline in YMRS Secondary: Change from baseline in CDRS, CGI-BP, Positive and Negative Syndrome Scale-Positive Subscale (PANSS-P), CDRS, response rate (CGI-BP-I ≤2), remission rate (YMRS ≤12), adverse events	Quetiapine-treated patients experienced a statistically significant improvement from baseline in YMRS scores (*P*<0.0001). Divalproex-treated patients experienced a statistically significant improvement from baseline in YMRS scores (*P*<0.0001). The difference between the two treatment groups in the change from baseline YMRS scores was not statistically significant (3.3; 95%CI, -3.5 to 10.1; *P*=0.3). Secondary: Both treatment groups were associated with a statistically significant improvement from baseline in CDRS scores (*P*<0.0001 for both). However, the difference between the two groups in the change in CDRS scores from baseline was not statistically significant (1.6; 95%CI, -11.5 to 8.4; *P*=0.7). Both treatment groups were associated with a statistically significant improvement from baseline in PANSS-P scores (*P*<0.00051 for both). However, the difference between the two groups in the change in CDRS scores from baseline was not statistically significant (3.5; 95%CI, -0.9 to 7.8; *P*=0.1). A significantly greater percentage of quetiapine-treated patients met the criteria for a CGI-BP-I overall response compared to patients randomized to divalproex therapy (72% vs. 40%; *P*=0.02). A significantly greater percentage of quetiapine-treated patients met the criteria for a CGI-BP-I mania response compared to patients randomized to divalproex therapy (84% vs. 56%; *P*=0.03). A significantly greater percentage of quetiapine-treated patients met the criteria for remission compared to patients randomized to divalproex therapy (60% vs. 28%; *P*=0.02).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Within a group of patients with psychosis, there was a significantly greater CGI-BP-I overall response rate in those randomized to quetiapine compared to patients receiving divalproex therapy (55% vs. 8%; *P*=0.03). Within a group of patients without psychosis, there was no significant difference in CGI-BP-I overall response rate between patients randomized to quetiapine compared to those receiving divalproex therapy (86% vs. 69%; *P*=0.4). Within a group of patients with psychosis, there was no significant difference in YMRS remission rate between patients randomized to quetiapine compared to those receiving divalproex (55% vs. 17%; *P*=0.09). Within a group of patients without psychosis, a statistically significant difference in YMRS remission rate between quetiapine and divalproex was not observed (64% vs. 38%; *P*=0.3). There was no statistically significant difference between quetiapine and divalproex in weight gain from baseline (4.4 kg vs. 3.6 kg; *P*=0.2). The most commonly reported adverse events in both groups were sedation, dizziness, and gastrointestinal upset.
Haas et al[121] Risperidone 0.5 to 2.5 mg daily vs risperidone 3 to 6 mg daily vs placebo	DB, PC, RCT Children and adolescents, aged 10 to 17 years, with a diagnosis of bipolar I disorder, experiencing a manic or mixed episode	N=169 3 weeks	Primary: Change in YMRS total score from baseline Secondary: Clinical response rate (≥50% reduction from baseline on the total YMRS), sustained YMRS response (≥50%	Primary: Patients randomized to the risperidone 0.5-2.5 mg group experienced significantly greater reduction in mean YMRS total scores from baseline compared to placebo (18.5 vs. 9.1; *P*<0.001). Patients randomized to the risperidone 3-6 mg group experienced significantly greater reduction in mean YMRS total scores from baseline compared to placebo (16.5 vs. 9.1; *P*<0.001). Significantly greater changes in the primary endpoint were observed in both risperidone groups by day-7 of therapy. Secondary:

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			improvement at ≥2 consecutive measurements and for the remainder of treatment), remission rate (YMRS score ≤12 and CGI-BP score ≤2 at the 21-day endpoint), CGI-BP, Brief Psychiatric Rating Scale for Children (BPRS-C), adverse events	Clinical response was achieved by 59% of patients randomized to risperidone 0.5-2.5 mg group (*P*=0.002), 63% of patients receiving risperidone 3-6 mg group (*P*<0.001), compared to 26% of patients in the placebo group. Statistically significant clinical response differences between risperidone and placebo, favoring risperidone, were noted starting day-14. Sustained clinical response was achieved by 44.9% of patients randomized to risperidone 0.5-2.5 mg group, 41.7% of patients receiving risperidone 3-6 mg group, compared to 15.8% of patients in the placebo group. Onset of sustained response was significantly more frequent and earlier in the risperidone 0.5-2.5 mg group (*P*=0.002) and risperidone 3-6 mg group (*P*<0.001) than in the placebo group. Both risperidone groups had higher remission rates compared to placebo (43% vs. 16%; *P* value not reported). Both risperidone groups exhibited a statistically significant improvement in CGI-BP scores from baseline compared to placebo (*P*<0.001). No dose-response relationship was noted. Both risperidone groups exhibited a statistically significant improvement in overall BPRS-C total scores from baseline compared to placebo (*P*<0.05). However, the change from baseline in the BPRS-C depression factor scores in the two risperidone groups was not significantly different from placebo (*P*>0.05). The most commonly reported adverse events in patients receiving risperidone therapy were somnolence (42-56%), headache (38-40%), and fatigue (18-30%). Somnolence and fatigue were noted to be dose-dependent adverse events. The incidence of extrapyramidal adverse events was comparable between placebo and risperidone 0.5-2.5 mg group (5% and 8%, respectively); though, it was higher in the risperidone 3-6 mg group

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				(25%). Mean weight gain was 0.7 kg, 1.9 kg and 1.4 kg in the placebo, risperidone 0.5-2.5 mg, and risperidone 3-6 mg groups, respectively. The following percentages of patients had gained at least 7% of their baseline weight at study endpoint: 5.3% (placebo), 14.3% (risperidone 0.5-2.5 mg), and 10% (risperidone 3-6 mg), respectively.
Biederman et al[122] Risperidone 0.25 mg/day to 2.0 mg/day vs olanzapine 1.25 mg/day to 10 mg/day	OL Children, aged 4 to 6 years, with bipolar I and bipolar disorder II	N=31 8 weeks	Primary: YMRS (Young Mania Rating Scale) and CGI-I (Clinical Global Impression-Improvement) mania scales Secondary: CDRS (Children's Depression Rating Scale) and BPRS (Brief Psychiatric Rating Scale) at baseline, week 4, week 8 or study end point	Primary: Both groups experienced clinical improvement and statistically significant improvement from baseline (P<0.05). No statistically significant difference between the treatments was seen. (P value not reported.) Secondary: Risperidone group had statistically significant improvement in depression as compared to olanzapine (P<0.01) All lab values were similar between treatment groups with the exception of prolactin levels, which were statistically significantly higher for risperidone (P=0.009). Systolic blood pressure significantly increased from baseline in the risperidone group (P<0.05). Both groups experienced significant weight gain as compared to baseline (P<0.05).
Pavuluri et al[123] Risperidone 0.5 to 2 mg daily vs divalproex, dose was titrated up to serum level of 60 to 120 mcg/ml	DB, RCT Children and adolescents, aged 8 to 18 years, with bipolar disorder I, medication-free or unstable on current	N=66 6 weeks	Primary: Change from baseline in YMRS Secondary: Change from baseline in CDRS-R, CGIS-BP, Overt Aggression Scale (OAS), BPRS-C,	Primary: Risperidone and divalproex therapies were both associated with a statistically significant reduction (-3.27 and -2.89, respectively) in the YMRS baseline scores at study endpoint (P<0.01). A mixed-effects regression analysis, evaluated by active drug and time, demonstrated more rapid improvement in YMRS scores from baseline in the risperidone-treated group compared to patients receiving divalproex (P=0.01). However, final YMRS scores did not significantly differ between treatment groups (P value not reported).

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	medication		response rate (≥50% improvement on the YMRS), remission rate (YMRS score of ≤12 and CDRS-R score of <28), adverse events	Secondary: Risperidone therapy was associated with statistically significant reductions in baseline CDRS-R, CGI-BP, BPRS-C, OAS-irritability, OAS-aggression, and CMRS-P scores (*P*<0.01). OAS-suicidality was the only secondary endpoint that wasn't significantly improved from baseline at study endpoint (*P*>0.05). Divalproex therapy was associated with statistically significant reductions in baseline CGI-BP, OAS-irritability, OAS-aggression, and CMRS-P scores (*P*<0.01). In contrast, OAS-suicidality, CDRS-R, and BPRS-C scores were not significantly improved from baseline at study endpoint (*P*>0.05). Reduction from baseline in CDRS-R scores was significantly greater among patients receiving risperidone compared to divalproex (*P*<0.05). The response rates were 78.1% and 45.5% in risperidone and divalproex groups, respectively (*P*<0.01). The remission rates were 62.5% and 33.3% in risperidone and divalproex groups, respectively (*P*<0.05). At study endpoint, there were significantly more patients continuing risperidone therapy compared to the divalproex group (25 vs. 17; *P*<0.05. There were no statistically significant differences between the groups in weight gain, weight gain over 7% if baseline body weight, ECG changes, liver function tests, extrapyramidal symptoms, or thyroid function tests (*P* value not reported). Prolactin level was significantly elevated in patients receiving risperidone compared to the divalproex group (*P*<0.05).
Biederman et al[124] Ziprasidone 1 mg/kg titrated up	OL, PRO Children and	N=21 8 weeks	Primary: Change from baseline in YMRS,	Primary: Starting at week-1 through study endpoint, patients receiving ziprasidone exhibited a statistically significant reduction from baseline in

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to 2 mg/kg by week-3 and up to the maximum daily dose of 80 mg twice daily	adolescents, aged 6 to 17 years, with bipolar I disorder or bipolar disorder not otherwise specified (NOS), with a YMRS score of ≥15		BPRS, and CDRS-R scores, adverse events Secondary: Not reported	the YMRS scores (*P*<0.001). At week-8, 57% of patients had a 30% reduction in baseline YMRS scores, while 33% of patients experienced a 50% reduction in baseline YMRS scores. Of the patients with baseline symptoms of either depression or ADHD, 50% and 33%, respectively, exhibited improved symptoms. At week-8, patients receiving ziprasidone exhibited a statistically significant reduction from baseline in the BPRS-mania symptom scores (*P*<0.02). At week-8, patients receiving ziprasidone exhibited a statistically significant reduction from baseline in the BPRS-positive symptom scores (*P*<0.02). There were no statistically significant changes from baseline in the BPRS- negative symptom and psychological discomfort scores among patients receiving ziprasidone (*P*=0.1). At week-8, patients receiving ziprasidone exhibited a statistically significant reduction from baseline in the CDRS-R scores (*P*<0.02). Ziprasidone therapy was not associated with a statistically significant weight gain (0.6 kg; *P*=0.2) or QTc interval change (-3.7; *P*=0.5) from baseline. Secondary: Not reported
Conduct Disorders/Disruptive Behavior Disorders (including aggression)				
Ercan et al[125] Aripiprazole 2.5 mg up to 10 mg daily	OL Children and adolescents,	N=20 8 weeks	Primary: Change from baseline in Clinical Global	Primary: The majority of patients (63.1%) receiving aripiprazole therapy were classified as treatment responders based on improvement on the CGI global improvement subscale (*P* value not reported).

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	aged 6 to 16 years, with a conduct disorder		Impressions-Severity and Improvement (CGI-S/CGI-S) scale, Turgay DSM-IV based child and adolescent behavior disorders screening and rating scale (T-DSM-IV), Child Behavior Checklist (CBCL), Teachers Report Form (TRF) Secondary: Not reported	Risperidone therapy was associated with significant improvements from baseline in the following endpoints: inattention, hyperactivity/impulsivity, oppositional defiant disorder (ODD) and conduct disorder subscales of the T-DSM-IV (*P* value not reported). Aggression subscale on the CBCL and TRF also improved from baseline (*P* value not reported). Secondary: Not reported
Findling et al[126] Aripiprazole dosed based on patient weight (<25 kg: 1 mg/day; 25-50 kg: 2 mg/day; >50-70 kg: 5 mg/day; >70 kg: 10 mg/day)	OL, MC Children and adolescents, aged 6 to 12 years, with conduct disorder, with or without comorbid ADHD	N=23 15 days (36 month extension)	Primary: Rapid Assessment and Action Planning Process (RAAPP), CGI-I, adverse events, pharmacokinetic data	Primary: RAAPP scores decreased from baseline by -1.00 and by -0.75 in children and adolescents, respectively, at month-36 of therapy (*P* value not reported). By day-14, 63.6% and 45.5% of children and adolescents, respectively, were rated as much or very much improved on the CGI-I score. At month-36, 66.7% and 100% of children and adolescents, respectively, exhibited this level of improvement (*P* value not reported). Serious adverse events were not reported. In addition, no one discontinued from the study due to adverse events. At week-72, mean weight gain from baseline was 9 kg among children and 13.3 kg among adolescents (*P* value not reported). Aripiprazole pharmacokinetics in children and adolescents are demonstrated to be linear and comparable with those in adults.

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				Secondary: Not reported
Bastiaens et al[127] Aripiprazole 2.5 mg daily (<12 years of age) or 5 mg daily (12 years and older) titrated up vs ziprasidone 20 mg daily (<12 years of age) or 40 mg daily (12 years and older) titrated up	OL Children and adolescents, aged 6 to 18 years, with clinically significant aggression	N=46 2 months	Primary: Change from baseline in Overt Aggression Scale (OAS) scores Secondary: Parent Young Mania Rating Scale (PYMRS), Health and Life Functioning Scale (HALFS), Global Assessment of Functioning Scale (GAF), Clinical Global Impression-Improvement Scale (CGI), adverse events	Primary: After two months of therapy, both treatment groups experienced a statistically significant improvement in OAS scores from baseline (P<0.005). There was no statistically significant difference between treatment groups in the degree of OAS improvement (P=0.52). Aripiprazole- and ziprasidone-treated groups experienced a greater than 50% reduction in the OAS (70% and 71%, respectively). Secondary: After two months of therapy, both treatment groups experienced a statistically significant improvement in PYMRS scores from baseline (P<0.005). There was no statistically significant difference between treatment groups in the degree of PYMRS improvement (P=0.78). After two months of therapy, aripiprazole group experienced a statistically significant improvement in HALFS scores from baseline (P=0.0013). Ziprasidone-treated patients also experienced an improvement in HALFS scores; however the change was not statistically significant. Never-the-less, there was no statistically significant difference between treatment groups in HALFS improvement from baseline after 2 months of therapy (P=0.43). As is indicated by the improvement in HALFS scores, quality of life improved by 41% in the treatment groups, combined. The CGI was rated as much improved in both treatment groups and there was no statistically significant difference between groups (P=0.68). After two months of therapy, both treatment groups experienced a statistically significant improvement in GAF scores from baseline (P<0.005). There was no statistically significant difference between treatment groups in the degree of GAF improvement (P=0.42).

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				Sedation was the most frequently reported side-effect in both groups, followed by dizziness, nausea and headaches. The incidence of these side-effects was comparable between groups. Extrapyramidal side effects were reported by two patients receiving aripiprazole and none in the ziprasidone group. Agitation was reported by two patients receiving ziprasidone and none in the aripiprazole group.
Masi et al[128] Olanzapine 5 mg to 20 mg daily Note: all patients were involved in psychotherapy, family therapy, or day-hospital group treatments.	RETRO Adolescents, aged 11 to 17.2 years, diagnosed with conduct disorder, treated with olanzapine, who had failed adequate doses of mood stabilizers (lithium or valproate)	N=23 6 to 12 months	Primary: Modified Overt Aggression Scale (MOAS), CGI-I, Children Global Assessment Scale (CGAS), response rate (defined as an improvement of ≥ 50% at MOAS and a score of 1 or 2 at CGI-I), weight gain Secondary: Not reported	Primary: At the end of follow-up period, 60.9% of patients were classified as responders. Patients were noted to have had a statistically significant improvement from baseline in MOAS scores (P<0.001). Patients were noted to have had a statistically significant improvement from baseline in CGAS scores (P<0.001). At the end of follow-up, mean weight gain among patients receiving olanzapine was 4.6 kg. Secondary: Not reported
Khan et al[129] Olanzapine IM 5 to 10 mg daily, on average vs ziprasidone 20 mg daily, on average	NAT, RETRO Children and adolescents under 18 years of age, hospitalized for any mental illness and requiring an IM antipsychotic for acute agitation or aggression	N=100 Study duration not reported	Primary: Mean length of stay, mean number of days on study agent, mean number of aggressive episodes, mean number of doses of emergency medication, mean number of doses of study agent, mean number of	Primary: There were no statistically significant differences between groups in the mean length of stay, mean number of days on study agent, mean number of aggressive episodes and the mean number of doses of study agent (P>0.05). Ziprasidone therapy was associated with significantly more doses of emergency medication for acute aggression or agitation during their hospitalization compared to olanzapine (P=0.009). Ziprasidone-treated patients received significantly more IM injections of ziprasidone in combination with lorazepam or antihistaminic agents compared to patients in the olanzapine study group (P<0.05).

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			restraints, mean time in restraint, adverse events Secondary: Not reported	There was no statistically significant difference between treatment groups in either the mean number of restraints or the mean time in restraint (P>0.05). Somnolence was the most frequently reported adverse event in both ziprasidone and olanzapine treatment groups (16% and 20%, respectively). There were no clinically significant treatment-related adverse events in either of the two groups.
Kronenberger et al[130] Quetiapine 50 to 300 mg twice daily, in addition to methylphenidate OROS 54 mg daily for 9 weeks (following treatment failure on a 3-week course of methylphenidate OROS monotherapy)	OL, PRO Adolescents, aged 12 to 16 years, diagnosed with ADHD-combined type and disruptive behavior disorder, exhibiting aggressive or destructive conduct with at least 3 outbursts per month involving destruction of property, verbal aggression, or physical aggression during the past 2 months, and failure on methylphenidate	N=24 13 weeks	Primary: Rating of Aggression Against People and Property (RAAP) Secondary: Modified Overt Aggression Scale (MOAS), CGI-S, ADHD Rating Scale-IV-Parent Version (ADHD-RS-I), SNAP-IV, adverse events	Primary: RAAP scores were significantly improved during the methylphenidate OROS phase of the study (P<0.001) and were further significantly improved following combination therapy with quetiapine (P<0.001). During the 9 weeks of combined quetiapine and methylphenidate OROS therapy RAAP scores were improved in 75% of patients from the 3 week period when patients receiving methylphenidate OROS monotherapy. Secondary: MOAS scores were significantly improved during the methylphenidate OROS phase of the study (P<0.001) and were further significantly improved following combination therapy with quetiapine (P<0.01). SNAP-ODD scores were significantly improved during the methylphenidate OROS phase of the study (P<0.001) and were further significantly improved following combination therapy with quetiapine (P<0.01). CGI-S scores were significantly improved during the methylphenidate OROS phase of the study (P<0.001) and were further significantly improved following combination therapy with quetiapine (P<0.001). ADHD-RS scores were significantly improved during the methylphenidate OROS phase of the study (P<0.001) and were further significantly improved following combination therapy with quetiapine (P<0.001).

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	OROS monotherapy			SNAP-ADHD scores were significantly improved during the methylphenidate OROS phase of the study (P<0.001) and were further significantly improved following combination therapy with quetiapine (P<0.01). The only side effects reported at a significantly greater incidence during quetiapine administration than the methylphenidate OROS monotherapy phase were weight gain and increase in BMI (P<0.05). No extrapyramidal adverse events were reported.
Connor et al[131] Quetiapine 100 to 300 mg twice daily vs placebo	DB, PC, RCT Adolescents, aged 12 to 17, with a primary diagnosis of conduct disorder and exhibiting a moderate-to-severe degree of aggressive behavior, as documented by OAS score of ≥25 and CGI-S score ≥4	N=19 7 weeks	Primary: CGI-S, CGI-I Secondary: Parent-assessed Q-LES-Q quality of life, Overt Aggression Scale (OAS), conduct problems subscale of the Conners' Parent Rating Scale (CPRS-CP)	Primary: Quetiapine-treated patients experienced a statistically significant improvement in CGI-S scores from baseline, compared to placebo-treated patients (P<0.05). Quetiapine-treated patients experienced a statistically significant improvement in CGI-I scores from baseline, compared to placebo-treated patients (P=0.0006). Secondary: Quetiapine-treated patients were associated with a statistically significant improvement in Q-LES-Q quality of life scores from baseline, compared to placebo-treated patients (P=0.005). There were no statistically significant differences between groups in the change in OAS scores from baseline (P value not reported). There were no statistically significant differences between groups in the change in CPRS-CP scores from baseline (P value not reported). The only adverse events which were reported at a significantly greater frequency in the quetiapine group compared to placebo were decreased mental alertness, diminished emotional expression, and diminished facial expression (P<0.05).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Weight gain of 2.3 kg was observed in the quetiapine group compared with a weight gain of 1.1 kg in patients receiving placebo (*P*=0.46). No significant differences in prolactin level was observed between groups (*P*=0.71).
Ercan et al[132] Risperidone 0.125 mg (<20 kg weight) or 0.25 mg daily (>20 kg weight) initially up to a maximum of 1.50 mg daily	OL, PRO Preschool-aged children, 29 to 72 months of age, with conduct disorder and comorbid ADHD	N=8 8 weeks	Primary: Change from baseline in CGI-I, CGI-S, T-DSM-IV-S, response (defined as 30% reduction on the T-DSM-IV-S or CGI-I score of ≤2), adverse events Secondary: Not reported	Primary: Risperidone therapy was associated with a 78% reduction in CGI-S scores from baseline (*P*<0.001) at week-8 of therapy. Statistically significant improvement was also seen at week-4 of the study (*P*<0.001). All the children exhibited clinically significant improvements in CGI-S scores (much improved or very much improved) from baseline. At week-8, risperidone therapy was associated with a statistically significant reduction in CGI-I scores from baseline (*P*=0.002). The T-DSM-IV-S scores were significantly improved from baseline by 37.8 and 40.8 on both parental and clinical forms, respectively (*P*≤0.001). All the patients were classified as responders, on both the CGI and T-DSM-IV scales. There was no statistically or clinically significant weight gain among children receiving risperidone therapy. The mean weight gain from baseline was 0.3 kg (*P*=0.061). There was a significant seven-fold increase in prolactin levels from baseline among risperidone-treated patients (*P*<0.05). Except for one child who accidently received a high dose, risperidone therapy was not associated with neurological side effects or extrapyramidal symptoms. Secondary: Not reported
Caldwell et al[133]	RETRO	N=129	Primary: The Mendota	Primary: Risperidone-treated group exhibited a statistically significant

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Risperidone 1 to 2.5 mg daily, on average, in addition to cognitive behavioral therapy vs control (group prescribed other forms of pharmacotherapy)	Adolescent, boys who were delinquent and incarcerated, mean age of 16 years, admitted to a juvenile treatment center, diagnosed with childhood onset and persistent conduct disorder	14-day treatment; 21-day baseline period	Juvenile Treatment Center (MJTC) behavioral assessment Secondary: Weight gain	improvement from baseline in the MJTC behavioral assessment measure (effect size, 0.44; P<0.0005). Risperidone-treated patients experienced an improvement in behavioral scores of 9.1%, on average, compared to 1.1% deterioration among patients receiving psychosocial therapy only. Secondary: The average weight gain among patients receiving risperidone therapy for an average of 9 months was 15 lbs.
Croonenbergs et al[134] Risperidone oral solution, 0.01 mg/kg/day to 0.02 mg/kg/day initially, titrated up to 0.06 mg/kg/day	MC, OL Children and adolescents 5 to 14 years of age, diagnosed with conduct disorder, oppositional defiant disorder or disruptive behavior disorder not otherwise specified, had a score of ≥24 on the Conduct Problem Subscale of the Nisonger Child Behavior Rating Form (N-CBRF)	N=504 1 year	Primary: Change from baseline in Conduct Problem Subscale of the Nisonger Child Behavior Rating Form (N-CBRF) Secondary: Change from baseline in the other N-CBRF subscales, CGI Scale, Aberrant Behavior Checklist total and subscale scores, visual analog scale, cognition, adverse events	Primary: Patients exhibited a 48% reduction from baseline in the mean N-CBRF conduct problem score at study endpoint (−15.8; *P* <.001). Improvements were seen as early as weeks 1 to 4, and the improvements were maintained during the subsequent 11 months. Secondary: Risperidone therapy was associated with significant improvements from baseline in the positive social behavior and problem behavior N-CBRF subscales (*P*<0.001). Compliant/calm and adaptive/social both increased significantly from baseline (*P*<0.001). Insecure/anxious, hyperactive, self-injury/stereotypic, self-isolated/ritualistic, and overly sensitive N-CBRF subscale scores decreased significantly from baseline (*P*<0.001). Risperidone therapy was associated with a statistically significant improvement from baseline in the Mean Aberrant Behavior Checklist total scores (*P*<0.001). Risperidone therapy was associated with a statistically significant improvement from baseline in CGI scores (*P*<0.001).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	and mild-moderate mental retardation or borderline intellectual functioning, and a Vineland Adaptive Behavior Scale score of ≤84			Risperidone therapy was associated with a statistically significant improvement in tests of patients' cognitive function (*P*<0.001). At baseline, the most troublesome symptoms were aggression in 33% of patients, oppositional defiant behavior in 30%, and hyperactivity in 16%. The visual analog scale scores of the most troublesome symptom were significantly reduced by 40.3 (*P*<0.001). The most commonly reported adverse events were somnolence (30%), rhinitis (27%), and headache (22%). Adverse events leading to discontinuation of risperidone were weight gain (9 patients), increased appetite (4 patients), gynecomastia (3 patients), somnolence (3 patients), and headache (3 patients). The mean ESRS total score decreased by 0.3 from baseline at study endpoint (*P*=.024). Mean body weight by 7.0 kg from baseline; however, 50% of this weight gain was attributed to developmentally expected growth. Weight gain was greatest in the first 6 months of therapy, with little change between 6 and 12 months.
Reyes et al[135] Risperidone oral solution, 1 to 3 mg daily (most patients)	ES, MC, OL Children and adolescents, aged 6 to 16 years with disruptive behavior disorder and subaverage intelligence, who had completed the original 1-year, open-label	N=35 2 years (total exposure to risperidone was 3 years)	Primary: CGI-S scores, adverse events Secondary: Not reported	Primary: The improvement in CGI-S scores observed at the end of the first year of therapy (original study) was maintained during the two-year extension study. At the end of the 2-year extension study, 62% of patients had symptom ratings from not ill to mild severity, 20.6% were rated as moderately severe, 14.7% had a rating of marked, and only 2.9% of patients had a rating of severe. Mean ESRS scores were low throughout the study and most patients scored a zero on the total ESRS at each time point. There were no reports of tardive dyskinesia. During the 2-year extension, adverse events occurred more frequently during the first year of the extension, with the exception of headache,

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	study by Croonenbergs et al			weight gain, somnolence, epistaxis, eosinophilia, and condition aggravated. There were no reports of adverse cognitive effects. Mean increases in weight and BMI were greatest during the first year of risperidone treatment, with measures stable during the 2-year extension. Secondary: Not reported
Pandina et al[136] Risperidone 0.25 to 0.75 mg daily (<50 kg) or 0.5 to 1.5 mg daily (≥50 kg) vs placebo	DB, I, MC, PC, RCT Children and adolescents, aged 5 to 17, without moderate or severe intellectual impairment (IQ≥54) with a disruptive behavior disorder	N=284 6 months (6 weeks OL, 6 weeks single-blind, 6 months DB)	Primary: Continuous Performance Test (CPT), modified version of Verbal Learning Test-Children's Version (MVLT-C) Secondary: Not reported	Primary: Statistically significant improvements from baseline were noted in risperidone-treated patients for CPT hard hit rates and discrimination ability (*P*<0.05). Statistically significant improvements from baseline were noted in placebo-treated patients for CPT easy false alarms rates and hard hit rates and discrimination ability (*P*<0.05). The easy and hard CPTs correct mean response time worsened with placebo compared to baseline. Compared to baseline, the MBLT-C short-delay free recall improved significantly in both risperidone-treated and placebo-treated groups (*P*<0.05). After performing a multivariable analysis, no significant differences between risperidone and placebo were found in terms of cognition (*P* value not reported). Secondary: Not reported.
Reyes et al[137] Risperidone oral solution, 0.50 mg once daily up to 0.75 mg daily (<50 kg) or up to 1.5 mg daily (≥50 kg)	DB, I, MC, PC, RCT Children and adolescents, aged 5 to 17 years, without	N=335 6 months 6 weeks of OL risperidone (acute	Primary: Time to symptom recurrence (defined as sustained deterioration on either the CGIS rating or the	Primary: Time to symptom recurrence was significantly shorter with placebo compared with maintenance risperidone therapy (*P*<0.001). Symptom recurrence occurred in 25% of patients after 119 days with risperidone and 37 days with placebo. Six-month Kaplan-Meier symptom recurrence estimates were 29.7% for risperidone and 47.1% for placebo.

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vs placebo once daily Note: responders from the acute treatment phase entered into the continuation treatment phase	moderate or severe intellectual impairment (IQ ≥55), diagnosed with conduct disorder, oppositional defiant disorder, or disruptive behavior disorder not otherwise specified	treatment); 6 weeks of single-blind risperidone (continuation treatment); 6 months of double-blind risperidone (maintenance)	conduct problem subscale of the Nisonger Child Behavior Rating Form (NCBRS) Secondary: Rates of discontinuation due to symptom recurrence, disruptive behavior disorder symptoms, and general function, NCBRS, adverse events	The hazard ratio for symptom recurrence was 2.24 (95% CI, 1.54–3.28) times higher after switching to placebo compared with continuing risperidone therapy. Secondary: Risperidone therapy was associated with a significantly lower rate of symptoms recurrence compared to placebo at the end of the maintenance period (27.3% vs. 42.3%; *P*=0.002). At the end of the maintenance period, patients randomized to placebo, after receiving risperidone during the acute treatment phase experienced significantly greater deterioration in conduct problem scores compared to the risperidone treatment group (*P*<0.001). Compared to placebo, patients receiving risperidone during the maintenance phase experienced statistically significant improvements in most NCBRS subscales (all except for the insecure/anxious, self-injury/stereotypic behavior, self-isolated/ritualistic, and overly sensitive subscales), the most troublesome symptom visual analogue subscales (aggression and oppositional defiant behavior), and the global measurements (CGI severity and Children's Global Assessment Scale) (*P*≤0.01) . Treatment-related adverse events were more frequently observed during acute treatment (54.8%) compared with the continuation phase (34.9%) and maintenance phase (47.7% with risperidone vs. 36.2% with placebo). The most frequently reported treatment-related adverse events were headache, somnolence, fatigue, and increased appetite. Patients experienced a mean weight gain of 3.2 kg from study onset to the end of the continuation phase. Subsequently, risperidone-treated patients experienced an additional weight gain of 2.1 kg, while placebo-treated patients exhibited a decrease in mean weight of 0.2 kg.

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				There was no clinically significant change in mean fasting glucose levels during treatment (*P* value not reported). The only clinically significant change from baseline in lab values was an increase in prolactin level observed with risperidone use (*P* value not reported). The incidence of extrapyramidal adverse events was 1.7% in the risperidone group and 0.6% in the placebo group (*P* value not reported).
Haas et al[138] Risperidone oral solution, 0.25 to 0.75 mg daily (<50 kg) or 0.5 to 1.5 mg daily (≥50 kg)	OL, ES Children and adolescents, aged 5 to 17 years, without moderate or severe intellectual impairment, with disruptive behavior disorder, who had either successfully completed or experienced symptom recurrence during the DB study by Reyes et al[135]	N=232 1 year	Primary: Change in N-CBRF, CGI-S, Visual Analog Scale for the Most Troublesome Symptom (VAS-MS), CGAS, adverse events Secondary: Not reported	Primary: At 1-year of the open-label extension phase, both patients who had previously been randomized to placebo and those who had previously received risperidone experienced similar improvement in scores on the N-CBRF Conduct Problem Subscale, despite higher baseline values among patients previously receiving placebo (*P* value not reported). At 1-year of the open-label extension phase, patients who had experienced symptoms recurrence achieved greater improvement from baseline in scores on the N-CBRF Conduct Problem Subscale than patients who were not experiencing symptom recurrence during the double-blind study phase. The improvement was comparable between patients previously treated with risperidone and placebo (*P* value not reported). At 1-year of the open-label extension phase, patients experienced improvements in the following efficacy measures: other N-CBRF subscales (with the exception of self-injury/stereotyped and self-isolated/ritualistic), CGI-S, VAS-MS, and CGAS (*P* value not reported). At 1-year of the open-label extension phase, improvements in N-CBRF subscales, VAS-MS, and CGI-S scores were comparable in patients who previously receiving risperidone and those who previously received placebo.

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				Patients had a weight gain of 4.3 kg over the course of the follow-up period. The expected normal weight gain for children between the ages of 6 and 12 is 3 to 3.5 kg per year. Weight gain and extrapyramidal side effects were reported in 4.3% of patients. There were no reports of tardive dyskinesia. Risperidone therapy was associated with increase in prolactin levels, though this effect decreased with prolonged use and was not commonly associated with adverse events. Secondary: Not reported
Van Bellinghen et al[139] Risperidone oral solution 0.01 to 0.04 mg/kg/day initially up to 0.09 mg/kg/day vs placebo	DB, PC, PG Children and adolescents, aged 6 to 18 years, with IQs between 45 and 85 indicating persistent behavioral disturbances (e.g., hostility, aggressiveness, irritability, agitation, or hyperactivity)	N=13 4 weeks	Primary: Change from baseline in Aberrant Behavior Checklist (ABC) scores, Clinical Global Impression scores (CGI), Visual Analogue Scale (VAS), Personal Assessment Checklist (PAC), and adverse events Secondary: Not reported	Primary: Compared to baseline, risperidone was associated with a significantly reduced ABC cluster scores for irritation (P<0.01), hyperactivity (P=0.001), and inappropriate speech (P<0.05). Placebo group experienced a statistically significant reduction in lethargy from baseline (P<0.05), but not the other ABC cluster scores. The risperidone-treated group exhibited significant reductions in ABC irritation (-10.8 vs. 0.1; P<0.05) and hyperactivity scores (-14.8 vs. 1.0; P< 0.01) at endpoint, compared to placebo-treated patients. CGI scores were “very much improved” or “much improved” from baseline in five of the six risperidone-treated patients, whereas all placebo-treated patients were either “unchanged” (4 of 7) or “minimally improved” (3 of 7). Risperidone therapy was associated with a statistically significant reduction in symptom VAS scores from baseline (P<0.05). Significant differences in VAS score were noted between risperidone and placebo treatment groups throughout the study, beginning from week-2 (P<0.05). Compared to placebo, PAC scores were significantly improved from

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				baseline in patients receiving risperidone in the following subscales: social relationship (P<0.05) and occupational attitudes (P<0.05); while there was a non-significant trend toward improvement in adaptation (P=0.066), temperament (P=0.051), and dominance (P=0.059). The onset of therapeutic action of risperidone was rapid. Significant differences between the two treatment groups were observed at week 1 for the ABC hyperactivity score (P<0.05), at week 2 for the VAS score (P<0.01) and CGI score (P< 0.05). While there was a weight gain of 7% from baseline in two risperidone-treated patients, the mean weight change was not significantly different compared to patients receiving placebo (11.8 kg vs. 10.6 kg; P=0.319). There were no statistically significant differences between risperidone and placebo in ESRS scores. Secondary: Not reported
Aman et al[140] Risperidone solution 0.01 to 0.06 mg/kg/day vs placebo	MA Children, aged 5 to 12 years, with or without comorbid ADHD, below average IQ scores, with either conduct disorder or oppositional defiant disorder, who had participated in either of two 6-	N=223 6 weeks	Primary: N-CBRF Conduct Problem subscale Secondary: N-CBRF social competence and problem behavior subscales, N-CBRF problem behavior subscales, adverse events	Primary: Risperidone-treated patients experienced a statistically significant improvement from baseline in the Conduct Problem subscale compared to placebo-treated patients (P<0.001). Secondary: Risperidone-treated patients experienced the most statistically significant improvements from baseline, compared to placebo, in the following N-CBRF social competence measures: “accepted redirection”, “initiated positive interactions”, “been patient, able to delay”, “expressed ideas clearly”, “participated in group activities”, and “shared with or helped others” (P<0.001). Risperidone-treated patients also experienced statistically significant improvements from baseline, compared to placebo, in the following N-CBRF social competence measures: “followed rules” and “stayed on-

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	week, R, DB, PC trials			task" (*P*<0.01). Risperidone-treated patients experienced the most statistically significant improvements from baseline, compared to placebo, in the following N-CBRF problem behavior measures: "nervous or tense", "says no one likes him or her", "secretive, keeps things to self", and "talks too much or too loud" (*P*<0.001). Risperidone-treated patients also experienced statistically significant improvements from baseline, compared to placebo, in the following N-CBRF problem behavior measures: "exaggerates abilities or achievements", "feels others are against him/her", "lying or cheating", "steals", "too fearful or anxious", and "sulks, is silent or moody (*P*<0.01). There were no statistically significant differences between the groups in the following N-CBRF problem behavior measures: "overly anxious to please people", "self-conscious or easily embarrassed" and "worrying" (*P*>0.05). On the Hyperactivity N-CBRF problem behavior subscale, risperidone was associated with greater improvement from baseline compared to placebo in the following measures: "overactive, doesn't sit still", "restless, high energy level" (*P*<0.001), "easily distracted", "fails to finish things he/she starts", and "short attention span" (*P*<0.01). On the Self-Injury/Stereotypic N-CBRF problem behavior subscale, risperidone was associated with greater improvement from baseline compared to placebo in the following measures: "physically harms/hurts self on purpose" (*P*<0.01). On the Self-Isolated/Ritualistic N-CBRF problem behavior subscale, risperidone was associated with greater improvement from baseline compared to placebo in the following measures: "isolates self from others", "refuses to talk", and "odd repetitive behavior" (*P*<0.01). There was no statistically significant improvement from baseline between the

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				groups in “disinterested or unmotivated”, “rituals”, and “shy/timid” behavior (*P*>0.05). On the Overly Sensitive subscale, the only significantly improved items was “easily frustrated” (*P*<0.001). “Sudden changes in mood” and “irritable” measures were also improved in the risperidone group compared to placebo (*P*<0.01). Headache and somnolence were the most frequently reported adverse events.
LeBlanc et al[141] Risperidone solution 0.01 to 0.06 mg/kg/day vs placebo	MA Boys, aged 5 to 12 years, with or without comorbid ADHD, below average IQ scores, with either conduct disorder or oppositional defiant disorder, who had participated in either of two 6-week, R, DB, PC trials	N=163 6 weeks	Primary: Change from baseline in aggression score Secondary: Not reported	Primary: Compared to placebo, risperidone-treated patients experienced significantly greater mean decreases from baseline in the aggression score week-1 through week-6 of the study (*P*<0.001). At week-6, aggression among risperidone-treated patients was reduced by 56.4% from baseline compared to a 21.7% reduction observed in the placebo group (*P* value not reported). Secondary: Not reported
Biederman et al[142] Risperidone solution 0.01 to 0.06 mg/kg/day vs	PHA Children, aged 5 to 12 years, with or without comorbid	N=110 6 weeks	Primary: Affective measures of the N-CBRF (explosive irritability; agitated, expensive,	Primary: Risperidone therapy was associated with a statistically significant improvement in all three affective measures of the N-CBRF subscale compared to placebo (*P*<0.03). The magnitude of effect was greatest for the non-affective measures (ES, 0.95), followed by “agitated, expansive, grandiose” (ES, 0.74), “explosive irritability” (ES, 0.69) and finally

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placebo	ADHD, below average IQ scores, with either conduct disorder or oppositional defiant disorder, who had participated in a 6-week, R, DB, PC trial (included in MAs by Aman et al and LeBlanc et al)		grandiose; and depression) Secondary: Not reported	"depression" (ES, 0.44). Secondary: Not reported
Scott et al[143] Ziprasidone 0.6 mg/kg to 1.8 mg/kg for 3 to 8 days	CS Pediatric patients, aged 9 months to 17 years, who developed severe agitation and/or aggression secondary to traumatic brain injury	N=20 18 months	Primary: Change in Riker Sedation-Agitation Scale (SAS) scores from baseline Secondary: Not reported	Primary: Patients experienced a statistically significant improvement in SAS scores from baseline 24 hours after ziprasidone initiation (*P*<0.001). Secondary: Not reported
Delirium				
Turkel et al[144] Atypical antipsychotics (olanzapine 3 mg to 10 mg daily, quetiapine 25 mg to 75 mg daily, risperidone 0.5 mg to	RETRO Children and adolescents, aged 1 to 18 years,	N=110 2 years	Primary: Delirium Rating Scale Revised-98 (DRS-R98) scores, adverse events	Primary: Children receiving any of the three studied atypical antipsychotics experienced a significant improvement in DRS-R98 scores from baseline (*P*<0.001). There was no statistically significant difference in the final DRS-R98

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1 mg daily) for up to 132 days	diagnosed with delirium and given an antipsychotic Note: drug induced, infection and neoplasm were the most common causes of delirium.		Secondary: Not reported	scores among any of the three medication groups (*P*=0.17). Neither did the final DRS-R98 scores differ between children and adolescent patients (*P*=0.796). Other than one case of dystonia, no adverse events were observed during the study. Secondary: Not reported
Major Depressive Disorder (MDD)-Treatment Resistant				
Pathak et al[145] Quetiapine 150 mg to 800 mg daily, in addition to an antidepressant	CS Adolescents, aged 13 to 18 years, with treatment resistant MDD, defined as a failure to respond to an adequate dose for at least 8 weeks of a selective serotonin reuptake inhibitor (SSRI), and treated with adjunctive quetiapine Note: adequate	N=10 4-16 weeks	Primary: Treatment response (final CGI-I of 1 or 2) Secondary Not reported	Primary: Treatment response, based on the CGI-I score, was achieved by 70% of patients. Sedation was observed in 40% of patients, which usually resolved in the first few weeks of therapy. Average weight gain was 4.5 lbs, but varied from 0 to 23 lbs. Secondary: Not reported

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	SSRI dose was defined as fluoxetine ≥20 mg, citalopram ≥20 mg, escitalopram >10 mg, sertraline ≥50 mg, or paroxetine ≥20 mg			
Obsessive Compulsive Disorder (OCD)-Treatment Resistant				
Masi et al[146] Aripiprazole at a mean dose of 12.2 mg daily, in addition to a SSRI	CS Adolescents, aged 12 to 18 years, with OCD which did not respond to 2 initial trials of SSRIs monotherapy, with CGI-S of ≥4 and CGAS of ≤60	N=39 Duration not reported	Primary: Treatment response (defined as CGI-I of 1 or 2 and CGI-S of ≤3 during 3 consecutive months), CGI-S, CGAS, adverse events Secondary: Not reported	Primary: CGI-S scores significantly improved from baseline in patients receiving adjunctive aripiprazole therapy (*P*<0.0001). Treatment response was achieved by 59% of patients. CGAS scores significantly improved from baseline in patients receiving adjunctive aripiprazole therapy (*P*<0.0001). Out of 16 patients with comorbid Tourette or tic disorder, 62.5% exhibited an improvement in tic symptoms after aripiprazole initiation. Only 3 patients had a weight gain between 2 and 5 kg. Mild transitory agitation (10.3%), mild sedation (10.3%), and sleep disorders (7.7%) were reported; however, none of the patients discontinued due to adverse events. Secondary: Not reported
Pervasive Developmental Disorders (PDD) including Autistic Disorder, Asperger's Disorder, or PDD not otherwise specified (NOS)				
Masi et al[147] Aripiprazole, average dose of	NAT, RETRO Children and	N=34 4 to 12 months	Primary: CGI-I, Children's Global Assessment	Primary: On the CGI-I scale, 32.4% of patients were rated as "much improved" or "very much improved", 35.3% were "minimally improved", and 29.4%

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
8.1 mg daily	adolescents, aged 4.5 to 15 years, diagnosed with PDD and a severe behavioral disorder, such as aggression against self and/or others, hostility, hyperactivity, and severe impulsiveness		Scale (C-GAS), Childhood Autism Rating Scale (CARS) Secondary: Not reported	were "unchanged" or "worsened" from baseline. Patients experienced a statistically significant improvement in C-GAS scores from baseline with aripiprazole therapy (*P*<0.0001). Patients experienced a statistically significant improvement in CARS scores from baseline with aripiprazole therapy (*P*<0.0001). Therapy discontinuation due to lack of efficacy or adverse events occurred in 35.3% of patients. Secondary: Not reported
Stigler et al[148] Aripiprazole 2.5 to 15 mg daily	OL, PRO Children and adolescents, aged 5 to 17 years, diagnosed with PDD not otherwise specified and Asperger's Disorder	N=25 14 weeks	Primary: CGI-I, ABC-irritability, treatment response (defined as a CGI-I score of 1 or 2 and a >25% improvement on the ABC-I) Secondary: Vineland Adaptive Behavior Scales (VABS), Compulsion Subscale of the Children's Yale-Brown Obsessive Compulsive Scale Modified for PDDs (CY-BOCS-PDD)	Primary: Aripiprazole therapy was associated with a statistically significant improvement in CGI-I scores from baseline (*P*=0.0001). Aripiprazole therapy was associated with a statistically significant improvement in ABC-I scores from baseline (*P*=0.001). Treatment response was achieved in 88% of patients. Secondary: Aripiprazole therapy was associated with a statistically significant improvement in the socialization domain of VABS (*P*=0.0001), but not the communication, motor skills, or daily living skills domains (*P*>0.05). VABS composite scores significantly improved from baseline among aripiprazole-treated patients (*P*=0.036). Aripiprazole therapy was also associated with statistically significant improvements in the maladaptive domains of VABS (*P*=0.0001).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Aripiprazole therapy was associated with a statistically significant improvement in CY-BOCS-PDD scores from baseline (*P*=0.0001). Aripiprazole therapy was not associated with statistically significant changes in blood pressure, heart rate, ECG, or extrapyramidal symptoms from baseline (P value not reported). Aripiprazole was associated with a weight gain of 2.7 kg, on average, and an increase in BMI by 0.8 from baseline (*P*≤0.04).
Marcus et al[149] Aripiprazole 5 mg, 10 mg, or 15 mg daily vs placebo	DB, MC, PG, PC, RCT Children and adolescents, aged 6 to 17 years, diagnosed with autism and behavioral problems, such as irritability, agitation, self-injurious behavior, or a combination of the above, mental age ≥18 months, CGI-S score ≥4 and ABC Irritability subscale score ≥18	N=218 8 weeks	Primary: Aberrant Behavior Checklist Irritability (ABC-Irritability) subscale Secondary: CGI-I scores, other ABC subtypes, CY-BOCS, adverse events	Primary: Aripiprazole-treated patients, at 5 mg through 15 mg daily dose, exhibited a statistically significant improvement from baseline in the ABC-Irritability score, compared to placebo (-12.4 to -14.4 vs. -.8.4, respectively; *P*<0.05). Secondary: All aripiprazole doses were associated with a statistically significant improvement from baseline in the mean CGI-I scores compared to placebo (*P*<0.005). Compared to placebo, aripiprazole 15 mg daily was associated with statistically significant improvements in the following ABC subscales: ABC stereotype, ABC Hyperactivity, and ABC Inappropriate Speech (*P*≤0.05). Compared to placebo, aripiprazole 5 mg and 10 mg daily doses were associated with statistically significant improvements in the following ABC subscales: ABC stereotype and ABC Hyperactivity (*P*≤0.05). ABC Lethargy/Social Withdrawal subscale was not significantly changed in any of the three aripiprazole dose groups, compared with placebo (*P*>0.05). Compared to placebo, significant improvements in CGI-S were seen in aripiprazole 10 mg and 15 mg groups (*P*≤0.05). A significant

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				improvement in CY-BOCS was only seen in the aripiprazole 15 mg group ($P \leq 0.05$). At week-8, response rate was significantly greater in the aripiprazole 5 mg group, compared to placebo (55.8% vs. 34.7%; $P=0.34$). However, there were no significant differences in response rate between patients receiving placebo and aripiprazole 10 mg or 15 mg daily. The most common adverse events leading to discontinuation were sedation, drooling, and tremor. No one in the aripiprazole groups discontinued due to inadequate efficacy. Extrapyramidal adverse events were reported in 11.8% of the placebo group and 22-23% of the aripiprazole group. Significantly more patients in the aripiprazole groups experienced weight gain compared to the placebo group (1.3-1.5 kg vs. 0.3 kg; $P<0.05$).
Owen et al[150] Aripiprazole 5 mg, 10 mg, or 15 mg daily vs placebo	DB, MC, PG, PC, RCT Children and adolescents, aged 6 to 17 years, diagnosed with autism and behavioral problems, such as irritability, agitation, self-injurious behavior, or a combination of the above, mental age $\geq$18	N=98 8 weeks	Primary: ABC-Irritability subscale Secondary: CGI-I, treatment response (reduction in ABC irritability score of $\geq$25%, CGI-I score $\leq$2), CGI-S, CY-BOCS, adverse events	Primary: At week-8, aripiprazole-treated patients experienced a significantly greater improvement from baseline in ABC-irritability scores compared with placebo (-12.9 vs. -7.9; $P<0.001$). Statistically significant benefit over placebo was seen as early as week-1. Secondary: At week-8, aripiprazole-treated patients experienced a significantly greater improvement from baseline in CGI-I scores compared with placebo ($P<0.001$), beginning at week-1. At week-8, significantly more patients randomized to aripiprazole experienced a treatment response compared to placebo (52.2% vs. 14.3%; $P<0.001$). At week-8, aripiprazole-treated patients experienced significantly greater improvements from baseline in the following ABC subtypes compared with placebo: ABC hyperactivity, ABC stereotypy, ABC inappropriate

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	months, CGI-S score ≥4 and ABC Irritability subscale score ≥18			speech (*P*<0.001). There was no statistically significant difference between aripiprazole and placebo in the change in ABC lethargy/social withdrawal subscale (*P*>0.05). At week-8, aripiprazole-treated patients experienced a significantly greater improvement from baseline in CGI-S scores compared with placebo (*P*<0.001). At week-8, aripiprazole-treated patients experienced a significantly greater improvement from baseline in CY-BOCS scores compared with placebo (*P*<0.001). Aripiprazole was associated with significantly greater weight gain from baseline compared with placebo (2 kg vs. 0.8 kg; *P*<0.005). In addition, significantly more patients exposed to aripiprazole experienced clinically significant weight gain compared to placebo-treated patients (28.9% vs. 6.1%; *P*<0.01). Extrapyramidal adverse events occurred in 14.9% and 8% of patients treated with aripiprazole and placebo, respectively. Aripiprazole was associated with a significant decrease in prolactin level from baseline, compared to placebo (-6.3 vs. 1.6 ng/ml; *P*<0.001).
Aman et al[151] Aripiprazole 5 mg, 10 mg, or 15 mg daily vs placebo	PHA (Marcus et al/Owen et al.) Children and adolescents, aged 6 to 17 years, diagnosed with autism and behavioral problems, such	N=316 8 weeks	Primary: Line-item analysis of the ABC-Irritability subscale, ABC social withdrawal, ABC stereotypic behavior, ABC hyperactivity subscale and ABC inappropriate	Primary: Aripiprazole therapy was associated with statistically significant improvements from baseline compared to placebo in the following ABC-Irritability subscale measures: “mood changes quickly”, “cries/screams inappropriately”, “stamps feet/bangs objects”, “temper tantrums”, “aggressive toward others”, “yells, demands must be met immediately”, “cries over minor hurts” (*P*<0.05). There were no statistically significant differences between groups in the following ABC-Irritability subscale measures: “injures self”, “physical violence” (*P*>0.05).

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	as irritability, agitation, self-injurious behavior, or a combination of the above, mental age ≥18 months, CGI-S score ≥4 and ABC Irritability subscale score ≥18		speech subscale Secondary: Not reported	Aripiprazole therapy was associated with a statistically significant improvement from baseline compared to placebo in only one ABC-Social Withdrawal subscale measure: "difficult to reach" (*P*<0.05). Aripiprazole therapy was associated with statistically significant improvements from baseline compared to placebo in the following ABC-Stereotypic Behavior subscale measures: "repetitive hand, body, or head movements", "odd, bizarre behavior" and "waves or shakes extremities" (*P*<0.05). Aripiprazole therapy was associated with statistically significant improvements from baseline compared to placebo in the following ABC-Hyperactivity subscale measures: "boisterous, constantly runs or jumps", "tends to be excessively active", "acts without thinking", "restless", "unable to sit still", "disobedient", "difficult to control", "disrupts group activities", "does not stay in seat", "easily distractible", " deliberately ignores direction", "pays no attention when spoken to" (*P*<0.05). Aripiprazole therapy was associated with a statistically significant improvement from baseline compared to placebo in only one ABC-Inappropriate Speech subscale measure: "talks excessively" (*P*<0.05). Secondary: Not reported
Marcus et al[152] Aripiprazole 2 to 15 mg daily	OL, ES, MC Children and adolescents, aged 6 to 17 years, diagnosed with autism and behavioral problems, such	N=330 52 weeks	Primary: Adverse events Secondary: Not reported	Primary: Commonly reported adverse events included weight gain, vomiting, nasopharyngitis, increased appetite, pyrexia, upper respiratory tract infection, and insomnia. Discontinuations due to adverse events occurred in 10.6% of patients. Most frequent adverse events leading to discontinuation were aggression and weight gain. Extrapyramidal adverse events were noted in 14.5% of patients and

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	as irritability, agitation, self-injurious behavior, or a combination of the above, mental age ≥18 months, CGI-S score ≥4 and ABC Irritability subscale score ≥18 ES of patients enrolled in studies by Marcus et al or Owen et al.			included tremor (3%), psychomotor hyperactivity (2.7%), akathisia (2.4%), and non-tardive dyskinesia (2.4%). The following metabolic abnormalities were noted in association with >9 month risperidone therapy: glucose (2%), total cholesterol (5%), low-density cholesterol (7%), high-density cholesterol (30%), and triglycerides (5%). Aripiprazole therapy was associated with a decrease in serum prolactin level. The mean weight gain from baseline was 6.3 kg. Secondary: Not reported
Hollander et al[153] Olanzapine 2.5 every other day to 2.5 mg once daily (<40 kg) or 2.5 to 5 mg daily (≥40 kg) initially up to a maximum of 20 mg daily vs placebo	DB, PC, RCT Children and adolescents, aged 6 to 14 years, with PDD	N=11 8 weeks	Primary: CGI-I Secondary: CY-BOCS, MOAS irritability and aggression subscales, adverse events	Primary: Olanzapine therapy was associated with significantly improved CGI-I scores compared to placebo, with a significant linear trend x group interaction (*P*=0.012). Response rates were 50% and 20% for olanzapine-treated and placebo-treated patients, respectively (*P* value not reported). Secondary: There were no statistically significant difference between the groups in the change from baseline in CY-BOCS, MOAS irritability or MOAS aggression scores (*P*>0.05). While patients receiving olanzapine experienced a weight gain of 7.5 lbs, placebo-treated patients gained an average of 1.5 lbs from baseline (*P*=0.028). Gain of more than 7% of baseline weight occurred in 66.6% olanzapine-treated patients and in 20% of placebo-treated patients.

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Corson et al[154] Quetiapine 25 to 600 mg daily	RETRO Patients, 12.1 years of age on average, with PDD, and therapy with quetiapine for at least 4 weeks	N=20 4-180 weeks	Primary: Change from baseline in CGI-S, CGI-I, treatment response (CGI-I score of 1 or 2), adverse events Secondary: Not reported	Primary: Patients experienced a statistically significant improvement in CGI-S scores from baseline (P=0.002). While 40% of patients met the criteria for response on the CGI-I scale, the mean CGI-I score reported in the study was only 3.0, corresponding with minimal improvement. Adverse events occurred in 50% of patients and led to drug discontinuation in 15% of patients. Patients gained 5.7 kg, on average, at the end of the study. Secondary: Not reported
Hardan et al[155] Quetiapine 200 to 800 mg daily	RETRO Patients, 5 to 19 years of age, with PDD, treated with quetiapine for at least 18 months, failure with psychosocial interventions and at least two psychoactive agents	N=10 10-48 weeks	Primary: Conner's Parent Scale (CPS) conduct, inattention, hyperactivity, psychosomatic, learning, and anxiety subscales, adverse events Secondary: Not reported	Primary: Patients experienced a statistically significant improvement from baseline in conduct ($P\leq$0.05), inattention ($P\leq$0.01), and hyperactivity CPS subscales ($P\leq$0.01). There were no statistically significant improvements from baseline in the following CPS endpoints: psychosomatic, learning, and anxiety (P>0.05). An average weight gain of 2.2 lbs was noted. Secondary: Not reported
Golubchik et al[156] Quetiapine 50 to 150 mg daily (low dose)	OL Adolescents, aged 13 to 17 years, with high-functioning Autistic	N=11 8 weeks	Primary: CGI-S, OAS, Child Sleep Habits Questionnaire (CSHQ), adverse events	Primary: Low-dose quetiapine was associated with a statistically insignificant improvement in CGI-S scores from baseline (P=0.08), suggesting a modest effect on ASD global behavioral symptoms. Low-dose quetiapine was associated with a statistically significant reduction in aggressive behavior from baseline, as indicated by OAS

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	Spectrum Disorder (ASD) who exhibited agitation and/or aggressive behavior		Secondary: Not reported	(*P*=0.028). Low-dose quetiapine was associated with significant reduction in sleep disturbances from baseline, as indicated by CSHQ (*P*=0.014). Only three patients experienced mild adverse events. They were nausea, decrease in appetite and sedation. There was no significant weight gain compared to baseline (*P*=0.075). Secondary: Not reported
Martin et al[157] Quetiapine 100 to 350 mg daily	OL Boys, aged 6.2 to 15.3 years, with autistic disorder	N=6 16 weeks	Primary: ABC-Irritability, CY-BOCS, CGI-I, response (defined as CGI scores of "improved" or "very much improved", adverse events Secondary: Not reported	Primary: There were no statistically significant changes from baseline in either ABC or the CY-BOCS scores (*P* value not reported). Only two patients completed the study and exhibited a positive response to therapy on the CGI scale. Three patients discontinued the study due to lack of response and sedation limiting further dose increases, while one patient experienced a possible seizure during the fourth week of therapy. Additional significant adverse events included behavioral activation, increased appetite and weight gain (ranged from 0.9 to 8.2 kg). Secondary: Not reported
Gagliano et al[158] Risperidone at a starting dose of 0.25 mg/day which was increased gradually to 0.75-2 mg/day, given at bedtime or twice a day in tablets or oral solution	PRO Children aged 3-10 years of age diagnosed with autism according to DSM-IV criteria	N=20 24 weeks Phase 1:12 weeks N=20 Phase 2: 12	Primary: CGI, CPRS, relationship between plasma levels and efficacy Secondary: EPS using the AIMS scale,	Primary: The CGI score in 2 of the 20 patients was 4, which was considered a nonresponder and did not continue to Phase 2. CPRS scores decreased significantly (improved) from baseline to week 12 (*P*<0.01). There was no significant improvement in CPRS scores at week 24 compared to week 12 (*P* value not reported).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
		weeks N=18 (responders at week 12 continued on Phase 2)	adverse events	There was significant correlation between percent improvement in CPRS score and plasma levels of risperidone or its active fraction (*P* value not reported). Secondary: No EPS were observed. A mean increase of 2.6 kg and 3.7 kg was observed at weeks 12 and 24 respectively. No major changes from baseline in electrocardiogram and laboratory tests.
Lemmon et al[159] Risperidone (dose not specified)	RETRO Children and adolescents, aged 3 to 15, with autism spectrum disorder	N=80 ≥6 months	Primary: Treatment success (based on CGI scores of improved), adverse events Secondary: Not reported	Primary: The most common indications for treatment included aggression (66%), impulsivity (14%), and stereotypies (4%). Overall, 66% and 53% of patients met criteria for treatment success at 6 months and 1 year, respectively. Weight gain was the most frequently observed adverse event in both groups, followed by somnolence, aggression, and abnormal movements. Among patients 5 years of age or younger, 69% of patients met criteria for treatment success at 6 months. Risperidone was used as a first-line agent in 70% of patients in this age group. Prior medications included clonidine, guanfacine, and valproic acid. Somnolence was the most robust predictor of treatment failure. Secondary: Not reported
Aman et al[160] Risperidone 0.5-3.5 mg/day in	DB, PC Individuals aged	N=101 Double-blind	Primary: Laboratory values, vital signs, height	Primary: After the 8-week comparison statistically significant changes in laboratory findings were found for red blood cell, neutrophil, and

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
two divided doses vs placebo	5-17 diagnosed with autism according to DSM-IV criteria	comparison: 8 weeks Open label extension: 16 weeks	and weight, adverse events Secondary: Not reported	lymphocyte counts and for SGPT/SGOT (*P* values not reported). An elevated white blood cell count in a patient was the only abnormal laboratory findings reported at the 4-month extension. Tired during the day (*P*<0.0001), excessive appetite (*P*<0.0001), difficulty waking (*P*=0.05), excessive saliva or drooling (*P*=0.04), and dizziness or loss of balance (*P*=0.04) were reported significantly more frequently in the risperidone group. Difficulty falling asleep (*P*=0.02) and anxiety (*P*=0.05) were significantly less in the risperidone group compared to placebo. Significant weight gain was noted in the risperidone group (*P*<0.001). There was no significant difference between placebo and risperidone in vital signs (*P*=0.15-0.65). Secondary: Not reported
Aman et al[161] Risperidone 0.5-3.5 mg/day in two divided doses vs placebo	SA (study by Aman et al 2005) Individuals aged 5-17 diagnosed with autism according to DSM-IV criteria	N=38 Double-blind comparison: 8 weeks	Primary: Cognition Secondary: Not reported	Primary: Risperidone was not associated with a decline in performance. The following performance tasks were better executed by patients receiving risperidone than placebo: cancellation task and verbal learning task. There were no significant differences between groups in performance in the Pegboard (hand-eye coordination) or the Analog Classroom (timed math test) tasks (*P* value not reported). Secondary: Not reported
Aman et al[162] Risperidone, 0.25-1.75 mg daily (14-20 kg), 0.5-2.5 mg daily	PG, MC, RCT Children, aged 4 to 13 years, with	N=124 24-week	Primary: Home Situations Questionnaire (HSQ) severity	Primary: After 24 weeks of therapy, HSQ scores significantly decreased by 71% in the COMB group compared with a 60% reduction from baseline observed in the medication group (*P*=0.006).

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(20-45 kg), 0.5-3.5 mg daily (>45 kg)* (Medication group) vs combined treatment with risperidone, dosed same as above, and parent training in behavior management (COMB group) *Patients who did not exhibit a positive response to risperidone at 8 weeks were switched to aripiprazole	PDD, ≥18 on the Irritability subscale of parent-rated ABC, CGI severity score ≥4, not taking psychotropic drugs for at least 2 weeks, IQ≥35 or mental age ≥18 months		score Secondary: ABC Irritability, ABC Stereotypic, ABC Hyperactivity, ABC Social Withdrawal, ABC Inappropriate Speech, Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS), adverse events	Secondary: After 24 weeks of therapy, improvement in ABC Irritability subscale scores from baseline was significantly greater among patients randomized to COMB therapy compared to medication alone (*P*=0.01). After 24 weeks of therapy, improvement in ABC Stereotypic subscale scores from baseline was significantly greater among patients randomized to COMB therapy compared to medication alone (*P*=0.04). After 24 weeks of therapy, improvement in ABC Hyperactivity subscale scores from baseline was significantly greater among patients randomized to COMB therapy compared to medication alone (*P*=0.04). After 24 weeks of therapy, there were no statistically significant differences between groups in improvement from baseline in the following endpoints: ABC Social Withdrawal (*P*=0.78), ABC Inappropriate Speech (*P*=0.20), and CY-BOCS (*P*=0.62). The only statistically significant difference between groups in terms of adverse events was with insomnia, which occurred more frequently in the medication alone group (*P*=0.04).
Luby et al[163] Risperidone 0.5-1.5 mg in two divided doses per day vs placebo	DB, PC, RCT Preschool children 2.5 to 6 years of age with autism or pervasive developmental disorder not otherwise specified according to DSM-IV criteria	N=25 6 months	Primary: CARS, GARS Secondary: Physiological measures, adverse events	Primary: No statistically significant difference was seen between the two treatment groups on any of the outcome measures of interest when differences in baseline developmental characteristics were accounted for. There was no significant difference between the two treatment groups in the effectiveness on anxiety (*P*=0.056). Secondary: There was a significant difference between risperidone and placebo in mean weight gain (2.96 kg compared to 0.61 kg; *P*=0.008) and prolactin change (33.38 ng/mL compared to 11.11 ng/mL; *P*=0.015).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				There was no significant difference in adverse events between groups (*P* value not reported).
McCracken et al[164] Risperidone 0.5 to 3.5 mg daily vs placebo	DB, MC, PC, RCT Children and adolescents, aged 5 to 17 years, diagnosed with autistic disorder with tantrums, aggression, self-injurious behavior, or a combination of above, exhibiting a mental age of ≥18 months, weighing ≥15 kg	N=101 8 weeks	Primary: ABC Irritability score, response rate (defined as >25% increase in ABC irritability score and a CGI-I rating of much improved or very much improved) Secondary: ABC Social Withdrawal, ABC Stereotype, ABC Hyperactivity, ABC Inappropriate Speech, CGI-I, adverse events	Primary: At week-8, risperidone-treated patients exhibited a 56.9% reduction in the mean ABC Irritability score from baseline, compared with a 14.1% reduction observed in the placebo group (*P*<0.001). A positive response was noted in 69% and 12% of patients randomized to risperidone and placebo therapy, respectively (*P*<0.001). In 2/3 of patients with a positive response at 8 weeks, the benefit was maintained at 6 months. Secondary: At week-8, risperidone-treated patients exhibited a significantly greater improvement in the mean ABC Social Withdrawal score from baseline, compared with the placebo group (*P*=0.03). At week-8, risperidone-treated patients exhibited a significantly greater improvement in the mean ABC Stereotype score from baseline, compared with the placebo group (*P*<0.001). At week-8, risperidone-treated patients exhibited a significantly greater improvement in the mean ABC Hyperactivity score from baseline, compared with the placebo group (*P*<0.001). At week-8, risperidone-treated patients exhibited a significantly greater reduction in the mean ABC Inappropriate Speech score from baseline, compared with the placebo group (*P*=0.03). At week-8, the proportion of patients whose behavior was rated as much improved on the CGI-I scale differed between the two groups by 64%, in favor of risperidone (*P*<0.001).

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				Risperidone group gained significantly more weight compared to the placebo group (2.7 kg vs. 0.8 kg; *P*<0.001). Increased appetite, fatigue, drowsiness, dizziness, and drooling were more common in the risperidone group compared to placebo (*P*<0.05).
Miral et al[165] Risperidone dosed 0.01 mg/kg up to 0.08 mg/kg daily vs haloperidol dosed 0.01 mg/kg up to 0.08 mg/kg daily	DB, RCT Children and adolescents, aged 8 to 18, with autistic disorder	N=30 12 weeks	Primary: CGI-I, Ritvo-Freeman Real Life Rating Scale (RF-RLRS), ABC, Turgay DSM-IV Pervasive Developmental Disorder Rating Scale (TPDDRS), adverse events Secondary: Not reported	Primary: The change in CGI-I scores from baseline was not significantly different between the two study groups at week-12 (P=0.11). At week-12, there was no statistically significant difference between groups in the change from baseline in any of the RF-RLRS subscale scores (*P*>0.05). Risperidone was associated with significant improvement from baseline in all RF-RLRS subtypes; whereas haloperidol was associated with a significant improvement in all but one measure (language subscale). While the change from baseline in ABC scores was significant in both groups (*P*<0.005), risperidone therapy was associated with significantly greater improvement compared to haloperidol (*P*=0.0062). While the change from baseline in TPDDRS scores was significant in both groups (*P*<0.005), risperidone therapy was associated with significantly greater improvement compared to haloperidol (*P*=0.0052). Patients receiving haloperidol experienced significantly more extrapyramidal events than at baseline (*P*=0.0477); whereas there was no significant increase in extrapyramidal events in the risperidone group (*P* value not reported). Haloperidol therapy was associated with increased heart rate, weight, height and prolactin (*P*<0.05). Risperidone therapy was associated with increased weight, height, hemoglobin and prolactin (*P*<0.05). The only statistically significant differences between groups in terms of adverse events were increases in ALT with haloperidol therapy and increases in prolactin with risperidone therapy (*P*<0.05).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Gencer et al[166] Risperidone dosed up to 0.08 mg/kg daily vs haloperidol dosed up to 0.08 mg/kg daily	ES (of Miral et al) Children and adolescents, aged 8 to 18, with autistic disorder	N=28 12 weeks DB; 12 weeks OL	Primary: CGI-I, Ritvo-Freeman Real Life Rating Scale (RF-RLRS), ABC, Turgay DSM-IV Pervasive Developmental Disorder Rating Scale (TPDDRS), adverse events Secondary: Not reported	Primary: Risperidone therapy was associated with significantly greater improvement from baseline in CGI-I scores compared to haloperidol (*P*=0.0186). At week-24, the change from baseline in RF-RLRS sensory-motor subscale scores was statistically significant in the risperidone group (*P*=0.018), but not in the haloperidol group (*P*=0.16). Risperidone therapy was associated with significantly greater improvement from baseline in RF-RLRS language subscale scores compared to haloperidol (*P*=0.0414). There were no statistically significant differences between groups in the change from baseline in the other RF-RLRS subscales (*P*>0.05). At week-24, the change from baseline in ABC scores was statistically significant in the risperidone group (*P*=0.0029), but not in the haloperidol group (*P*=0.53). However, there was no statistically significant difference in the change in ABC scores from baseline between the two groups (*P*=0.07). Both risperidone and haloperidol groups experienced a statistically significant improvement in TPDDRS scores from baseline at week-24 of therapy (*P*<0.05). At week-24, both groups experienced statistically significant weight gain from baseline. However, haloperidol was associated with more weight gain than risperidone therapy (*P*=0.04). At week-24, there was no statistically significant difference between the groups in serum prolactin levels (*P*=0.55) or extrapyramidal adverse events (*P* value not reported).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Nagaraj et al[167] Risperidone 0.5 mg daily for the first week then 1 mg daily vs placebo	DB, PC, RCT Children 2-9 years of age diagnosed with autism according to DSM-IV criteria	N=40 6 months	Primary: CARS, CGAS, global impression of parents, analysis of parents questionnaire Secondary: Safety	Primary: In the risperidone group 63% of the patients demonstrated an improvement of at least 20% from baseline in their CARS score compared to none of the patients in the placebo group (*P*<0.001). In the risperidone group 89% of the patients demonstrated an improvement of at least 20% from baseline in their CGAS score compared to 9% of the patients in the placebo group (*P*=0.035). There was no significant difference between the treatment groups in the global impression of the parents (*P* value not reported). In the analysis of the parent questionnaire risperidone significantly improved functioning in the domains of social responsiveness (*P*=0.014), nonverbal communication (*P*=0.008), decreased symptoms of hyperactivity (*P*=0.002), and aggression and irritability (*P*=0.016). No significant difference was reported with regard to restricted interests, emotional interaction or verbal communication. Secondary: An increased appetite, mild sedation in 20% and transient dyskinesias in 10% were reported (*P* value not reported). In the risperidone group, the mean weight gain was 2.81 kg, an increase of 17% compared to 1.71 kg, an increase of 9.3% in the placebo group, a difference that was statistically significant (*P* value not reported).
Malone et al[168] Ziprasidone 20 mg to 160 mg daily	OL Adolescents, aged 12.1 to 18.5 years, with autism and a	N=12 6 weeks	Primary: CGI Secondary: ABC subtypes, Children's	Primary: At week-6, 75% of patients experienced a response on the CGI scale. The change from baseline in CGI-S was not statistically significant (*P*=0.07). Secondary:

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	CGI-S score of ≥4		Psychiatric Rating Scale (CPRS) subtypes, adverse events	Statistically significant improvement from baseline was seen in respect to the irritability and hyperactivity subtypes of the ABC ($P \leq 0.05$). However, the other ABC subtypes (lethargy/social withdrawal, stereotypic behavior and inappropriate speech) were not significantly changed from baseline ($P > 0.05$). Statistically significant improvement from baseline was only seen in respect to the autism measure of the CPRS ($P=0.009$). There were no significant changes from baseline in the anger, hyperactivity, or speech deviance measures of the CPRS ($P > 0.05$). Ziprasidone was weight neutral, significantly increased QTc by a mean of 14.7 msec ($P=0.04$), significantly decreased baseline total cholesterol levels ($P=0.04$), was not associated with significant changes in LDL, HDL cholesterol, triglycerides, or prolactin levels.
Schizophrenia				
Findling et al[169] Aripiprazole 10 mg daily vs aripiprazole 30 mg daily vs placebo	DB, MC, PC, RCT Children and adolescents between the ages of 13 and 17, with a diagnosis of schizophrenia, baseline PANSS score of 70 or higher	N=302 6 weeks	Primary: Mean change from baseline in PANSS total score Secondary: Mean change in the PANSS positive and negative subscale scores, Clinical Global Impression (CGI) improvement and severity, clinician-rated Children's Global Assessment scale, quality of life and patient satisfaction,	Primary: Compared to placebo, patients randomized to the aripiprazole 10 mg and 30 mg groups experienced a statistically significant improvement in the primary endpoint from baseline ($P=0.05$ and $P=0.007$, respectively) at week-6. Secondary: Patients randomized to the aripiprazole 10 mg and 30 mg groups experienced a statistically significant improvement in the PANSS positive subscale scores from baseline ($P=0.02$ and $P=0.002$, respectively) at week-6, compared to placebo. Only patients randomized to the aripiprazole 10 mg treatment group experienced a statistically significant improvement in the PANSS negative subscale scores from baseline at week-6, compared to placebo ($P=0.05$). At week-6, patients randomized to the aripiprazole 10 mg and 30 mg groups experienced a statistically significant improvement in the CGI

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			adverse effects	severity and improvement scores from baseline compared to placebo (*P*<0.05). At week-6, patients randomized to the aripiprazole 10 mg and 30 mg groups experienced a statistically significant improvement in the Children's Global Assessment Scale scores from baseline compared to placebo (*P*=0.006 and *P*=0.005, respectively). At week-6, patients randomized to the aripiprazole 10 mg and 30 mg groups experienced a statistically significant improvement in the Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire overall scores from baseline compared to placebo (*P*=0.005 and *P*=0.003, respectively). However, there was no statistically significant difference between the two aripiprazole groups and placebo in the change from baseline of the Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire total scores (*P*>0.05). At week-6, 53% and 56%, respectively, of patients in the aripiprazole 10 mg and 30 mg treatment groups achieved disease remission, compared with 35% of patients in the placebo group (*P*=0.02 and *P*=0.003, respectively). The most frequently reported treatment-emergent adverse effects that occurred at an incidence of at least 5% were extrapyramidal disorder (5% with placebo, 13% with aripiprazole 10 mg, 22% with aripiprazole 30 mg), somnolence (6% with placebo, 11% with aripiprazole 10 mg, 22% with aripiprazole 30 mg), and tremor (2% with placebo, 2% with aripiprazole 10 mg, 12% with aripiprazole 30 mg). The most common types of experienced extrapyramidal events were parkinsonism (7% with placebo, 15% with aripiprazole 10 mg, 30% with aripiprazole 30 mg) and akathisia (6% with placebo, 6% with aripiprazole 10 mg, 12% with aripiprazole 30 mg).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Patients randomized to the aripiprazole 30 mg group gained an average of 0.2 kg from baseline compared to a weight loss of an average of 0.8 kg in the placebo group (*P*=0.009). The 10 mg aripiprazole group did not exhibit changes in weight. There were no clinically significant differences among treatment groups in glucose or lipid measures. Both aripiprazole treatment groups exhibited statistically significant reductions in prolactin levels compared to placebo (P<0.005). There were no statistically significant differences among groups with respect to time to discontinuation (*P*>0.05).
Kryzhanovskaya et al[170] Olanzapine 2.5mg to 20 mg daily vs placebo	DB, I, MC, PC, RCT Children and adolescents, aged 13 to 17 years, with schizophrenia of the paranoid, disorganized, catatonic, undifferentiated, and residual types, had a BPRS-C score of at least 35, and a score of at least 3 on any one of the following BPRS-C items:	N=107 6 weeks (double-blind); 26 weeks (open label)	Primary: Change from baseline in the Brief Psychiatric Rating Scale (BPRS-C) total score Secondary: Change from baseline in the Clinical Global Impression (CGI-S), Positive and Negative Syndrome Scale (PANSS), and the Overt Aggression Scale (OAS) scores, patients response rate (30%	Primary: Compared to placebo, olanzapine-treated patients exhibited significantly greater improvements in BPRS-C scores from baseline (-19.4 vs. -9.3; Effect Size, 0.63; *P*=0.003). This improvement became significant at week-2 and remained so for the duration of the study. Secondary: Compared to placebo, olanzapine-treated patients exhibited significantly greater improvements in CGI-S scores from baseline (-1.1 vs. -0.5; *P*=0.004). Compared to placebo, olanzapine-treated patients exhibited significantly greater improvements in PANSS total scores from baseline (-21.3 vs. -8.8; Effect Size, 0.6; *P*=0.005). Compared to placebo, olanzapine-treated patients exhibited significantly greater improvements in OAS physical aggression toward others subtype scores from baseline (-0.1 vs. -0.0; *P*=0.019). The other components of the OAS total score were not significantly different between groups (*P*>0.05).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	hallucination, delusion, peculiar fantasy		or greater reduction in the BPRS-C total score from baseline and a CGI-S score of ≤3 at the last measurement), adverse events	The response rate was not significantly different between olanzapine and placebo (37.5% vs. 25.7%; *P*=0.278). Treatment-emergent adverse events occurring at anytime during treatment in at least 5% of olanzapine-treated patients included weight gain (30.6% vs. 8.6%; *P*=0.14), somnolence (23.6% vs. 2.9%; *P*=0.006); headache (16.7% vs. 8.6%; *P*=0.138), increased appetite (16.7% vs. 8.6%; *P*=0.376), sedation (15.3% vs. 5.7%; *P*=0.214), dizziness (8.3% vs. 2.9%; *P*=0.423), nasopharyngitis (5.6% vs. 5.7%; *P*=1.00), and pain in extremity (5.6% vs. 2.9%; *P*=1.0). Olanzapine therapy was associated with significantly increased from baseline fasting triglycerides (*P*=0.029) and uric acid (*P*<0.001). In addition, olanzapine-treated patients experienced a weight gain of 4.3 kg compared with 0.1 kg in the placebo group (*P*<0.001). Olanzapine therapy was associated with liver function test elevation compared to placebo (*P*<0.05), reduction in bilirubin (*P*=0.001), hemoglobin (*P*=0.004), and an increase in prolactin levels (*P*=0.002).
Cianchetti et al[171] Antipsychotics (aripiprazole 10 to 20 mg daily, clozapine 200 to 500 mg daily, haloperidol 3 to 8 mg daily, olanzapine 10 to 20 mg daily, quetiapine 250 to 450 mg daily, risperidone 3 to 6 mg daily)	RETRO Children and adolescents, 10 to 17 years, with schizophrenia or schizoaffective disorder	N=47 3 years to11 years	Primary: Response rate, PANSS, CGI scores, adverse events Secondary: Not reported	Primary: At year-3 of follow-up, clozapine therapy was associated with the highest response rate (81.5%), followed by aripiprazole (75%), quetiapine (50%), risperidone (37.5%), olanzapine (8.3%), and finally haloperidol (10%). Response rates were significantly greater among patients who had received clozapine compared to risperidone (*P*<0.01) or olanzapine (*P*<0.001). A comparison of the degree of clinical improvement at the 5 years of follow-up showed a statistically greater improvement in PANSS and CGI scores in patients treated with clozapine compared to either risperidone or olanzapine treatment (*P*<0.05). At 3-year through 11-year follow-up, clozapine was associated with a significantly greater improvement in GAF scores compared to the other antipsychotics, combined (*P*<0.05).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Excessive weight gain was observed in 60% of patients receiving olanzapine, 35.5% and 28.6% of patients receiving risperidone and clozapine, respectively. After 5 years of therapy, olanzapine was associated with the greatest rate of discontinuations due to adverse events (33.3%), followed by risperidone (28.1%), clozapine (16%), and aripiprazole (14.3%). Of note all the patients receiving olanzapine discontinued therapy by year-5 of follow-up. The reasons for discontinuing olanzapine were weight gain in 25% and amenorrhea in 16.7%. The reasons for discontinuing risperidone were weight gain in 6%, amenorrhea in 6%, neurodysleptic crisis in 6%, and adenoma, parkinsonism, or seizures in 1%, each. The reasons for discontinuing clozapine were weight gain in 3.6%, neutropenia in 7.1% and seizures in 3.6%. Only one patient discontinued aripiprazole therapy and that was due to anorexia. Secondary: Not reported
Fleischhaker et al[172] Olanzapine average dose 16.6 mg/day vs risperidone average dose 3.9 mg/day vs clozapine average dose 321.9 mg/day	MC, OL Patients with an average age of 16 years, with various psychiatric disorders, with the majority diagnosed with schizophrenia	N=51 Average 7.4 weeks of drug therapy (range 1-34)	Primary: Dosage Record Treatment Emergent Symptom Scale DOTES) Secondary: Adverse events	Primary: Significant change in weight was noted between the olanzapine and clozapine groups (P<0.03), and between the olanzapine and risperidone groups (P<0.03 for both). Secondary: Risperidone was associated with: reduced motor activity and/or drowsiness (6/19), weight gain (7/19), rigidity (2/19), dystonia (2/19), and depressive effect (3/19). Olanzapine was associated with: weight gain (4.6 kg at week 6) (11/16), reduced motor activity (6/16), drowsiness (9/16), rigidity and tremor (2/16), akathisia (1/16), dry mouth or increase salivation (4/16), and depressive effect (4/16). Clozapine was associated with: reduced motor activity (9/16), drowsiness (9/16), orthostatic hypotension (5/16), depressive effect

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				(4/16), and increased salivation (10/16).
Gothelf et al[173] olanzapine average dose 12.9 mg/day vs risperidone 3.3 mg/day vs haloperidol 8.3 mg/day	MC, PRO Patients with a confirmed diagnosis of schizophrenia	N=43 risperidone – 17 olanzapine – 19 haloperidol – 7 8 weeks	Primary: Positive and Negative Syndrome Scale (PANSS) Secondary: Adverse events	Primary: A significant change in PANSS scores was seen for positive, negative and total scores from baseline to 4 weeks and 8 weeks (P<0.01). Secondary: Increased fatigue occurred: 11.8% in the risperidone group, 42.1% in the risperidone group and 71.4% in the haloperidol group (P<0.01).
Mozes et al[174] Olanzapine 2.5 to 20 mg daily vs risperidone 0.25 to 4.5 mg daily Prior non-antipsychotic therapy was continued.	OL, PRO, R Hospitalized children (mean age 10.71 years), diagnosed with Childhood-Onset Schizophrenia (COS)	N=25 12 weeks	Primary: Change in the total PANSS score Secondary: PANSS positive and negative subscale scores, Brief Psychiatric Rating Scale (BPRS) scores, Children's Global Assessment Scale (CGAS), drop-out rate, adverse events	Primary: Both treatment groups were associated with a statistically significant improvement in the total PANSS scores from baseline (P<0.001). However, the difference between risperidone and olanzapine-treated groups was not statistically significant (P=0.236). Secondary: Both treatment groups were associated with a statistically significant improvement in the PANSS positive subscale scores from baseline (P<0.001). However, the difference between risperidone and olanzapine-treated groups was not statistically significant (P=0.318). Both treatment groups were associated with a statistically significant improvement in scores on the PANSS negative subscale from baseline (P<0.001). However, the difference between risperidone and olanzapine-treated groups was not statistically significant (P=0.144). Both treatment groups exhibited a statistically significant improvement in the BPRS scores from baseline (P<0.001). However, the difference between risperidone and olanzapine-treated groups was not statistically significant (P=0.254).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Both treatment groups exhibited a statistically significant improvement in the CGAS scores from baseline (*P*<0.001). However, the difference between risperidone and olanzapine-treated groups was not statistically significant (*P*=0.791). Of the olanzapine-treated children, 91.7% completed the 12 weeks of the study as compared with 69.2% in the risperidone-treated group (*P*=0.161). The two treatment groups were not associated with statistically significant differences in the incidence of extrapyramidal side effects or changes in blood pressure and pulse. Olanzapine and risperidone therapies were associated with a weight gain of 5.78 kg and 4.45 kg, respectively (*P*=0.33). The weight gain was statistically significant from baseline in both treatment groups (*P*<0.001).
Kumra et al[175] Olanzapine 10 to 30 mg daily vs clozapine 50 to 700 mg daily	DB, PG, RCT Children and adolescents, aged 10 to 18 years, diagnosed with schizophrenia or schizoaffective disorder and treatment-refractory (defined as treatment failure of at least two prior adequate antipsychotic trials), a	N=39 12 weeks	Primary: Responder rate (defined as a decrease of 30% or more in total BPRS score from baseline and a CGIS improvement rating of 1 (very much improved) or 2 (much improved) Secondary: Change in BPRS, CGI, SANS and SGAS, adverse effects	Primary: A significantly greater responder rate was observed in the clozapine group compared with olanzapine-treated patients (66% vs. 33%, *P*=0.038). Among patients who were previously treated with standard olanzapine doses, a trend of greater response rate was seen in patients who switched to clozapine as opposed to patients who received high olanzapine dose (*P*=0.093). Secondary: The two treatment groups were associated with comparable changes from baseline in the total BPRS, BPRS-Psychosis Cluster, CGAS, and CGI scores (*P*>0.05 for all). Patients receiving clozapine exhibited significantly greater reduction (improvement) in the SANS total scores from baseline (*P*=0.02).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	baseline BPRS total score of at least 35 and a score of at least moderate on at least one psychotic items on the BPRS			Both clozapine and olanzapine were associated with significant weight gain from baseline. Overall, 13% of patients (3 clozapine and 2 olanzapine) gained more than 7% of their baseline weight in 12 weeks of the study. The only statistically significant differences between the two groups were in the incidence of increased salivation and sweating, which were more common with clozapine therapy ($P<0.05$).
Kumra et al[176] Olanzapine 10 to 30 mg daily vs clozapine 50 to 700 mg daily	OL, ES Children and adolescents, aged 10 to 18 years, diagnosed with schizophrenia or schizoaffective disorder and treatment-refractory (defined as treatment failure of at least two prior adequate antipsychotic trials), a baseline BPRS total score of at least 35 and a score of at least moderate on at least one psychotic items on the BPRS	N=33 (of original 39 patients) 12 weeks	Primary: Adverse effects, treatment discontinuation, change in BPRS, CGI, SANS and SGAS, adverse effects Secondary: Not reported	Primary: At week-24, a significantly higher proportion of patients who were initially assigned to clozapine therapy remained on their initial assigned drug compared with patients initially randomized to olanzapine therapy (86% vs. 42%; $P=0.01$). Of the patients who changed therapy from olanzapine to clozapine, all but one did so due to inadequate therapeutic effect. At week-24, olanzapine-treated patients had significantly greater body weight compared to clozapine-treated group, though the weight appeared to stabilize after the initial 12 weeks of therapy ($P=0.05$). Prolactin level elevation was significantly greater among olanzapine-treated patients compared to clozapine ($P=0.02$); though the steep rise in prolactin level in the olanzapine group occurred during the first 12 weeks of therapy and tended to decrease during the open-label extension study. Patients who changed therapy from olanzapine to clozapine due to inadequate response to therapy exhibited statistically significant improvements in the BPRS, SANS, CGI, and CGAS scores at the end of the 12 week extension phase ($P<0.05$). Secondary: Not reported
Kumra et al[177]	DB, PG, RCT	N=39	Primary:	Primary:

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Olanzapine 10 to 30 mg daily vs clozapine 50 to 700 mg daily	Children and adolescents, aged 10 to 18 years, diagnosed with schizophrenia or schizoaffective disorder and treatment-refractory (defined as treatment failure of at least two prior adequate antipsychotic trials), a baseline BPRS total score of at least 35 and a score of at least moderate on at least one psychotic items on the BPRS	12 weeks	Responder rate (defined as a decrease of 30% or more in total BPRS score from baseline and a CGIS improvement rating of 1 (very much improved) or 2 (much improved) Secondary: Change in BPRS, CGI, SANS and SGAS, adverse effects	A significantly greater responder rate was observed in the clozapine group compared with olanzapine-treated patients (66% vs. 33%, *P*=0.038). Among patients who were previously treated with standard olanzapine doses, a trend of greater response rate was seen in patients who switched to clozapine as opposed to patients who received high olanzapine dose (*P*=0.093). Secondary: The two treatment groups were associated with comparable changes from baseline in the total BPRS, BPRS-Psychosis Cluster, CGAS, and CGI scores (*P*>0.05 for all). Patients receiving clozapine exhibited significantly greater reduction (improvement) in the SANS total scores from baseline (*P*=0.02). Both clozapine and olanzapine were associated with significant weight gain from baseline. Overall, 13% of patients (3 clozapine and 2 olanzapine) gained more than 7% of their baseline weight in 12 weeks of the study. The only statistically significant differences between the two groups were in the incidence of increased salivation and sweating, which were more common with clozapine therapy (*P*<0.05).
Sikich et al[178] TEOSS Study Olanzapine 2.5–20 mg daily vs risperidone 0.5-6 mg daily	DB, MC, RCT Children and adolescents, 8 to 19 years of age, diagnosed with schizophrenia, schizophreniform disorder, or	N=116 8 weeks	Primary: Responder status (defined as Clinical Global Impression (CGI) improvement score of 1 (“very much improved”) or 2 (“much improved”), plus ≥20% reduction in	Primary: No statistically significant differences were found among treatment groups in response rates (molindone: 50%, olanzapine: 34%, risperidone: 46%) or magnitude of symptom reduction. Secondary: The reduction in total PANSS scores from baseline was statistically significant in all three treatment groups (molindone: 27%, olanzapine: 27%, risperidone: 23%; *P*≤0.001 for all comparisons). There were no statistically significant differences in the total PANSS score reduction

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs molindone 10-140 mg daily, in addition to benztropine 1 mg	schizoaffective disorder and had current positive psychotic symptoms of at least moderate intensity		baseline PANSS score and the ability to tolerate 8 weeks of treatment) Secondary: PANSS total scores, PANSS positive and negative symptom subscales, the Brief Psychiatric Rating Scale for Children (BPRS-C), and the Child and Adolescent Functional Assessment Scale (CAFAS), adverse effects	from baseline across the three treatment groups (*P* value not reported). The reduction in PANSS positive subscale scores from baseline was statistically significant in all three treatment groups (molindone: 34%, olanzapine: 34%, risperidone: 32%; $P \leq 0.001$ for all comparisons). There were no statistically significant differences in the total PANSS score reduction from baseline across the three treatment groups (*P* value not reported). The reduction in PANSS negative subscale scores from baseline was statistically significant in all three treatment groups (molindone: 24%, olanzapine: 21%, risperidone: 20%; $P \leq 0.001$ for all comparisons). There were no statistically significant differences in the total PANSS score reduction from baseline across the three treatment groups (*P* value not reported). The reduction in the BPRS-C total scores from baseline was statistically significant in all three treatment groups (molindone: 39%, olanzapine: 41%, risperidone: 34%; $P \leq 0.001$ for all comparisons). There were no statistically significant differences in the total PANSS score reduction from baseline across the three treatment groups (*P* value not reported). The reduction in CAFAS scores from baseline was statistically significant in all three treatment groups (molindone: 32%, olanzapine: 40%, risperidone: 47%; $P \leq 0.001$ for all comparisons). There were no statistically significant differences in the total PANSS score reduction from baseline across the three treatment groups (*P* value not reported). Olanzapine-treated patients experienced a statistically significant weight gain of 6.1 kg and exhibited a 2.2 kg/m_2 increase of body mass index from baseline ($P \leq 0.0001$). Risperidone-treated patients experienced a statistically significant weight gain of 3.6 kg and exhibited a 1.3 kg/m_2 increase of body mass index from baseline ($P \leq 0.0001$). Molindone therapy was not associated with a

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				statistically significant weight gain. Olanzapine-treated patients exhibited a statistically significant increase in their total cholesterol (19.9 mg/dl) and LDL cholesterol (14.7 mg/dl) levels from baseline over the 8-week treatment course ($P \leq 0.05$). Neither molindone nor risperidone therapies were associated with significant changes in cholesterol levels. Molindone was associated with a statistically significant risk of akathisia ($P<0.027$); 18% of patients experienced moderate-severe akathisia. Prolactin levels were significantly increased from baseline in the risperidone group, but not in the olanzapine or molindone groups ($P \leq 0.0001$). Rate-corrected QT intervals increased significantly by 11.2 msec in the olanzapine group, but not in the molindone or risperidone groups ($P \leq 0.05$). Olanzapine, molindone and risperidone therapies were associated with the following discontinuation rates: 51%, 38% and 32%, respectively.
Findling, et al[179] TEOSS Study Olanzapine 2.5–20 mg daily vs risperidone 0.5-6 mg daily vs molindone 10-140 mg daily, in addition to benztropine 1 mg	DB, ES Children and adolescents, 8 to 19 years of age, diagnosed with schizophrenia, schizophreniform disorder, or schizoaffective disorder and had current positive	N=54 44 weeks	Primary: PANSS total score Secondary: PANSS positive and negative symptom subscales, the Brief Psychiatric Rating Scale for Children (BPRS-C), CGI severity, and the Child and	Primary: There was no statistically significant difference among treatment groups in the PANSS total score over the course of the maintenance study period. Secondary: Over the course of the maintenance phase, risperidone was associated with a statistically significant increase from baseline in the CAFAS 8 total score, indicating worse functioning (29.4; $P<0.05$). However, when assessing the change from baseline over the overall 52-week treatment course, risperidone led to a reduction in CAFAS total scores (-44.7). There were no statistically significant differences between groups in any of the other clinical outcome measures.

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	psychotic symptoms of at least moderate intensity		Adolescent Functional Assessment Scale (CAFAS), adverse effects	There were no statistically significant treatment group differences in the length of maintenance study participation (P=0.467). However, olanzapine was associated with the shortest time until study discontinuation compared to risperidone and malindone (23 weeks, 25.3 weeks and 29.9 weeks, respectively). There were no significant differences among the treatment groups in adverse events at the beginning of the extension study. The most common reason for study discontinuation during maintenance was adverse events. Weight gain (39% of all patients) and anxiety (26% of all patients) were the most common adverse events reported, though the rates did not significantly differ across the treatment groups. Olanzapine, risperidone and molindone experienced the following weight gains during the overall 52 weeks of treatment: 11.1 kg, 11 kg, and 7.6 kg. All olanzapine-treated patients experienced at least one adverse event, compared with 71% and 85% in the risperidone and molindone groups, respectively. Over the 52 weeks of therapy, prolactin level was reduced in the molindone and olanzapine groups, but increased in the risperidone group. However, during the 44 weeks of maintenance therapy, risperidone was associated with a reduction in prolactin level (*P*<0.05). This suggests an initial steep rise in prolactin with risperidone therapy and subsequent reduction in levels.
Singh et al[180] Paliperidone 1.5 mg once daily (low-dose)	DB, PG, PC, RCT Adolescents, aged 12 to 17	N=201 6 weeks	Primary: Change from baseline in PANSS total scores	Primary: Compared to placebo, the mean change in PANSS total score from baseline was statistically significant only in the paliperidone medium-treatment group (*P*=0.006). There was no significant difference from placebo with the other doses.

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs paliperidone 3 mg once daily (medium-dose) vs paliperidone 6 mg once daily (medium dose for patients weighing <51 kg and high-dose for patients weighing ≥51 kg) vs paliperidone 12 mg once daily (high dose for patients weighing ≥51 kg) vs placebo	years of age, diagnosed with schizophrenia for at least 1 year prior to study, with PANSS total score between 60 and 120, with a history of at least 1 adequate antipsychotic trial		Secondary: CGI-S, CGAS, responder rate (at least 20% improvement in PANSS total scores), PANSS Marder factor scores	When evaluated by the actual dose, the mean change in PANSS total score was significant for the 2 mg, 6 mg, and 12 mg doses compared to placebo (P<0.05). Secondary: The CGI-S scores were significantly improved in the paliperidone ER medium- and high-dose treatment groups, compared to placebo (P<0.05). The CGAS scores were significantly improved only in the paliperidone ER medium-dose treatment groups, compared to placebo (P<0.05). The responder rate was significantly higher in the medium-dose (64.6%) and high-dose (51.1%) groups, compared to placebo (P<0.05). Paliperidone medium-dose group was associated with significant improvement in all PANSS Marder factor scores, except for depression/ anxiety (P<0.05). Paliperidone high-dose group was associated with significant improvement in positive symptoms, uncontrolled hostility and excitement, compared to placebo (P<0.05).
McConville et al[181] Quetiapine 333 mg to 695 mg a day; average dose 600 mg/day	OL Individuals 12-17 years of age with schizoaffective disorder or bipolar disorder with psychotic features	N=10 88 weeks	Primary: Brief Psychiatric Rating Scale (BPRS), Clinical Global Severity of Illness (CGI-S), Scale of the Assessment of Negative Symptoms (SANS) Secondary:	Primary: Significant improvement was measured from baseline to week 64 for BPRS and CGI scores and to week 52 for SANS scores (P<0.05 for each). Secondary: No significant change from baseline SAS score or AIMS scores was seen (P value not provided). Change in weight (gain) from baseline was not significant; however, 3 patients reported it as a mild adverse event.

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Tolerability, EPS, Simpson-Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), adverse events	
Schimmelmann et al[182] Quetiapine 200 to 800 mg daily	OL Adolescents, aged 12 to 17 years, diagnosed with schizophrenia-spectrum disorder, with a Positive and Negative Syndrome Scale (PANSS) score of at least 60 points	N=56 12 weeks	Primary: Change from baseline in the PANSS total score Secondary: PANSS positive, negative, disorganization, impulsivity/ hostility, and anxiety/ depression subscales, Clinical Impressions-Severity of Illness Scale (CGI-S), Subjective Wellbeing under Neuroleptic Treatment Scale (SWN), PANSS response (50% reduction in PANSS scores, adverse events	Primary: Quetiapine-treated patients experienced a statistically significant reduction from baseline in the PANSS total score (24.9 points; 95%CI, 17.3 to 32.4; effect size=0.92; *P*<0.0001). Secondary: At week-12, quetiapine therapy was associated with a statistically significant improvements from baseline in the PANSS positive, negative, disorganization, impulsivity/hostility, and anxiety/depression subscales (P<0.001 for all variables). Quetiapine-treated patients experienced a statistically significant reduction from baseline in the CGI scores and the SWN total score (*P*<0.0001 for both). The 50% reduction in baseline PANSS scores was observed in 34.6% of patients (*P* value not reported). Quetiapine-treated patients experienced a statistically significant weight gain (6.2 kg) and an increase in BMI (2.1 kg/m^2) from baseline (P<0.001). At week-12, 60.7% of patients had gained more than 7% of their baseline weight. While quetiapine-treated patients experienced a statistically significant decrease in total serum thyroxin and an increase in thyroid-stimulating hormone (TSH), no one exhibited clinical signs of hypothyroidism (*P*<0.05).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Increases in prolactin, total cholesterol, and blood pressure from baseline were not statistically significant (*P*>0.05).
Jensen et al[183] Risperidone, mean dose 3.4 mg vs olanzapine, mean dose 14 mg vs quetiapine, mean dose 611 mg	OL, PG, R Children and adolescents 10 to 18 years of age with schizophrenia, schizoaffective disorder, schizophreniform, or psychotic disorder not otherwise specified	N=30 12 weeks	Primary: Change in the PANSS total score Secondary: Change in the PANSS positive and negative subscale scores and the Children's Global Assessment Scale (SGAS), response rate (defined as at least a 40% reduction in PANSS total and subscale scores, adverse effects	Primary: There was no statistically significant difference among groups in the change in the primary endpoint (P=0.06), though there was a trend towards a better outcome in patients treated with risperidone compared to quetiapine (d=1.10; 95% Confidence Interval [CI], 0.09 to 2.01). Secondary: There were no statistically significant differences among groups in respect to the positive and negative PANSS subscale scores as well as the CGAS scores (P>0.05). Risperidone was associated with a greater improvement on the PANSS general symptoms subscale compared to quetiapine (P=0.04). A non-significantly greater proportion of patients in the risperidone treatment group (7/10) met the responder criteria compared to patients in the quetiapine (3/10) or olanzapine (5/10) groups (P=0.65). All three treatment groups were associated with a significant increase in weight and body mass index from baseline. Sixty-three percent of patients gained >7% of their baseline weight during the course of the study (risperidone: 8, olanzapine: 6, quetiapine: 5).
Olfson et al[184] Risperidone vs other atypical antipsychotics (olanzapine, aripiprazole, quetiapine, ziprasidone) Note: risperidone was chosen	Matched CC 45-state Medicaid data was used to identify children and adolescents, aged 6-17 years, diagnosed with	N=1,745 180 days	Primary: Drug discontinuation rate, days to discontinuation, psychiatric hospital admission during the first 180 days, days to admission Secondary:	Primary: Compared to risperidone, olanzapine, quetiapine, aripiprazole, and ziprasidone were associated with comparable rates of drug discontinuation during the first 180 days (74.69%, 74.72%, 70.68%, 76.47%, 73.33%, respectively; *P*=0.79). Compared to risperidone, olanzapine, quetiapine, aripiprazole, and ziprasidone were associated with comparable number of days prior to drug discontinuation during the first 180 days (56.03, 51.60, 57.70, 57.77, and 51.03 days, respectively; *P*=0.37).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
as a reference drug due to high utilization	schizophrenia, schizoaffective disorder or schizophreniform disorder, who were free of any antipsychotic drug for at least 180 continuous days before filling the study medication		Not reported	Compared to risperidone, olanzapine, quetiapine, aripiprazole, and ziprasidone were associated with comparable rates of psychiatric hospital admission during the first 180 days (8.42%, 7.58%, 8.81%, 7.19%, 9.89%, respectively; *P*=0.94). Compared to risperidone, olanzapine, quetiapine, aripiprazole, and ziprasidone were associated with comparable number of days prior to psychiatric hospital admission during the first 180 days (37.50, 34.81, 40.59, 38.80, and 35.89 days, respectively; *P*=0.99). The percentage of patients in each treatment group with a psychiatric hospital admission ranged from 14.21% for the risperidone group to 16.06% for the quetiapine group (*P*=0.98).
Ardizzone et al[185] Atypical antipsychotics (olanzapine, risperidone, aripiprazole)	MA Multicenter, randomized, double-blind clinical trials evaluating the role of atypical antipsychotics in adolescents (13-17 years) diagnosed with Schizophrenia	N=not reported Study durations varied	Primary: Change in Positive and Negative Syndrome Scale (PANSS) total score, PANSS positive subscale score, Clinical Global Impression Scale-Severity of Illness (CGIS-SI) score, adverse effects Secondary: Not reported	Primary: All three atypical antipsychotics were associated with significant improvements in the total PANSS score from baseline (*P*<0.001). All three atypical antipsychotics were associated with significant improvements in the PANSS positive subscale score from baseline (*P*<0.001). All three atypical antipsychotics were associated with significant improvements in the CGIS-SI score from baseline (*P*<0.001). Olanzapine group exhibited the greatest amount of weight gain from baseline (*P* value not reported). Risperidone therapy was associated with a significantly greater incidence of akathisia, tremor, and dystonic events compared to controls. High aripiprazole dose was associated with a significantly greater incidence of tremor and Parkinsonism compared to control (*P*<0.01). Aripiprazole 10 mg was associated with the lowest incidence of

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				extrapyramidal symptoms and was not associated with significant weight gain (*P* value not reported). Secondary: Not reported
Schizophrenia, Schizoaffective Disorder, or Bipolar Disorder				
DelBello, Versavel et al[186] Ziprasidone 20 mg daily initially, titrated to 80 mg daily for three weeks, followed by flexible dosing in the range of 20 mg to 160 mg daily (low-dose group) vs ziprasidone 40 mg daily initially, titrated to 160 mg daily for three weeks, followed by flexible dosing in the range of 20 mg to 160 mg daily (low-dose group)	OL, MC Children and adolescents, aged 10 to 17 years, with a manic or mixed episode of bipolar I disorder or with schizophrenia or schizoaffective disorder	N=63 3 weeks fixed dose period/ 24 weeks flexible dose period	Primary: Young Mania Rating Scale (YMRS), Brief Psychiatric Rating Scale-Anchored Version (BPRS-A), CGI-S, adverse events Secondary: Not reported	Primary: The low ziprasidone dose (40 mg twice daily) was associated with a 17.2 (95% CI, 11.7 to 22.7) point reduction on the YMRS scale and a 1.5 (95% CI, 0.6 to 2.3) point reduction on the CGI-S scale in patients with bipolar mania (*P* value not reported). The high ziprasidone dose (80 mg twice daily) was associated with a 13.1 (95% CI, 8.6 to 17.7) point reduction on the YMRS scale and a 1.3 (95% CI, 0.8 to 1.8) point reduction on the CGI-S scale in patients with bipolar mania (*P* value not reported). The low ziprasidone dose (40 mg twice daily) was associated with a 9.5 (95% CI, -21.0 to 2.0) point reduction on the BPRS-A scale and a 0.7 (95% CI, -1.5 to 0.2) point reduction on the CGI-S scale in patients with schizophrenia or schizoaffective disorder (*P* value not reported). The high ziprasidone dose (80 mg twice daily) was associated with a 15 (95% CI, 11.2 to 19.2) point reduction on the BPRS-A scale and a 0.8 (95% CI, 0.2 to 1.4) point reduction on the CGI-S scale in patients with schizophrenia or schizoaffective disorder (*P* value not reported). The most common adverse events during the fixed-dose phase were sedation (32%), somnolence (30%), and nausea (25%); while, the most common adverse events during the flexible-dosing phase were sedation (30%), somnolence (30%), and headache (25%). Nausea and vomiting were reported during the initial fixed-dose phase and were considerable less frequent in the subsequent flexible-dosing phase. The incidence of movement disorders in the fixed-dose and flexible-dose

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				phases was 22% and 16%, respectively. While 13% and 40% of patients in the low- and high-dose groups, respectively, discontinued from the study due to adverse events during the fixed-dose phase, only 4.5% and 8.8% of patients in the low- and high-dose groups, respectively, discontinued during the flexible-dosing phase. Adverse events tended to occur more frequently during the initial three weeks and there were more adverse events reported in the high-dose group. Overall, 33% of patients gained at least 7% of their baseline weight. More patients experienced weight gain with continued flexible-dose therapy (4/63 patients during fixed-dose phase vs. 20/56 patients during the flexible-dose phase). The mean weight gain at week-3 was 1kg; while the mean weight gain at week-27 was 2.8 kg. There were no clinically significant changes in lipid profiles with either of the two dose groups. QT prolongation was not observed during the fixed-dose phase, while one case occurred during the flexible-dosing phase. Secondary: Not reported
Stewart et al[187] Ziprasidone 20 mg daily initially, titrated to 80 mg daily for three weeks, followed by flexible dosing in the range of 20 mg to 160 mg daily (low-dose group) vs	PH Children and adolescents, aged 10 to 17 years, with a manic or mixed episode of bipolar I disorder or with schizophrenia or	N=63 3 weeks fixed dose period/ 24 weeks flexible dose period	Primary: Children's Global Assessment Scale (CGAS) Secondary: Not reported	Primary: At week-3, the mean increase in CGAS score from baseline was 14.4 in the low-dose group compared with a 17.4 increase observed in the high-dose group (*P* value not reported). While there no one scored at the level of normal functioning (SGAS ≥70) at baseline, five patients scored ≥70 on the SCAS scale. Improvements in CGAS scores occurred as early as the first week of therapy.

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ziprasidone 40 mg daily initially, titrated to 160 mg daily for three weeks, followed by flexible dosing in the range of 20 mg to 160 mg daily (low-dose group)	schizoaffective disorder			Secondary: Not reported
Tourette Disorder (TD)				
Budman et al[188] Aripiprazole 2.5 mg to 40 mg daily	RETRO Children and adolescents, aged 8 to 18, with Tourette Disorder with or without intermittent explosive disorder	N=37 6-12 weeks	Primary: Reduction in tic severity on the CGI-Tic scale, reduction in rage on the CGI-Rage scale, adverse events Secondary: Not reported	Primary: Reduction in tic severity on the CGI-Tic scale was noted in 100% of the patients at the end of the study (*P* value not reported). Reduction in rage on the CGI-Rage scale was noted in 96% of the patients at the end of the study (*P* value not reported). Among the 8 patients who discontinued the study due to adverse events, 16% experienced akathisia, 8% experienced agitation, 8% experienced increased mood lability and/or anxiety, and 3% experienced symptoms of drug-induced Parkinsonism. Weight gain was noted in 87% of patients. Among these patients, there was a mean weight gain of 18 lbs. Secondary: Not reported
Cui et al[189] Aripiprazole 1.25 to 2.5 mg (prepubertal age) or 2.5 to 5 mg (children) initially and titrated up to effect Final mean dose was 8.17 mg or 0.19 mg/kg	OL Children and adolescents, aged 6 to 18 years, with TD and a CGI-S of at least 4 (moderately ill)	N=72 8 weeks	Primary: Yale Global Tic Severity Scale (YGTSS) subscale scores, Clinical Global Impressions-Tics (CGI-Tics) Secondary: CBCL, adverse events	Primary: Over the course of the study, there was a 50% reduction in tic severity, as assessed by YGTSS. A reduction of 56.5% in YGTSS Global impairment was also noted. A significant reduction from baseline in YGTSS motor tic and phonic tic scores was observed beginning at week-2 and continued through the end of the study (*P*=0.000). YGTSS total tic scores were also significantly improved from baseline, beginning at week-2 of therapy (*P*=0.000).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Aripiprazole therapy was associated with a significant reduction from baseline in mean CGI-Tics severity score (*P*=0.000). Secondary: Aripiprazole therapy was associated with significant improvements in the following subscales of the CBCL: somatic complaints (*P*<0.05), anxious/depressed (*P*<0.01), thought problems (*P*<0.01), attention problems (*P*<0.05), aggressive behavior (*P*<0.05), externalizing (*P*<0.01), internalizing (*P*<0.01) and total problem scales (*P*<0.01). There were no extrapyramidal adverse events reported during the study. Nausea and vomiting were the most frequently reported adverse events and occurred at an incidence of 29.2% and 26.4%, respectively. Patients receiving aripiprazole did not experience any clinically significant changes in laboratory parameters, including BMI.
Lyon et al[190] Aripiprazole 1.25 mg to 13.75 mg daily	OL, PRO Children and adolescents, aged 7 to 18, with Tourette's Disorder or chronic motor tic disorder, had failed trials with clonidine, guanfacine or neuroleptic medication in the past, tics caused significant distress, and had normal	N=10 10 weeks	Primary: YGTSS subscales, CGI-Tics Secondary: Children's Global Assessment Scale (C-GAS), Children's Depression Rating Scale (CDRS-R), Clinical Global Impressions Scale for Obsessive Compulsive Disorder (CGI-OCD), CGI-ADHD, CY-BOCS, Multidimensional	Primary: Aripiprazole therapy was associated with statistically significant reduction from baseline in YGTSS motor (-6.09; *P*=0.005) and vocal tic scores (-5.36; *P*=0.008). Aripiprazole therapy was associated with statistically significant reduction from baseline in YGTSS total tic (-11.45; *P*=0.003) and global severity scores (-28.09; *P*=0.003). Aripiprazole therapy was associated with statistically significant reduction from baseline in CGI-Tic severity scores (-1.27; *P*=0.004). On the CGI-Tic improvement scale, 91% of patients had a rating of 1 ("very much improved") or 2 ("much improved") at the end of the study. Secondary: Aripiprazole therapy was associated with statistically significant improvements from baseline in the C-GAS scores, both attention and hyperactivity/impulsivity measures of ADHD-RS, CGI-OCD, and the obsession subscale of CY-BOCS (*P*<0.05).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	intelligence		Anxiety Scale for Children (MASC), Attention Deficit Hyperactivity Disorder Rating Scale (ADHD-RS)	Aripiprazole therapy was not associated with statistically significant improvements from baseline in CDRS-R, CGI-ADHD, MASC total score, and the compulsion subscale of the CY-BOCS (*P*>0.05). Most frequently reported adverse events were appetite increase and weight gain, mild extrapyramidal effects, headaches, and tiredness/fatigue. Patients gained an average of 2.16 lbs over the course of the study, which was not significantly different from baseline (*P*=0.286). There were no significant changes from baseline in ECGs (*P* value not reported). Patients experienced a significant reduction in prolactin levels (*P*=0.03).
Murphy et al[191] Aripiprazole 1.25 mg to 7.5 mg daily	OL Children and adolescents, aged 8 to 17 years, with a primary diagnosis of a chronic tic disorder	N=16 6 weeks	Primary: Yale Global Tic Severity Scale (YGTSS), CY-BOCS, CGI-Tic Secondary: CGI-OCD, Abbreviated Symptom Questionnaire for Parents (ASQ-P), CDRS, adverse events	Primary: Aripiprazole therapy was associated with statistically significant reduction from baseline in YGTSS motor (-8.9; *P*<0.0001), phonic (-8.6; *P*<0.0001), and total tic scores (-17.5; *P*<0.0001). Aripiprazole therapy was associated with statistically significant improvement from baseline in CY-BOCS Obsessions, Compulsions, and total OCD subscale scores (*P*<0.005). Aripiprazole therapy was associated with statistically significant improvement from baseline in CGI-Tic Severity (-1.75; *P*<0.0001) and Improvement scores (2.5; *P*<0.0001). Secondary: Aripiprazole therapy was associated with statistically significant improvement from baseline in CGI-OCD Severity (-1.1; *P*<0.0001) and Improvement scores (2.0; *P*<0.0001). Aripiprazole therapy was associated with statistically significant reduction from baseline in ASQ-P scores (*P*=0.012).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Aripiprazole therapy was associated with statistically significant reduction from baseline in CDRS scores (*P*=0.002). Aripiprazole was associated with an average weight gain of 2.3 kg overall (*P*<0.003), and 4.1 kg among patients concurrently receiving a selective serotonin reuptake inhibitor (SSRI). There were no statistically significant changes in metabolic test results or ECG (*P* value not reported).
Seo et al[192] Aripiprazole 2.5 mg to 15 mg daily	OL, PRO Children and adolescents, aged 7 to 19 years, with Tourette Disorder or chronic tic disorder	N=15 12 weeks	Primary: Yale Global Tic Severity Scale (YGTSS) Secondary: CGI-I, CGI-S, adverse events	Primary: Aripiprazole therapy was associated with statistically significant improvement in YGTTS motor tic, phonic tic, and total tic scores compared to baseline (*P*<0.001 for all). Secondary: At week-12, aripiprazole therapy was associated with statistically significant improvement from baseline in CGI-I and SGI-S scores, beginning at week-3 of the study (*P*<0.001 for both). Nausea and sedation were the most frequently reported adverse events. There was no statistically significant change from baseline in BMI (*P*=0.749).
McCracken et al[193] Olanzapine 2.5 mg up to a maximum of 20 mg daily	OL, PRO Children and adolescents, aged 7 to 17 years, with Tourette Disorder, CGI ≥4 (moderately ill) Note: all patients had at least one	N=12 6 weeks	Primary: YGTSS motor tic, YGTSS vocal tic, YGTSS total tic severity scores Secondary: Swanson, Nolan and Pelham Questionnaire (SNAP-IV), Overt Aggression Scale (OAS), Multidimensional	Primary: Aripiprazole was associated with statistically significant improvements in all measures of the YGTSS motor tic scale, including the total motor tic severity score (*P*<0.05 for all). Aripiprazole was associated with a statistically significant improvement in the YGTSS vocal tic interference scores (*P*<0.05), though the other measures of this category were not significantly changed from baseline. Aripiprazole was associated with statistically significant improvements in most measures of the YGTSS total tic scale, including the total tic severity score (*P*<0.05 for all). The only measures that were not significantly changed from baseline were YGTSS total tic number and complexity (*P*>0.05).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	comorbid condition, most commonly ADHD		Anxiety Scale for Children (MASC) Child, MASC Parent scores, adverse events	Secondary: Significant changes from baseline were noted in the YGTSS Overall Impairment and Global Severity scores (*P*<0.001). Significant changes from baseline were noted in all of the following categories of SNAP IV: ADHD Inattention, ADHD Hyperactivity/Impulsivity, ODD, Inattention/overactivity, Aggression/Defiance, and Conners' Index (*P*<0.01). Significant changes from baseline were also noted in the OAS number of episodes scores and MASC Child Physical Symptoms scores (*P*<0.05). No significant changes from baseline were observed in the remaining categories of OAS or MASC-Child, as well as the MASC-Parent scores (*P*>0.05). Olanzapine therapy was associated with a statistically significant weight gain from baseline (*P*<0.001). The mean percentage change from baseline to week 6 was 8.4 (*P*<0.001). Drowsiness/sedation was also frequently reported.
Stephens et al[194] Olanzapine 2.5 mg up to a maximum of 20 mg daily for 8 weeks	OL, PRO Children and adolescents, aged 7 to 13 years, with a primary diagnosis of Tourette Disorder and a history of aggressive behavior	N=10 10 weeks	Primary: CBCL, Achenbach Teacher Rating Form (TRF), CGI-Aggression, YGTSS, CGI-Tic, adverse events Secondary: Not reported	Primary: Olanzapine therapy was associated with a statistically significant improvement in CBCL scores from baseline (*P*<0.009). Olanzapine therapy was not associated with a statistically significant improvement in mean TRF scores from baseline (*P*>0.05). Olanzapine therapy was associated with a statistically significant improvement in CGI-Aggression scores from baseline (*P*<0.03). Olanzapine therapy was associated with a statistically significant improvement in YGTSS total tic scores from baseline (*P*<0.007). Olanzapine therapy was associated with a statistically significant improvement in CGI-Tic severity scores from baseline (*P*<0.04).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Patients exhibited an average weight gain of 12 lbs from baseline (*P*<0.005). Weight gain occurred most rapidly during the first two weeks of therapy. Extrapyramidal adverse events were not reported during the study. Secondary: Not reported
Copur et al[195] Quetiapine 25 mg daily and titrated up to effect	RETRO Children and adolescents, aged 8 to 18 years, with Tourette's syndrome	N=12 8 weeks	Primary: YGTSS scores Secondary: Adverse events	Primary: At both 4 and 8 weeks after therapy initiation, quetiapine therapy was associated with a statistically significant improvement in YGTSS scores from baseline (*P*<0.003). Secondary: There were no statistically significant changes in laboratory parameters and serum prolactin levels from baseline (*P*>0.05). Mild but significant weight gain was noted during the study duration (*P* value not reported).
Sallee et al[196] Ziprasidone 5 mg up to a maximum of 40 mg daily	PC, RCT Children and adolescents, aged 7 to 17 years, with Tourette's syndrome and chronic tic disorders	N=28 56 days	Primary: YGTSS Global Severity scores, Total Tic scores, tic frequency, adverse events Secondary: Not reported	Primary: Compared to placebo, ziprasidone was associated with a statistically significant improvement from baseline in the YGTSS Global Severity scores (*P*=0.016) and Total Tic scores (*P*=0.008). Compared to placebo, ziprasidone was associated with a statistically significant improvement from baseline in tic frequency, as determined by blind videotape tic counts (*P*=0.039). There were no clinically significant extrapyramidal adverse events. Mild transient somnolence was the most common adverse event. Secondary: Not reported
Miscellaneous Mental Health Disorders/Multiple Conditions				
Capone et al[197] Risperidone 0.25 mg to	NAT Children, aged 3 to 13	N=23 95.8 days on	Primary: ABC subscales, adverse events	Primary: Risperidone therapy was associated with a statistically significant improvement in the ABC composite score from baseline (*P*<0.001).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
1.5 mg once daily at bedtime	years, with Down Syndrome, severe intellectual disability, and a comorbid autistic spectrum disorder	average	Secondary: Not reported	The greatest improvement from baseline occurred in regard to the following ABC subtypes: lethargy, stereotypy, and hyperactivity (P<0.001). However, the other two ABC subtypes were also significantly improved from baseline (P<0.05). Children with both disruptive behavior and self-injury were associated with the greatest improvement in symptoms with risperidone therapy. Among patients with pre-existing sleep disturbances, 88% experienced an improvement in sleep quality. Risperidone therapy was associated with an average weight gain of 2.8 kg. Secondary: Not reported
Erickson et al[198] Aripiprazole, 9.8 mg daily on average	OL, PRO Patients, aged 6 to 25, with Fragile X syndrome (FXS) Note: FXS is a form of genetic developmental disability and one of the causes of autism	N=12 12 weeks	Primary: Treatment response (defined as CGI-I score of much improved or very much improved and a ≥25% improvement on the ABC-Irritability subscale) Secondary: Not reported	Primary: Aripiprazole therapy was associated with a treatment response in 87% of patients. Discontinuations from the study occurred in 2/12 patients and were due to the following adverse events: akathisia, drooling, and tiredness. There were no significant changes from baseline in weight or laboratory measures. Secondary: Not reported
Krieger et al[199] Risperidone 0.5 to 3 mg daily	OL Children and adolescents, aged 7 to 17 years, with irritability at least three	N=21 8 weeks	Primary: Aberrant Behavior Checklist-Irritability (ABC-Irritability) Secondary:	Primary: At week-8, patients experienced a statistically significant reduction in ABC-irritability scores from baseline (P<0.05). Secondary: At week-8, patients exhibited a statistically significant reduction in CGI

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	times weekly, abnormal mood (anger or sadness) for at least half the day on most days, hyperarousal, severe impairment in at least one setting and at least mild impairment in the second setting, symptom onset before the age of 12 and present for at least 12 months without symptom-free periods of greater than 2 months, and no psychotropic use within 6 months		CGI, Clinical Global Assessment Scale (CGAS), Swanson, Nolan, and Pelham Scale-version IV (SNAP-IV), Young Mania Rating Scale (YMRS), Children Depression Rating Scale (CDRS), Mood Symptom Questionnaire (MSQ), The Screen for Child Anxiety-Related Emotional Disorders (SCARED), adverse events	scores from baseline (P<0.05). At week-8, risperidone therapy was associated with significantly increased CGAS scores from baseline (P<0.05). At week-8, patients exhibited a statistically significant reduction in SNAP-IVI scores from baseline (P<0.05). At week-8, patients exhibited a statistically significant reduction in YMRS scores from baseline (P<0.05). At week-8, patients exhibited a statistically significant reduction in CDRS scores from baseline (P<0.05). At week-8, patients exhibited a statistically significant reduction in MSQ scores from baseline (P<0.05). At week-8, patients exhibited a statistically significant reduction in SCARED scores from baseline (P<0.05). At week-8, risperidone therapy was associated with statistically significant increases in prolactin level, serum glucose, and weight from baseline (P<0.05).
Castro-Fornieles et al[200] Antipsychotic agents (risperidone, quetiapine, olanzapine) administered at varying doses	PRO, OL Children and adolescents, aged 9 to 17 years, with a first psychotic episode attributed to a psychotic disorder not otherwise specified,	N=110 6 months	Primary: PANSS, CGI, Disability Assessment Scale (DAS), Global Assessment Functioning (GAF), adverse events	Primary: At 6 months of follow-up, PANSS total scores were significantly improved from baseline in patients treated with risperidone, quetiapine or olanzapine ($P\leq$0.001). There were no significant differences among the three treatment groups in the reduction of PANSS total scores from baseline (P=0.876). At 6 months of follow-up, PANSS positive symptom scores were significantly improved from baseline in patients treated with risperidone,

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	schizophrenia-type disorder, depressive disorder with psychotic symptoms, and bipolar mania with psychotic features		Secondary: Not reported	quetiapine or olanzapine ($P \leq 0.001$). There were no significant differences among the three treatment groups in the reduction of PANSS positive symptom scores from baseline ($P=0.681$). At 6 months of follow-up, PANSS negative symptom scores were not significantly changed from baseline in the risperidone group ($P=0.53$), but were significantly improved from baseline in patients treated with quetiapine or olanzapine ($P<0.01$). There were no significant differences among the three treatment groups in the reduction of PANSS negative symptom scores from baseline ($P=0.195$). At 6 months of follow-up, PANSS general scores were significantly improved from baseline in patients treated with risperidone, quetiapine or olanzapine ($P \leq 0.001$). There were no significant differences among the three treatment groups in the reduction of PANSS general scores from baseline ($P=0.741$). At 6 months of follow-up, CGI scores were significantly improved from baseline in patients treated with risperidone, quetiapine or olanzapine ($P \leq 0.001$). There were no significant differences among the three treatment groups in the reduction of CGI scores from baseline ($P=0.237$). At 6 months of follow-up, DAS scores were significantly improved from baseline in patients treated with risperidone, quetiapine or olanzapine ($P<0.05$). There were no significant differences among the three treatment groups in the reduction of DAS scores from baseline ($P=0.075$). At 6 months of follow-up, GAF scores were significantly improved from baseline in patients treated with risperidone, quetiapine or olanzapine ($P<0.05$). There were no significant differences among the three treatment groups in the reduction of GAF scores from baseline ($P=0.069$).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Olanzapine therapy was associated with significantly greater weight gain (11.7 kg) from baseline compared to either risperidone (6.1 kg; *P*=0.02) or quetiapine (6.0 kg; *P*=0.04). Risperidone was associated with a significantly greater frequently of neurological side effects, compared with olanzapine (*P*=0.022). Hypokinesia was the most frequent neurological adverse event reported in association with risperidone therapy and occurred at a significantly greater incidence compared to quetiapine and olanzapine (50% vs. 13.3% vs. 15.4%, respectively; *P*=0.001).
Sikich et al[201] Olanzapine 2.5 mg to 12.5 mg daily, up to a maximum daily dose of 20 mg vs risperidone 0.5 to 3 mg daily, up to a maximum daily dose of 6 mg vs haloperidol 1 to 5 mg daily, up to a maximum daily dose of 8 mg	DB, PG, RCT Children and adolescents, 8 to 19 years, with psychotic symptoms secondary to either schizophrenia spectrum or affective disorders	N=50 8 weeks	Primary: BPRS-C, Secondary: CGI-S, CGI-I, CPRS, response (defined as CGI-I score of 1 or 2 and at least a 20% reduction in BPRS-C total score), adverse events	Primary: All treatment groups experienced a statistically significant improvement in BPRS-C scores from baseline (*P*<0.05), though the difference in BPRS-C score change among the three groups was not statistically significant (*P*=0.2). Secondary: CPRS-total scores were significantly improved from baseline in the risperidone and olanzapine groups (*P*<0.005). The change in CPRS-total scores did not significantly differ among the groups (*P*=0.416). CPRS-positive scores were significantly improved from baseline in all three treatment groups (*P*<0.05), though the difference in CPRS-positive scores was not statistically significant among the three groups (*P*=0.252). CPRS-negative scores were significantly improved from baseline only in the risperidone group (*P*=0.005); however, there was no significant difference among the three groups (*P*=0.47). CGI-S scores were significantly improved from baseline in the risperidone and olanzapine treatment groups (*P*<0.01), though the difference in CGI-S scores was not statistically significant among the three groups (*P*=0.064).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				CGI-I scores were significantly improved from baseline in the risperidone and olanzapine treatment groups (*P*=0.0018), though the difference in CGI-I scores was not statistically significant among the three groups (*P*=0.15). Treatment response was achieved by 88% of patients in the olanzapine group, 74% of patients in the risperidone group, and 53% of patients in the haloperidol group. The difference among the three groups was not statistically significant (*P*=0.12). However, there were differences in the mean time to response among the three antipsychotic groups: 1.6 weeks with olanzapine, 2.3 weeks with risperidone, and 2.4 weeks with haloperidol (*P*<0.045). While more than 50% of patients treated with either olanzapine or risperidone experienced Parkinsonian symptoms, the incidence of extrapyramidal adverse events was significantly greater in the haloperidol group, compared to either of the atypical antipsychotics (*P*<0.05). A larger percentage of patients in each group required low-dose anticholinergics to control their extrapyramidal symptoms: 67% with haloperidol, 56% with olanzapine, and 53% with risperidone. Significant weight gain from baseline was noted in all treatment groups: 15.7 lbs with olanzapine, 10.9 lbs with risperidone, and 7.8 lbs with haloperidol (*P*<0.001). The difference in weight gain was statistically significant among groups (*P*=0.039). Compared to the other treatment groups, patients receiving olanzapine experienced a statistically significant glucose level elevation (*P*=0.008), although the change from baseline did not reach statistical significance (*P*=0.06). Haloperidol-treated patients experienced a statistically significant QTc elevation compared to baseline (*P*=0.031); none of the other treatment groups experienced significant ECG changes from baseline.

*Agent not available in the United States

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Study abbreviations: AC-active controlled, CC=case-control, CI=confidence interval, DB=double-blind, ES=extension study, I=International, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, PH=post-hoc, PRO=prospective trial, R=randomized, RCT=randomized controlled trial, RETRO=retrospective, SR-systematic review, XO=cross-over
Miscellaneous abbreviations: BAC=Aberrant Behavior Checklist, AD=Alzheimer's Disease, ADHD=Attention Deficit Hyperactivity Disorder, ADHD-RS-IV=ADHD Rating Scale-Version IV, AIMS=Abnormal Involuntary Movement Scale, ASD=Autistic Spectrum Disorder, ASQ-P=Abbreviated Symptom Questionnaire for Parents, BAS=Barnes Akathisia Scale, BIS=Mody Image Software, BMI=body mass index, BOCS=Yale-Brown Obsessive Compulsive Scale, BPRS=Brief Psychiatric Rating Scale, BPRS-A=Brief Psychiatric Rating Scale-Anchored Version, BSPS=Brief Social Phobia Scale, CAFAS=Child and Adolescent Functional Assessment Scale, CAPT=Color-A-Person Test, CARS-Childhood Autism Rating Scale, CBCL=Child Behavior Checklist, CDRS=Children's Depression Rating Scale, CGAS=Children's Global Assessment Scale, CGI=Clinical Global Impressions Scale, CGI-BP=Clinical Global Impressions-Bipolar Version Scale CGI-C=Clinical Global Impression of Change, CGAS=Children's Global Assessment Scale, CGI-C=Clinical Global Impression of Change, CGI-I=Clinical Global Impression-Improvement, CGI-S=Clinical Global Impression Severity, CGI-SI=Clinical Global Impression—Severity of Illness, CMAI=Cohen-Mansfield Agitation Inventory, CMRS-P=Child Mania Rating Scale-Parent Version, CPRS-CP=Connors' Parent Rating Scale, CPRS=Children's Psychiatric Rating Scale, CPS= Connors' Parent Scale, CPT=Continuous Performance Test, DRS-R98=Delirium Rating Scale Revised-98, CY-BOCS-PDD=Compulsion subscale of the Childrens Yale Brown Obsessive Compulsive Scale Modified for PDD, DAS=Disability Assessment Scale, DOTES=Dosage Record Treatment Emergent Symptom Scale, DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th edition, EAT=Eating Attitude Test, EDI-2=Eating Disorder Inventory, ECG=electrocardiogram, EPS=extrapyramidal side effects, ESRS=Extrapyramidal Symptom Rating Scale, GAD=generalized anxiety disorder, GAF=Global Assessment of Functioning Scale, GARS=Gilliam Autism Rating Scale, HALFS-Health and Life Functioning Scale, HAM-A=Hamilton Rating Scale for Anxiety, HAM-D=Hamilton Rating Scale for Depression, IBW=Ideal Body Weight, KADS=Kutcher Adolescent Depression Scale, MADRS=Montgomery-Asberg Depression Rating Scale, MASC=Multidimensional Anxiety Scale for Children, MBW=Median Body Weight, MDD=major depressive disorder, MJTS=Mendota Juvenile Treatment Center, MOAS=Modified Overt Aggression Scale, MSQ=Mood Symptom Questionnaire, MVLT-C=Modified Verbal Learning Test-Children's Version, N-CBRF=Nisonger Child Behavior Rating Form, NNH=number needed to harm, NNT=number needed to treat, NOS=Not Otherwise Specified, NPI=Neuropsychiatric Inventory, OAS=Overt Aggression Scale, OCD=Obsessive Compulsive Disorder, OR=Odds Ratio, PANSS=Positive and Negative Syndrome Scale, PAC=Personal Assessment Checklist, PANSS-P=Positive and Negative Syndrome Scale-Positive Subscale, PDD=Pervasive Developmental Disorder, PTSD=Post Traumatic Stress Disorder,PYMRS=Parent Young Mania Rating Scale, RAAPP=Rapid Assessment and Action Planning Process, REE=Resting Energy Expenditure, RF-RLRS=Ritvo-Freeman Real Life Rating Scale, SANS=Scale for the Assessment of Negative Symptoms, SAPS=Scale for the Assessment of Positive Symptoms, SAS=Simpson-Angus Scale, SAS=Riker Sedation Agitation Scale, SCARED=Screen for Child Anxiety-Related Emotional Disorders, SMC=standardized mean changes, SIAB-EX=Structured Inventory for Anorexic and Bulimic Syndromes-Exert Form, SNAP-IV=Swanson, Nolan, Pelham Scale-Version IV, PGDRS=Psychogeriatric Dependency Rating Scales, TPDDRS-Turgay DSM-IV Pervasive Developmental Disorder Rating Scale, TD=Tourette's Disorder, TRF=Teacher's Report Form, TSH=thyroid stimulating hormone, VABS=Vineline Adaptive Behavior Scale, VAS-MS=Visual Analog Scale for Most Troublesome Symptom, YBOCS=Yale-Brown Obsessive Compulsive Scale, YGTSS=Yale Global Tic Severity Scale, YMRS=Young Mania Rating Scale

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Table 7. Strength of Evidence for Off-Label Use of the Atypical Antipsychotics (2011 AHRQ Report)[91,202]

Disease State	Aripiprazole	Olanzapine	Quetiapine	Risperidone	Ziprasidone
Anxiety Disorder					
General	NA	-	Moderate/High	-	-
Social Phobia	NA	Low	-	NA	NA
ADHD					
No comorbidity	NA	NA	NA	Low	NA
Bipolar	-	NA	NA	NA	NA
Mental Retardation	NA	NA	NA	Low	NA
Dementia					
Overall	Moderate/High	Low	Low	Moderate/High	NA
Psychosis	Low	Mixed	Mixed	Moderate/High	NA
Agitation	Low	Moderate/High	Mixed	Moderate/High	NA
Depression					
Augmentation of SSRI/SNRI	Moderate/High*	Low*	Moderate/High*	Moderate/High	Low
Monotherapy	NA	-	Moderate/High	NA	NA
Eating Disorders	NA	--	-	NA	NA
Insomnia	NA	NA	-	NA	NA
Obsessive Compulsive Disorder					
Augmentation of SSRI	NA	Low	--	Moderate/High	-
Augmentation of citalopram	NA	NA	Low	Low	NA
Personality Disorder					
Borderline	Low	Mixed	Low	NA	-
Schizotypal	NA	NA	NA	Mixed	NA
Post Traumatic Stress Disorder	NA	Mixed	Low	Moderate/High	NA
Substance Abuse					
Alcohol	--	-	-	NA	NA
Cocaine	NA	-	NA	-	NA
Methamphetamine	-	NA	NA	NA	NA
Methadone	NA	NA	NA	-	NA
Tourette's Syndrome	NA	NA	NA	Low	-

*FDA-approved for the indication
-Low or very low evidence of inefficacy
-- Moderate or high evidence of inefficacy
NA=No studies analyzed in this patient population or insufficient information.
ADHD=Attention Deficit Hyperactivity Disorder; SSRI=Selective Serotonin Reuptake Inhibitor; SNRI=Serotonin-Norepinephrine Reuptake Inhibitor

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Table 8. Safety Clinical Trials Using the Antipsychotics in Adults

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Mortality/Cardiovascular				
Strom et al[203] ZODIAC Study Ziprasidone at varying doses vs olanzapine at varying doses	I, MC, OL, R Patients, 18 years or older, diagnosed with schizophrenia	N=18,154 1 year	Primary: Non-suicide mortality in the year after initiation of assigned treatment Secondary: All-cause mortality, mortality due to sudden death, mortality due to cardiovascular causes, mortality due to suicide, all-cause hospitalization, hospitalization for cardiovascular causes, diabetic ketoacidosis or psychiatric hospitalization, discontinuation rate	Primary: There was no significant difference between ziprasidone and olanzapine treatment groups with respect to non-suicide mortality (RR, 1.02; 95%CI, 0.76 to 1.39). Secondary: There was no significant difference between ziprasidone and olanzapine treatment groups with respect to all-cause mortality (RR, 1.01; 95%CI, 0.77 to 1.33). There was no significant difference between ziprasidone and olanzapine treatment groups with respect to mortality due to sudden death (RR, 0.67; 95%CI, 0.11 to 3.99). There was no significant difference between ziprasidone and olanzapine treatment groups with respect to cardiovascular mortality, including fatal myocardial infarction and fatal arrhythmia (0.03% vs. 0.09%; RR, 0.38; 95%CI, 0.10 to 1.41). There was no significant difference between ziprasidone and olanzapine treatment groups with respect to mortality due to suicide (RR, 1.19; 95%CI, 0.61 to 2.31). Significantly more patients were hospitalized for any cause in the ziprasidone group compared to patients receiving olanzapine (15.1% vs. 10.9%; RR, 1.39; 95%CI, 1.29 to 1.50). There was no significant difference between ziprasidone and olanzapine treatment groups with respect to hospitalization for myocardial infarction (RR, 1.18; 95%CI, 0.53 to 2.64). There was no significant difference between ziprasidone and olanzapine treatment groups with respect to hospitalizations for arrhythmia or

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				arrhythmia reported during hospitalization for other reasons (RR, 1.75; 95%CI, 0.51 to 5.98). There was no significant difference between ziprasidone and olanzapine treatment groups with respect to hospitalization for diabetic ketoacidosis (RR, 1.00; 95%CI, 0.29 to 3.45). Significantly more patients in the ziprasidone group experienced psychiatric hospitalizations compared to patients receiving olanzapine (11.1% vs. 7.5%; RR, 1.48; 95%CI, 1.35 to 1.62). At 6 months, 64.6% of ziprasidone-treated patients and 73% of olanzapine-treated patients remained on study medication (*P*<0.001). At 12 months, 52.7% of ziprasidone-treated patients and 61.5% of olanzapine-treated patients remained on study medication (*P*<0.001).
Metabolic				
Lamberti et al[204] Clozapine vs general population	RETRO, cohort Adult outpatients with DSM-IV diagnosis of schizophrenia or schizoaffective disorder receiving clozapine for >3 months without a documented history of diabetes prior to age 18	N=101 1 year	Primary: Diagnosis of diabetes Secondary: Not reported	Primary: Point prevalence of diabetes mellitus was 25.7% compared with 7.9% of the general population (no statistical analysis provided). BMI, percentage of body fat, and gender were not associated with development of diabetes (*P*=0.23 to 0.75). Mean age at time of clozapine initiation was higher in patients with diabetes (*P*=0.05). Development of diabetes was associated with a positive family history (*P*=0.002). Secondary: Not reported
Reist et al[205] Second generation antipsychotics, (aripiprazole, clozapine, olanzapine, quetiapine, risperidone, or	CC, OS Data was collected from the Nationwide Inpatient Sample	N=exact numbers not reported 15 years	Primary: Prevalence of obesity, diabetes, and diabetic ketoacidosis with or	Primary: The prevalence of obesity in controls increased from 1.2% in 1988 to 3.8% in 2002, yielding a 2.6% net increment in obesity prevalence rate. In contrast, there was a net increase of 12.6% in obesity prevalence from 1988 (5.9%), before the adoption of second generation antipsychotics, to

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ziprasidone) Doses for all regimens not reported.	database which includes 5-8 million inpatient hospital stays/year in order to approximate a 20% sample of United States community hospitals, for both schizophrenia and schizoaffective disorder; data was overlaid with data regarding the market penetration of the second generation antipsychotics in order to examine the prevalence rates of obesity, diabetes mellitus, and diabetic ketoacidosis with or without hyperosmolar coma among inpatients with schizophrenia compared with controls		without hyperosmolar coma in cases and controls for each study year Secondary: Not reported	2002 (18.5%), when second generation antipsychotics accounted for 86.0% of all new and repeat antipsychotic prescriptions. From 1988 to 1991, there was no significant change in obesity rates for cases or controls (*P*>0.60). However, both groups showed significant increases in prevalence of obesity in the subsequent years, but notably, the increase was markedly larger for the cases (*P*=0.016). For diabetes mellitus, the prevalence in controls was 7.5% in 1988 and 15.3% in 2002, reflecting a net increase of 7.8% during this period. In cases, the prevalence of diabetes was 6.1% in 1988 and 17.4% in 2002. This represents a net increase of diabetes in cases (11.3%) vs controls (7.8%) during the 15-year study period. Analysis of variance of the data on diabetes from 1988 to 1997 found a significant increase in prevalence in both groups (*P*=0.001) but no difference in rates of change (*P*=0.96). For the years after 1997, however, the rate of change accelerated much faster for the cases vs the controls (*P*<0.0001). For diabetic ketoacidosis with or without hyperosmolar coma, a regression analysis indicated that the diabetic ketoacidosis with or without hyperosmolar coma prevalence versus time curve for the cases started at a significantly lower minimum value (0.20%) vs the controls (0.26%) (*P*=0.04) and reached a higher maximum value (0.47% in cases vs 0.41% in controls) (*P*=0.02). Secondary: Not reported
Lambert et al[206] Atypical antipsychotics	Matched CC California Medicaid	N=18,186 5 years	Primary: Risk of developing diabetes	Primary: At 12 weeks, there was an increased risk of developing diabetes with clozapine (OR, 1.34; 95% CI, 1.16 to 1.55), olanzapine (OR, 1.36; 95%

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(administered as either a low, medium or high dose)	data was used to identify patients (cases) who developed diabetes subsequent to being diagnosed with schizophrenia, patients were exposed to at least one antipsychotic during the 12 weeks preceding diabetes diagnosis		Secondary: Not reported	CI, 1.20 to 1.53), and combination atypical therapy (OR, 1.58; 95% CI, 1.33 to 1.88). There was no increased risk with risperidone or quetiapine vs conventional antipsychotics. At 24 weeks, an increased risk of developing diabetes was seen with clozapine (OR, 1.32; 95% CI, 1.14 to 1.53), olanzapine (OR, 1.38; 95% CI, 1.22 to 1.56), or combination therapy (OR, 1.54; 95% CI, 1.29 to 1.84). At 52 weeks, increased risk of developing diabetes was seen with clozapine (OR, 1.41; 95% CI, 1.21 to 1.65), olanzapine (OR, 1.41; 95% CI, 1.24 to 1.60), or combination therapy (OR, 1.58; 95% CI, 1.31 to 1.90). Hispanic, African American, and unknown ethnicity were also significant risk factors for development of diabetes (OR, 1.4-1.6) as was exposure to combination therapy (OR, 1.6; 95% CI, 1.3 to 1.9). Secondary: Not reported
Olfson et al[207] Antipsychotic medications (aripiprazole, clozapine, olanzapine, quetiapine, risperidone ziprasidone or a first generation agent) vs no antipsychotic agent Doses for all regimens not reported.	CC, Cohort Claims data was collected from California Medicaid, cases included those aged 18-64 years with schizophrenia, major depression, bipolar disorder, or other affective psychoses and incident hyperlipidemia	N=85,273 4 years	Primary: Relative risk of developing hyperlipidemia after treatment with antipsychotics Secondary: Not reported	Primary: There was a significant increase in the risk of incident hyperlipidemia with clozapine (OR, 1.82; 95% CI, 1.61 to 2.05), olanzapine (OR, 1.56; 95% CI, 1.47 to 1.67), quetiapine (OR, 1.52; 95% CI, 1.40 to 1.65), risperidone (OR, 1.53; 95% CI, 1.43 to 1.64), ziprasidone (OR, 1.40; 95% CI, 1.19 to 1.65), and first generation antipsychotics (OR, 1.26; 95% CI, 1.14 to 1.39), but not aripiprazole (OR, 1.19; 95% CI, 0.94 to 1.52). Secondary: Not reported

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Gianfrancesco et al[208] Olanzapine, risperidone, or high-potency (haloperidol, fluphenazine) or low-potency (chlorpromazine, thioridazine) conventional antipsychotics vs no treatment	RETRO Claims data for the period January 1996 through December 1997 were analyzed for patients with mood disorders, patients either received no antipsychotics or received them for at least 60 consecutive days	N=7,933 1 year	Primary: Association of antipsychotic use and newly reported diabetes Secondary: Not reported	Primary: The risk of newly reported diabetes in patients who received risperidone was not significantly different compared to untreated patients (OR, 0.88; 95% CI, 0.372 to 2.070). However, there was a much greater risk of diabetes in patients treated with olanzapine (OR, 3.10; 95% CI, 1.620 to 5.934), high-potency conventional antipsychotics (OR, 2.13; 95% CI, 1.097 to 4.134) and low-potency conventional antipsychotics (OR, 3.46; 95% CI, 1.552 to 7.785) compared to untreated patients. There was also a dose dependent increase in risk based on olanzapine dose (OR, 1.161; *P*<0.01). This correlates to an increased risk of diabetes equal to 16.1% for each 2.6 mg increase in olanzapine dose. Secondary: Not reported
Etminan et al[209] Atypical neuroleptics (olanzapine, quetiapine, or risperidone) vs typical neuroleptics (chlorpromazine, chlorprothixene*, clorazepate, fluphenazine, flupenthixol*, haloperidol, loxapine, mesoridazine*, perphenazine, pimozide, prochlorperazine, or trifluoperazine)	RETRO Cohort Residents in long-term care institutions ≥65 years of age	N=11,104 Duration not specified	Primary: Development of a diabetic event defined as prescribing of antidiabetic medication Secondary: Not reported	Primary: In comparing diabetes incidence rates per 1,000 patient years, the highest incidence was observed in the corticosteroid group (190) followed by typical neuroleptics (47), benzodiazepines (40) and atypical neuroleptics (31). Increased risk of developing diabetes was not observed in older adults receiving atypical neuroleptic medications vs those receiving benzodiazepines (adjusted HR, 0.89; 95% CI, 0.66 to 1.21; adjusted HR for typical neuroleptic treatment vs benzodiazepine group was 1.27; 95% CI, 0.91 to 1.77). The corticosteroid treatment group was nearly twice as likely to develop diabetes vs the benzodiazepine group (adjusted HR, 2.2; 95% CI, 1.41 to 3.12). The number of diabetic events did not differ between the risperidone, olanzapine, or quetiapine groups (HR, 2.1%, 1.0%, and 2.1%

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs control group (benzodiazepines) vs corticosteroids (positive control group)				respectively; *P* values not provided). Secondary: Not reported
Simpson et al[210] Atypical antipsychotics (mean doses listed; clozapine 323.0 mg daily, olanzapine 15.8 mg daily, quetiapine 384.4 mg daily, or risperidone 5.78 mg daily vs typical antipsychotics (mean doses listed; chlorpromazine 100.0 mg daily, fluphenazine 34.2 mg daily, haloperidol 9.0 mg daily, molindone 50.0 mg daily, perphenazine 23.8 mg daily, pimozide 2.5 mg daily, thioridazine 200.0 mg daily, or trifluoperazine 23.3 mg daily vs antipsychotic free period of	NAT, RETRO Review of all patients admitted to Schizophrenia Research Unit of New York Psychiatric Institute from 1994-1999	N=121 5 years Specific time per individual patient not specified (range 6.4-12.4 weeks of therapy)	Primary: Weight gain per week, rate of weight gain, weekly change in BMI Secondary: Not reported	Primary: More weight gain per week was observed in the atypical antipsychotic group compared to antipsychotic free periods (*P*=0.031); however, there was no difference in rate of weight gain between antipsychotic free and typical antipsychotic treatment periods (*P* value not reported). Olanzapine treatment resulted in a higher rate of weight gain compared to clozapine and risperidone (*P*=0.001) and there was no difference in rates of weight gain between clozapine and risperidone (*P* value not reported). Olanzapine treatment was associated with a higher rate of weight gain compared with the antipsychotic free period, typical antipsychotics and treatment with other atypical antipsychotics (*P*=0.001). Olanzapine and clozapine were associated with significantly higher weekly weight gain compared with the antipsychotic free period treatment group (*P*=0.001 and 0.036); no difference in weekly weight gain was observed between risperidone treatment and the antipsychotic free period (*P*=0.833). There was no significant association between length of treatment and weight gain (*P* value not reported). Secondary: Not reported

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
2-4 weeks				
Guo et al[211] Atypical antipsychotics (clozapine, olanzapine, quetiapine, risperidone, or ziprasidone) vs conventional antipsychotics (chlorpromazine, fluphenazine, haloperidol, loxapine, molindone, perphenazine, pimozide thioridazine, thiothixene, or trifluoperazine) Doses for all regimens not reported.	CC, RETRO Medicaid claims from 7 states were analyzed for 283 patients with diabetes (cases) and 1,134 controls matched by age, sex, and date when bipolar disorder was diagnosed, all patients had at least a 3-month exposure to either conventional or atypical antipsychotics or three prescriptions related to treatment of bipolar disorder	N=1,417 4 years	Primary: Risk of developing diabetes Secondary: Not reported	Primary: Compared with patients receiving conventional antipsychotics, the risk of diabetes was greatest with risperidone (HR, 3.8; 95% CI, 2.7 to 5.3), olanzapine (HR, 3.7; 95% CI, 2.5 to 5.3), and quetiapine (HR, 2.5; 95% CI, 1.4 to 4.3). The risk for developing diabetes was associated with weight gain (HR, 2.5; 95% CI, 1.9 to 3.4), hypertension (HR, 1.6; 95% CI, 1.2 to 2.2), and substance abuse (HR, 1.5; 95% CI, 1.0 to 2.2). Secondary: Not reported
Guo et al[212] Atypical antipsychotics (41% of patients received either clozapine, olanzapine, risperidone, or ziprasidone) vs conventional antipsychotics (34% of patients received either chlorpromazine, fluphenazine, haloperidol,	CC, RETRO Patients with diabetes (N=928) were matched with controls (N=5,258) according to age, sex, and bipolar index.	N=6,178 5 years	Primary: Risk of diabetes Secondary: Not reported	Primary: The risk of developing diabetes was greatest with clozapine (HR, 7.0; 95% CI, 1.7 to 28.9), olanzapine (HR, 3.2; 95% CI, 2.7 to 3.8), quetiapine (HR, 1.8; 95% CI, 1.4 to 2.4), and risperidone (HR, 3.4; 95% CI, 2.8 to 4.2), compared to conventional antipsychotics (HR, 1.5; 95% CI, 1.3 to 1.8). Secondary: Not reported

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
pimozide, thioridazine, thiothixene, or trifluoperazine)				
Ostbye et al[213] Atypical antipsychotic(s) (clozapine, olanzapine, quetiapine, risperidone, ziprasidone or a combination of two or more of these drugs) vs conventional antipsychotics (acetophenazine*, chlorpromazine, chlorprothixene*, fluphenazine, haloperidol, loxapine, mesoridazine*, molindone, perphenazine, prochlorperazine, promazine*, thioridazine, thiothixene, trifluoperazine, triflupromazine*) vs antidepressants vs antibiotic Doses not reported.	RETRO Cohort A pharmaceutical benefit manager database was used to identify outpatients with at least 1 claim for an atypical antipsychotic (cases; N=10,265) compared to (controls) claims for traditional antipsychotics (N=4,607), antidepressants (N=60,856) or antibiotics (N=59,878)	N=135,606 2 years	Primary: Incidence of new onset diabetes Secondary: Not reported	Primary: The annual incidence rates of diabetes (new cases per 1,000 per year) were 7.5 for atypical antipsychotics, 11.3 for traditional antipsychotics, 7.8 for antidepressants and 5.1 for antibiotics (*P* value not reported). In multivariable analyses, age, male sex and Chronic Disease Score were associated with greater odds of diabetes onset (*P* value not reported). There were no statistically significant differences in outcome between the atypical antipsychotic, traditional antipsychotic and antidepressant groups (*P* value not reported). Comparisons among specific agents showed an increased risk of diabetes for clozapine, olanzapine, ziprasidone and thioridazine (relative to risperidone); however, these results were not statistically significant (no *P* values reported). Secondary: Not reported

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ollendorf et al[214] Atypical antipsychotics (clozapine, olanzapine, quetiapine, or risperidone) vs acetophenazine*, chlorpromazine, chlorprothixene*, fluphenazine, haloperidol, loxapine, mesoridazine*, molindone, perphenazine, pimozide, promazine*, thioridazine, thiothixene, trifluoperazine, or triflupromazine* Doses for all regimens not reported.	RETRO Analyzed medical and pharmacy claims for patients with schizophrenia who were treated with atypical or conventional antipsychotics between September 1996 and June 2001	N=2,443 4 years	Primary: Rate of new-onset diabetes Secondary: Not reported	Primary: The incidence of diabetes did not differ for atypical antipsychotics and conventional antipsychotics (2.46% vs 2.76%, respectively; *P*=0.525). The mean time to event across both groups was 62.2±35.8 days. When the overall atypical and conventional antipsychotic cohorts were compared, atypical antipsychotic use was temporally associated with a moderately increased risk of diabetes at 1 year after therapy initiation compared to conventional antipsychotics (HR, 1.172; 95% CI, 1.061 to 1.300; *P*=0.0063). Each increase in calendar year of therapy initiation was associated with a more than threefold increase in diabetes risk independent of therapeutic choice (HR, 3.581; 95% CI, 3.492 to 3.659; *P*<0.0001). When atypical medication cohorts were compared, there were no significant differences with respect to the risk of new-onset diabetes (HR, 1.049; 95% CI, 0.930 to 1.168; *P*=0.4308; HR, 1.170; 95% CI, 0.967 to 1.372; *P*=0.1291; and HR, 1.467; 95% CI, 0.967 to 1.968; *P*=0.1332 for olanzapine vs risperidone, quetiapine, and clozapine, respectively). Secondary: Not reported
Huang et al[215] Conventional antipsychotics (haloperidol 10-15 mg/day, loxapine 100-150 mg/day, sulpiride* 800-1,200 mg/day) vs atypical antipsychotics (clozapine 100-300 mg daily, olanzapine 10-20 mg daily,	PRO Adult patients with schizophrenia as diagnosed by one psychiatrist using semi-structured clinical interview for DSM-IV criteria; >1 week drug free prior to enrollment	N=182 1 year	Primary: Relationship between serum lipid profiles and schizophrenia, effects of conventional antipsychotics and atypical antipsychotics on serum lipid profiles	Primary: Schizophrenia was associated with increased HDL (*P*=0.046), VLDL (*P*=0.004) and decreased ratios of total cholesterol/HDL (*P*=0.021) and LDL/HDL (*P*=0.002). No changes in total cholesterol, triglycerides, and LDL levels were associated with schizophrenia (no *P* value provided). No changes in any lipid profile levels were observed in the haloperidol treatment group (*P*=0.200 to 0.521), loxapine was associated with decreased total cholesterol/HDL (*P*=0.009) and LDL/HDL (*P*<0.05). Increased total cholesterol (*P*=0.032) and HDL (*P*<0.05) and decreased total cholesterol/HDL and LDL/HDL (*P*=0.006) were observed in the risperidone group.

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risperidone 3-5 mg daily) vs control group, no antipsychotics			Secondary: Not reported	Olanzapine treatment was associated with increased total cholesterol (*P*=0.049) and VLDL levels (*P*=0.044). Patients with a positive response to treatment were observed to have increased total cholesterol (*P*=0.040) and VLDL levels (*P*=0.002) and decreased LDL/HDL (*P*=0.005). No difference in total cholesterol/HDL change between responders and nonresponders was noted. Secondary: Not reported
Wirshing et al[216] Novel antipsychotics (clozapine, olanzapine, quetiapine, or risperidone) vs typical antipsychotics (fluphenazine or haloperidol)	R Adult patients receiving any one of the listed antipsychotics	N=215 All laboratory values within 2.5 years before or after initiation of antipsychotic included	Primary: Change in glucose and lipid measurements Secondary: Clinically significant elevations in glucose (fasting blood glucose ≥126 mg/dL) and lipid measurements (total cholesterol ≥200 mg/dL, LDL ≥160 mg/dL, HDL <35 mg/dL)	Primary: Treatment with clozapine, olanzapine, and haloperidol were associated with an increase in glucose levels from baseline (14%, 21%, and 7% respectively; *P*=0.05, 0.03 and 0.04). Clozapine and olanzapine treatment groups showed increases in maximum glucose levels (31% and 37% respectively; *P*=0.03 and 0.04). No difference was observed between mean or maximum glucose between groups (*P*=0.3 and 0.8). Risperidone was associated with a decrease in maximum total cholesterol. In post hoc analysis, clozapine treatment was associated with higher mean total cholesterol levels compared with fluphenazine (*P*=0.03) and higher total cholesterol levels versus risperidone *(P*=0.02). Initiation of a cholesterol lowering agent was required in 15% of patients treated with clozapine and a dose increase cholesterol lowering agent was required in 13% of patients in the olanzapine treatment group; *P* value not reported. Secondary:

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				No differences were found in the percentage of patients with clinically significant changes in glucose levels between groups (*P* value not reported). Clinically significant elevations in total cholesterol were observed in 48% of clozapine-treated patients, 25% of olanzapine-treated patients, 21% of risperidone-treated patients and 25% of quetiapine-treated patients compared with 25% of patients receiving haloperidol and 28% of patients receiving fluphenazine (*P*=0.4). Clinically significant elevations in triglycerides were observed in 56% of patients receiving clozapine, 39% of patients receiving olanzapine, and 40% of patients receiving quetiapine compared with 0% of patients in the haloperidol treatment group and 8% of patients in the fluphenazine treatment group (*P*=0.002). Mean triglyceride levels in the clozapine and olanzapine treatment groups increased from baseline (*P*=0.01 and 0.02). Maximum triglyceride levels were also increased in the clozapine treatment group (*P*=0.02). Post hoc comparisons found higher triglyceride levels in patients treated with clozapine and olanzapine in comparison to those treated with haloperidol (clozapine vs haloperidol *P*=0.008, olanzapine vs haloperidol *P*=0.02) and fluphenazine (clozapine vs fluphenazine *P*=0.0003 and olanzapine vs fluphenazine *P*=0.002). Clozapine and olanzapine use resulted in higher triglyceride levels vs fluphenazine (*P*=0.004 and 0.02). No difference was observed in the percentage of patients that developed clinically significant decreases in HDL levels between the two treatment groups (*P*=0.1).
Wirshing et al[217] Clozapine, olanzapine, risperidone, and sertindole*	RETRO An analysis of 122 clinical records was conducted involving	N=92 6 years	Primary: Differences in weight gain Secondary:	Primary: The most weight gain was seen with clozapine and olanzapine (16.8±13.3 lb and 17.8±13.3 lb, respectively; *P*=0.01). Patients treated with clozapine and olanzapine appeared to gain weight

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs haloperidol	92 male patients with schizophrenia		Not reported	over a prolonged period of time, whereas risperidone and sertindole demonstrated a more limited period of weight gain (*P*=0.04). Secondary: Not reported
Hardy et al[218] Olanzapine 7.5-25 mg daily vs risperidone 2-7.5 daily vs typical antipsychotics (agents and doses not provided, although fluphenazine and haloperidol described as most frequently used agents in this group)	MC Adult outpatients with a DMS-IV diagnosis of schizophrenia or schizoaffective disorder for ≥5 years, psychiatrically stable, ≥3 months with no inpatient hospitalizations	N=211 ≥1 year	Primary: Comparison of lipid panel Secondary: Not reported	Primary: Mean fasting triglyceride levels were higher in the olanzapine group compared to the risperidone group (*P*=0.022). Median triglyceride levels did not differ between treatment groups (*P* value not provided). No between group differences were observed in mean fasting total cholesterol, direct LDL-C, or HDL-C, or in total cholesterol /HDL-C ratios (*P* values not provided). VLDL-C and ApoB levels were higher in the olanzapine group compared to the risperidone group (*P*=0.43 and 0.011). Olanzapine treatment was associated with low HDL-C levels in comparison to typical antipsychotic treatment (*P*=0.03) but not to the risperidone group (*P* value not provided). Calculated VLDL-C and LDL particle concentrations were higher in the olanzapine group in comparison to the risperidone group (*P*=0.043, *P*=0.44); no differences in VLDL-C and LDL particle concentrations were observed between olanzapine and typical antipsychotic treatment groups (*P* value not provided). No differences were observed between mean LDL, HDL, or VLDL particle size; mean fasting serum glucose, insulin levels, hemoglobin A1c, leptin, and uric acid values were also comparable (*P* values not provided). Secondary: Not reported

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
McQuaid et al[219] Olanzapine 10-20 mg/day vs aripiprazole 15-30 mg/day	AC, DB, MC, R Adult patients with DSM-IV schizophrenia in acute relapse and requiring hospitalization	N=316 26 weeks	Primary: Change in weight Secondary: Serum lipids, reduction in symptoms of schizophrenia (CGI and PANSS), incidence of EPS, blood pressure, heart rate, QTc, mean fasting glucose, serum prolactin levels	Primary: A greater proportion of patients receiving olanzapine experienced significant (>7%) weight gain compared with those treated with aripiprazole (37% vs 14%; *P*<0.001). Secondary: Treatment with olanzapine when compared to aripiprazole was associated with increased serum triglycerides and decreased HDL (*P*<0.05) and increased total cholesterol and LDL levels (not statistically significant; *P* value not reported). Treatment with olanzapine was associated with increased incidence of new lipidemias, increased total cholesterol, LDL, and triglycerides (*P*<0.05), as well as decreased HDL (*P* value not reported). No significant difference was observed between the two agents in reduction of symptoms of schizophrenia, change in serum glucose levels, and rate of EPS (*P* value not reported). Mean decreases in serum prolactin from elevated baseline levels were observed in both treatment groups (*P* value not reported). Patients with normal baseline levels treated with olanzapine and aripiprazole were observed to have prolactin levels above the upper limits of normal at some point during the trial (37% vs 8%; *P* value not reported).
Zipursky et al[220] Olanzapine 2-20 mg daily vs haloperidol 5-20 mg daily	DB, MC, R Patients aged 16-40 with first episode DSM-IV diagnosis of schizophrenia, schizophreniform disorder, or schizo-	N=263 2 years	Primary: Clinically significant weight gain (>7%) Secondary: BMI, nonfasting blood glucose, non-fasting cholesterol, clinical	Primary: Olanzapine was associated with a faster rate of clinically significant weight gain in comparison to haloperidol (*P*<0.0001). Likelihood of clinically significant weight gain was more than five times greater for the olanzapine treatment group versus the haloperidol treatment group (HR, 5.19; *P*<0.001). Higher baseline weight was associated with longer time to weight gain

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	affective disorder		improvement defined as PANNS reduction of ≥10 points	(*P*<0.0001). Secondary: Increase in BMI was not correlated with increases in nonfasting glucose (*P* value not reported). Increased BMI was associated with increases in nonfasting cholesterol levels (*P*<0.01 olanzapine, *P*<0.29 haloperidol). Clinical improvement was associated with the amount of weight gained and increase in BMI at week 1 and week 6 (*P*=0.02 and *P*<0.001) but not after week 12 (*P* value not reported for weight, *P*<0.001 for BMI).
Moisan et al[221] Olanzapine vs risperidone	RETRO Ambulatory patients receiving an atypical antipsychotic medication from January 1997 through August 1999	N=19,582 44 months	Primary: Initiation of antidiabetic drug therapy, initiation of lipid-lowering drug therapy Secondary: Not reported	Primary: The risk of initiating antidiabetic drug therapy was higher in the olanzapine treatment group in comparison to the risperidone treatment group (IRR, 1.33; 95% CI, 1.03 to 1.73). Olanzapine therapy was associated with a higher risk of initiating a lipid-lowering agent in comparison with risperidone therapy (IRR, 1.49; 95% CI, 1.22 to 1.83). Risk of initiating either an antidiabetic or lipid lowering medication was higher among patients receiving olanzapine when compared to risperidone (IRR, 1.47; 95% CI, 1.23 to 1.76). Secondary: Not reported
Caro et al[222] Olanzapine vs risperidone	RETRO Outpatients receiving olanzapine and risperidone	N=32,328 2 years	Primary: Primary diagnosis of diabetes identified by ICD-9 code or claim for insulin or oral hypoglycemic agent	Primary: Crude hazard ratio of diabetes for all patients was 1.08 (95% CI, 0.89 to 1.31; *P*=0.43). Proportional hazard analyses adjusting for duration of olanzapine exposure indicated a RR of diabetes with olanzapine of 1.9 during the first three months of therapy (95% CI, 1.40 to 2.57; *P*<0.0001) when compared to risperidone.

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Secondary: Not reported	Secondary: Not reported
Brown et al[223] Olanzapine vs ziprasidone	RETRO Adults with schizophrenia and other psychoses	N=191 Duration not specified	Primary: QT_C interval, weight, metabolic parameters Secondary: Not reported	Primary: No significant differences in QT_C intervals were found (*P* value not reported). Significant weight gain was seen in the olanzapine group (*P*<0.001) but not in the ziprasidone group (*P*>0.05). Significant metabolic changes were seen in the olanzapine group: increased total cholesterol (*P*=0.01), increased triglycerides (*P*=0.05) and increased hemoglobin A1c (*P*<0.05). Favorable metabolic changes were observed for the ziprasidone group for total cholesterol (*P*<0.05), LDL (*P*<0.01), HDL (*P*<0.05), and hemoglobin A1c (*P*<0.05). Secondary: Not reported
Basson et al[224] Study 1: Olanzapine vs haloperidol Study 2: Olanzapine 10-20 mg daily vs risperidone 4-12 mg daily	DB, MC, R Study 1: Adult patients with DSM-III-R criteria for schizophrenia, schizoaffective disorder or schizophreniform disorder Study 2: Adult patients with DSM-IV-R criteria for schizophrenia,	Study 1: N=1,996 6 weeks Study 2: N=339 28 weeks	Primary: Change in weight, appetite Secondary: Change in BPRS	Study 1: Primary: Treatment with olanzapine was associated with significantly greater weight gain than haloperidol (*P*<0.001). Low BBMI (≤25) was associated with more weight gain than high BBMI (>25; *P*<0.001) without regard to treatment group. Olanzapine was associated with a greater increase in appetite compared to haloperidol (*P*<0.001) and this increase in appetite correlated with weight gain (*P*<0.001). Age was not a predictor of weight change (*P*=0.573). More weight gain was observed in males vs females with olanzapine (*P*<0.001), and nonwhite patients gained more weight than white patients across both

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Doses for Study 1 varied per patient and ranges were not specified.	schizoaffective disorder or schizophreniform disorder			treatment groups (*P*<0.001). Dose was not correlated with weight gain (*P*=0.059). Secondary: Better clinical outcome (BPRS≤18) was associated with more weight gain (*P*<0.003) with no correlation to treatment group. Study 2: Primary: Differences in weight change between olanzapine and risperidone were not significant (*P*<0.387). Low BBMI (≤25) was associated with more weight gain than high BBMI (>25; *P*<0.001). The effects of both clinical outcome and BBMI on weight change did not differ between the two groups (*P* value not reported). No significant difference in appetite increase was observed between olanzapine and risperidone (25.6% vs 23.0%; *P*=0.230). Age <34.7 was associated with more weight gain (*P*=0.29), but no difference in the effect of age was observed between the two treatment groups (*P* value not reported). No significant association was observed between gender and weight gain (*P*=0.057). Race (*P*=0.154) and dose (no *P* value reported) were not predictors of weight change. Secondary: Better clinical outcome (BPRS≤17) was associated with more weight gain (*P*=0.001).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Wu et al[225] Clozapine 200-400 mg once daily vs olanzapine 10-20 mg once daily vs risperidone 2-5 mg once daily vs sulpiride* 600-1,000 mg once daily	PRO Adult patients aged 18-45 with first episode schizophrenia diagnosed in accordance with DSM-IV criteria	N=112 ≥16 weeks	Primary: Effect on glucose and lipid metabolism Secondary: Change in BMI, WHR, fasting blood sugar, fasting insulin, C-peptide, cholesterol, triglyceride levels	Primary: Clozapine and olanzapine treatment were associated with increases in cholesterol and triglyceride levels (*P*=0.035 to 0.040). Mean blood glucose levels were decreased in all treatment groups (*P*=0.09 to 0.172). Secondary: A significant increase in mean BMI and WHR were observed in the clozapine, olanzapine and sulpiride groups (*P*=0.008 to 0.047) but not in the risperidone group (*P*=0.07 and 0.085). Increases in insulin and C-peptide levels were observed in all treatment groups (*P*=0.009 to 0.044). A decrease in mean blood glucose was observed in each of the four groups (*P*=0.09 to 0.172). Pairwise comparisons revealed a higher change in BMI in those treated with clozapine in comparison to olanzapine (*P*=0.011) and clozapine and olanzapine were associated with increases in rates of elevated insulin and C-peptide levels in comparison to risperidone and sulpiride (*P*=0.001 to 0.043).
Mukundan et al[226] Switching to a different antipsychotic depot formulation, switching from olanzapine to another atypical antipsychotic, or switching to aripiprazole from another atypical antipsychotic vs continuation on previous	SR Patients diagnosed with schizophrenia or schizophrenia-like illness, with weight or metabolic problems	N=636 ≤26 weeks	Primary: Change in weight and physiological measures Secondary: Fasting blood glucose, discontinuation, mental state, global state, adverse events	Primary: Patients who switched to aripiprazole or quetiapine from olanzapine experienced a nonsignificant mean weight loss of 1.94 kg (95%CI, -3.9 to 0.08). BMI decreased when patients were switched from olanzapine to quetiapine (MD, -0.52; 95%CI, -1.26 to 0.22) and aripiprazole (RR, 0.28; 95%CI, 0.13 to 0.57). Secondary: Fasting blood glucose levels were significantly decreased when patients were switched from olanzapine to aripiprazole or quetiapine (MD, -2.53 95%CI, -2.94 to -2.11).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
antipsychotic regimen				Patients were less likely to discontinue from the study early when they remained on olanzapine compared to switching to quetiapine or aripiprazole. There were no significant differences in outcomes of mental state, global state, and adverse events between groups that switched medications and those that remained on previous medication.
Rummel-Kluge et al[227] Aripiprazole vs clozapine vs olanzapine vs quetiapine vs risperidone vs ziprasidone	MA Randomized, controlled, head-to-head studies in patients receiving atypical antipsychotics for the treatment of schizophrenia or related disorders	N=not reported (48 studies) Study duration not reported	Primary: Weight change Secondary: Change in cholesterol, glucose level	Primary: Clozapine was associated with significantly more weight gain from baseline compared to risperidone (mean difference [MD], 2.86 kg). Olanzapine was associated with significantly more weight gain from baseline compared to aripiprazole (MD, 3.9 kg), quetiapine (MD, 2.68 kg), risperidone (MD, 2.44 kg), and ziprasidone (MD, 3.82 kg). No significant differences in weight gain were observed between aripiprazole and risperidone, clozapine and olanzapine, clozapine and quetiapine, quetiapine and risperidone, quetiapine and ziprasidone, and risperidone and ziprasidone (*P* values not reported). Secondary: Olanzapine was associated with significantly greater cholesterol increase compared to aripiprazole (MD, 15.35 mg/dl), risperidone (MD, 12.92 mg/dl), and ziprasidone (MD, 15.83 mg/dl). Quetiapine was associated with significantly greater cholesterol increase compared to ziprasidone (MD, 16.01 mg/dl) and risperidone (MD, 8.61 mg/dl). Risperidone was associated with significantly greater cholesterol increase compared to aripiprazole (MD, 22.3 mg/dl) and ziprasidone (MD, 8.58 mg/dl). There was no statistically significant difference in cholesterol change from baseline between olanzapine and quetiapine groups (*P* value not

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				reported). Olanzapine was associated with significantly greater increase in glucose levels from baseline compared to aripiprazole (MD, 4.13 mg/dl), quetiapine (MD, 9.32 mg/dl), risperidone (MD, 5.94 mg/dl), and ziprasidone (MD, 8.25 mg/dl). There were no statistically significant differences in glucose changes from baseline between aripiprazole and risperidone, quetiapine and risperidone, quetiapine and ziprasidone, risperidone and ziprasidone, clozapine and olanzapine, and between clozapine and risperidone.
Extrapyramidal Symptoms				
Ghaemi et al[228] Chart review of patients with a trial of at least one of the following atypical neuroleptics: aripiprazole, olanzapine, quetiapine, risperidone and ziprasidone	OL, RETRO, descriptive study Patients with bipolar disorder type I and II	N=34 (51 trials) 107 weeks	Primary: Assessing the risk of EPS using the AIMS, BAS and SAS scales Secondary: Not reported	Primary: The combined AIMS, BAS, and SAS scores demonstrated that EPS were reported most frequently with risperidone (76.5%) and quetiapine (72.7%), followed by ziprasidone (50.0%), and olanzapine (46.2%), (individual scores and *P* vales not reported). Less akathisia was observed with low potency agents compared to high potency agents (OR, 0.22; 95% CI, 0.05 to 0.96), and with older age (OR, 0.95; 95% CI, 0.91 to 1.00). Secondary: Not reported
Gharabawi et al[229] Risperidone long-acting 25 mg intramuscularly every 2 weeks plus risperidone by mouth unspecified dosage for first 2 to 3 weeks (separate entities) vs	MC, OL Clinically stable patients 18-84 years of age with DSM-IV diagnosis of schizophrenia or schizoaffective disorder	N=662 (530 no dyskinesia at baseline, 132 with dyskinesia at baseline; 25 mg, 114; 50 mg, 192; 75 mg, 224)	Primary: Treatment-emergent persistent tardive dyskinesia, severity of dyskinesia Secondary: ESRS	Primary: For patients with no dyskinesia at baseline, treatment-emergent persistent tardive dyskinesia occurred in 0.94% of patients in all treatment groups, with a calculated one year rate of 1.19% (95% CI, 0.15 to 2.24). Treatment-emergent persistent tardive dyskinesia occurred in 0.88%, 1.04%, and 0.89% of patients receiving 25 mg, 50 mg, and 75 mg of long-acting risperidone, respectively (*P* values not reported). For patients with dyskinesia at baseline, the mean ESRS physician's exam for dyskinesia score improved by -2.77 points and the mean CGI for dyskinesia score improved by -1.2 points by 50 weeks (*P*<0.001).

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risperidone long-acting 50 mg intramuscularly every 2 weeks plus risperidone orally unspecified dosage for first 2 to 3 weeks (separate entities) vs risperidone long-acting 75 mg intramuscularly every 2 weeks plus risperidone orally unspecified dosage for first 2 to 3 weeks (separate entities)		50 weeks		Improvement that lasted the study duration occurred in 27.3% of these patients. There was no significant difference in improvement between patients receiving anticholinergic agents or not (*P*=0.243). Secondary: For all patients, the mean ESRS physician's exam for Parkinsonism score improved by -5.6 points and the mean CGI for Parkinsonism score improved by -1.7 points by 50 weeks (*P*<0.001). There was no significant difference in improvement between patients receiving anticholinergic agents or not (*P*=0.85).
Emsley et al[230] Haloperidol 5 mg by mouth per day for 4 days, 10 mg by mouth per day for ≥3 days, then flexible dose adjustments as needed up to 20 mg by mouth per day vs quetiapine 100 mg by mouth per day for 2 days, 200 mg by mouth per day for 2 days, 300 mg by mouth per day for 2 days, 400 mg by mouth per day for ≥1 day, then flexible dose adjustments as needed up to 800 mg by mouth per day	PG, RCT, SB Clinically stable patients 18-65 years of age with DSM-IV diagnosis of tardive dyskinesia and schizophrenia or schizoaffective disorder	N=45 52 weeks	Primary: Change in dyskinesia scores over time Secondary: Treatment effect on psychotic symptoms, other EPS, weight change, BMI changes, serum prolactin changes, glycosylated hemoglobin changes	Primary: ESRS dyskinesia subscale scores decreased over time for both treatment groups (*P*<0.001). Patients receiving quetiapine had significantly lower ESRS scores than patients receiving haloperidol at 6 months (*P*=0.01) and 9 months (*P*=0.004), but not at 12 months (*P*=0.1). Patients receiving quetiapine had significantly lower CGI scores than patients receiving haloperidol at 6 months (*P*=0.03), 9 months (*P*=0.001) and at 12 months (*P*=0.03). Response of ≥50% reduction in CGI dyskinesia score in patients receiving quetiapine and haloperidol was 64% and 37% at 6 months, and 55% and 28% at 12 months, respectively (*P* values not reported). Secondary: PANSS scores were not significantly different between treatment groups (*P* value not reported). EPS other than dyskinesia decreased more in patients receiving quetiapine than haloperidol at 3 months (*P*=0.01), 6 months (*P*=0.01), and 9 months (*P*=0.002), but not at 12 months (*P*=0.3). Anticholinergic

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				medication was needed in 27% and 61% of patients receiving quetiapine and haloperidol, respectively (*P* value not reported). There was no significant difference in weight change for either treatment group (*P* value not reported). In patients receiving haloperidol and quetiapine, mean serum prolactin levels changed +10.3 ng/mL and -16.3 ng/mL, respectively (*P*=0.005). There was no significant difference in glycosylated hemoglobin levels for either treatment group (*P* value not reported).
Ritchie et al[231] Olanzapine 5 mg daily or risperidone 0.5 mg daily	OL, XO Elderly patients over the age of 60 with schizophrenia who were taking conventional neuroleptics	N=66 3 years	Primary: Quality of life, efficacy, safety Secondary: Not reported	Primary: Patients switched to risperidone showed no significant change to any aspect of their quality of life. Patients switched to olanzapine demonstrated significant improvement in psychological well being (*P*=0.002), physical well being (*P*=0.006), and their perceived health status (*P*=0.04). Secondary: Not reported
Mullen et al[232] Quetiapine 329 mg/day (maximum mean daily dose) vs risperidone 5.0 mg/day (maximum mean daily dose)	MC, OL, RCT Patients older than 18 years of age classified by the DSM-IV criteria as having schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, MDD with psychotic features, dementia of	N=728 4 months	Primary: Comparison of relative safety, tolerability (EPS, adverse events), and efficacy Secondary: Not reported	Primary: After adjusting for baseline differences, patients receiving risperidone were significantly more likely to develop EPS and substantial EPS over long-term treatment (*P*=0.003 and *P*<0.001). During initial (1 month) treatment there was no difference in the chance of developing EPS amongst the two groups with 41.1% of quetiapine patients and 47.3% of risperidone patients experiencing EPS initially. Anti-EPS medication was required in 51.6% of risperidone-treated patients compared to 31.7% of quetiapine-treated patients (*P*<0.001). The rate of withdrawal in the quetiapine group was 31.8% and 33.7% in the risperidone group. Risperidone withdrawals were mostly attributed to lack of efficacy and quetiapine withdrawals due to the incidence of side effects.

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	Alzheimer's disease with psychotic symptoms, vascular dementia, or dementia due to substance abuse			Somnolence occurred more frequently in the quetiapine group (31.1% vs 15.4%; *P*<0.001). Other measured side effects, including dry mouth, dizziness, and agitation were found to be more frequent in the quetiapine group (*P*<0.05). Although insomnia and headache were reported more frequently with quetiapine, the difference was not significant. Both groups were found to be efficacious as determined by the CGI-Global Improvement scores (*P*=0.087). While there were no changes in PANSS total scores between the two groups, the quetiapine group showed a significant increase in the improvement of depressive symptoms (*P*=0.028). Secondary: Not reported
Modestin et al[233] Clozapine vs typical neuroleptic vs clozapine in combination with a typical neuroleptic	Cohort 200 inpatients with an average age of 45 for men and 53 for women who had received continuous typical neuroleptic treatment for at least 3 days	N=200 Duration not reported	Primary: EPS (Parkinson syndrome, akathisia and tardive dyskinesia) Secondary: Not reported	Primary: Tardive dyskinesia was noted significantly more often in the clozapine group compared to the typical neuroleptic group (*P*=0.024). Older subjects were found to be more susceptible to EPS than younger subjects in all groups (*P*=0.020). There was no significant difference found between the groups in Parkinson syndrome and akathisia (*P* value was not reported). Secondary: Not reported
Schillevoort et al[234] Haloperidol vs risperidone	Cohort Patients 15-54 years of age initiating treatment with risperidone, olanzapine, or haloperidol for the	N=848 Duration not reported	Primary: Antiparkinsonian medications usage Secondary: Not reported	Primary: After cohort, 13.2% of the patients using haloperidol, 11.9% of the patients using risperidone and 5.0% of the patients using olanzapine started antiparkinsonian medications. Compared with haloperidol there was an adjusted relative risk of 0.57 (95% CI, 0.31 to 1.04) for risperidone and 0.19 (95% CI, 0.08 to 0.48) for olanzapine. Prior use of antiparkinsonian medication was significantly more common

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs olanzapine	first time between January 1, 1994, and June 30, 1999			among the risperidone and olanzapine group when compared to those using haloperidol (*P*=0.001). Prior to cohort entry, 12, 11, and 5 antiparkinsonian medications were received by users of risperidone, olanzapine, and haloperidol, respectively (*P*<0.05). Secondary: Not reported
Rummel-Kluge et al[235] Aripiprazole 10 mg to 30 mg daily vs clozapine 300 mg to 800 mg daily vs olanzapine 10 mg to 20 mg daily vs quetiapine 250 mg to 750 mg daily vs risperidone 4 mg to 6 mg daily vs	MA Randomized, blinded, head-to-head studies comparing atypical antipsychotics in patients diagnosed with schizophrenia or related disorders	N=not reported (54 studies) Study duration not reported	Primary: Use of antiparkinson medication Secondary: Barnes Akathisia Scale (BAS), Simpson Angus Scale (SAS)	Primary: Risperidone was associated with significantly more use of antiparkinson medication than all other atypical antipsychotics (vs. clozapine: RR, 2.57; *P* =0.0009, NNH=6; vs. olanzapine: RR, 1.28; *P* =0.01; NNH=17; vs. quetiapine: RR, 1.98; *P*=0.01; NNH=20; vs. ziprasidone: RR, 1.42; *P*=0.03; NNH=17), except for aripiprazole (RR, 1.68; *P*=0.11) where no significant differences were found. Ziprasidone was associated with significantly more use of antiparkinson medication than olanzapine (RR, 1.43; *P*=0.03; NNH = 20) and quetiapine (RR, 2.32; *P*=0.03; NNH=25). No significant difference was found between ziprasidone and clozapine (RR, 1.11; *P*=0.39). Aripiprazole was associated with significantly more use of antiparkinson medication compared to olanzapine (RR, 1.8; *P*=0.005; NNH=14). There was no statistically significant difference between aripiprazole and risperidone (*P*=0.11). Clozapine was associated with significantly less use of antiparkinson medication than risperidone (RR, 0.39; *P*=0.0009; NNT=6). Olanzapine was associated with significantly less antiparkinson medication compared to aripiprazole (RR, 0.55; *P*=0.005; NNT=14), risperidone (RR, 0.78; *P*=0.01; NNT=17), and ziprasidone (RR, 0.7; *P*=0.03; NNT=20). There was no significant difference compared with clozapine (*P*=0.69). However, olanzapine was associated with

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ziprasidone 120 mg to 160 mg daily				significantly more EPS than quetiapine (RR, 2.05; *P*=0.004; NNH=25). Quetiapine was associated with the least use of antiparkinson medication compared to all three other agents for which comparisons were available (vs. olanzapine: RR, 0.49; *P*=0.004; NNT = 25; vs. risperidone: RR, 0.5; *P*=0.01; NNT=20; vs. ziprasidone: RR, 0.43; *P*=0.03; NNT=25). Secondary: Aripiprazole was associated with more akathisia than olanzapine (*P*=0.04) and clozapine more than ziprasidone (*P*<0.0001). Risperidone was associated with more akathisia than ziprasidone (*P*<0.00001). Risperidone was associated with more extrapyramidal symptoms according to the SAS than quetiapine (*P*=0.04) and ziprasidone (*P*<0.00001).
Sexual Dysfunction				
Byerly et al[236] Quetiapine 200 mg/day titrated to 300-400 mg/day Patients were previously treated with risperidone 4-5 mg/day or haloperidol 10 mg/day.	Cohort, OL, OS Adult males 24-50 years of age with schizophrenia or schizoaffective disorder; excluded if they were taking clozapine, had medical conditions or medications known to cause sexual dysfunction	N=8 6 weeks	Primary: Sexual functioning evaluated using ASEX scores Secondary: Prolactin levels, PANSS	Primary: Quetiapine was associated with a clinically and statistically significant improvement in ASEX total scores at the end of the study when compared to baseline ASEX (*P*=0.008). Secondary: PANSS total scores decreased significantly from baseline to study end with quetiapine (*P*=0.03). A nonsignificant change was noted in plasma prolactin levels after transitioning to quetiapine (*P*=0.09).
Aizenberg et al[237] Clozapine 100-400 mg by mouth once daily vs	CS, OS Healthy male patients 20 to 60 years of age with DSM-IV criteria	N=60 Patients completed a one time survey	Primary: Evaluate and compare sexual function and behavior	Primary: Patients receiving clozapine reported a higher incidence in frequency of sexual thoughts (*P*=0.006), frequency of masturbation (*P*=0.013), number of orgasms per month (*P*=0.037), frequency of orgasm during sex (*P*=0.046), sexual desire (*P*=0.0073), enjoyment of sex with partner (*P*=0.013), and satisfaction with own sexual function (*P*=0.0004)

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
classical antipsychotics, including: fluphenazine deaconate 12.5-50 mg intramuscularly every 4 weeks, haloperidol deaconate 100-200 mg intramuscularly every 4 weeks, and perphenazine 24-48 mg by mouth once daily	diagnosis of chronic schizophrenia in a stable relationship with female partner and no alcohol or drug abuse	Recruitment period unspecified	Secondary: PANSS scores, serum prolactin levels	compared to classical antipsychotics. Only frequency of desire for sex was lower for patients receiving clozapine than classical antipsychotics (*P*=0.025). All other sexual differences were not significant (*P* values not reported). Secondary: In patients receiving classical antipsychotics and clozapine, the mean PANSS positive scores were 16.2 and 9.5 (*P*<0.0001), negative scores were 16.5 and 24.6 (*P*<0.001), respectively, and general psychopathology scores were not significantly different (*P* value not reported). There was no significant difference in mean serum prolactin levels.
Knegtering et al[238] Quetiapine administered daily with the dose ranging from 200-1,200 mg a day vs risperidone administered daily with the dose ranging from 1-6 mg a day	OL, R Patients between the ages of 18 and 40 with schizophrenia and not on other medications with known effects on sexual functioning	N=51 6 weeks	Primary: Clinical response and sexual dysfunction based on PANSS and ASFQ scores after 6 weeks of treatment Secondary: Not reported	Primary: Based on the results of the ASFQ, 50% of the patients taking risperidone experienced sexual dysfunction compared to only 16% of patients using quetiapine (*P*<0.01). No significant differences were found in the PANSS total scores between patients treated with quetiapine and patients treated with risperidone. Secondary: Not reported
Serretti et al[239] Atypical antipsychotics (aripiprazole, clozapine, olanzapine, quetiapine, risperidone, ziprasidone) and typical antipsychotics (haloperidol, thioridazine)	MA Patients receiving antipsychotic therapy and who had experienced sexual dysfunction	N=not reported Study duration not reported	Primary: Rate of sexual dysfunction Secondary: Not reported	Primary: Quetiapine, ziprasidone, perphenazine, and aripiprazole were associated with relatively low incidence of sexual dysfunction (16-27%). Olanzapine, risperidone, haloperidol, clozapine, and thioridazine were associated with higher incidence of sexual dysfunction (40-60%). Secondary: Not reported
Wirshing et al[240]	MA	N=25 (3 trials	Primary: Degree of sexual	Primary: Decline in sexual functioning was significantly less common in the

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Clozapine vs risperidone vs haloperidol/fluphenazine	Adult males 24 to 58 years of age with DSM-IV diagnosed schizophrenia, who were participants in one of three different R, DB, clinical studies	referenced for records) Duration not reported	functioning (erectile frequency, enjoyment of orgasm, interest, erectile maintenance, and ejaculatory volume) Secondary: Not reported	clozapine group compared to the risperidone group (*P*=0.01) and the haloperidol/fluphenazine group (*P*=0.02). Decline in the erectile frequency was significantly more common in the risperidone group compared to the clozapine group (93% vs 40%; *P*=0.01). Decline in the erectile frequency was significantly more common in the haloperidol/fluphenazine group compared to the clozapine group (93% vs 50%; *P*=0.03). Fewer subjects in the clozapine group compared to the risperidone group reported a decline in the enjoyment of orgasm and ejaculatory volume (20% vs 86%; *P*=0.01). Risperidone (71%) and haloperidol/fluphenazine (67%) treated subjects but not clozapine (40%) treated subjects reported over-all worsening of sexual functioning (*P* value was not reported). Objective global rating revealed 80% of the clozapine group, 86% of the risperidone group, and 83% of the haloperidol/fluphenazine groups were viewed as having sexual dysfunction (*P* value was not reported). Secondary: Not reported
Byerly et al[241] Olanzapine administered daily with the dose ranging from 5-40 mg a day vs risperidone administered daily with the dose ranging	QE Outpatients evaluating the sexual dysfunction in patients over the age of 18 with a DSM-IV diagnosis of schizophrenia or schizoaffective	N=238 4 years	Primary: Measuring the severity of sexual dysfunction using ASEX and Likert-type scales in schizophrenic patients Secondary:	Primary: The adjusted average ASEX total scores were lower in the quetiapine group compared to the risperidone or olanzapine groups. Individual comparisons of the treatments on adjusted average ASEX total scores indicated a significant difference between olanzapine and quetiapine (*P*<0.04) but no difference between risperidone and quetiapine (*P*>0.17) or olanzapine and risperidone (*P*>0.76). Secondary: Not reported

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
from 1-8 mg a day vs quetiapine administered daily with the dose ranging from 50-900 mg a day	disorder without a general medical condition or history of a surgical procedure known to cause sexual dysfunction		Not reported	
Bobes et al[242] Haloperidol 1-50 mg orally per day vs olanzapine 2.5-30 mg orally per day vs quetiapine 100-800 mg orally per day vs risperidone 1-15 mg orally per day	CS, MC, OS Adult patients mean 32.2-41.2 years of age with a DSM-IV diagnosis of schizophrenia receiving ≥4 weeks of single antipsychotic treatment (haloperidol, olanzapine, quetiapine, or risperidone)	N=636 (haloperidol, 131; olanzapine, 228; quetiapine, 43; risperidone, 234) Patients completed a one time survey Recruitment period: November 5 to December 7, 2000	Primary: Treatment duration, sexual side effects, other reproductive side effects Secondary: Not reported	Primary: Mean treatment duration for patients receiving haloperidol, olanzapine, quetiapine and risperidone was 4.5, 1.5, 0.1 and 1.8 years, respectively. Treatment duration was significantly longer for patients receiving haloperidol and significantly shorter for patients receiving quetiapine (*P*<0.05). Sexual dysfunction reported in patients receiving haloperidol, olanzapine, quetiapine and risperidone was 38.1%, 35.3%, 18.2%, and 43.2%, respectively. For patients receiving quetiapine, the incidence was significantly lower compared to haloperidol and risperidone (*P* values <0.05), but not to olanzapine (*P*=0.55). For patients receiving olanzapine and risperidone, incidence increased significantly with dose (*P*<0.05). The risk of sexual dysfunction for olanzapine (OR, 0.9; 95% CI, 0.5 to 1.5), and quetiapine (OR, 0.4; 95% CI, 0.1 to 0.955) was lower than haloperidol but higher for risperidone (OR, 1.2; 95% CI, 0.7 to 2.0). There was no significant difference in incidence of other reproductive side effects between treatment groups, except when stratified by sex. For women receiving olanzapine, there was a lower incidence of other reproductive side effects and amenorrhea compared to risperidone (*P*<0.05). Secondary: Not reported
Dossenbach et al[243] Olanzapine	OS, PRO Outpatients with	N=3,828 3 years	Primary: Patient reported sexual side effects,	Primary: Patients perceived that the odds of experiencing sexual side effects were significantly lower with olanzapine and quetiapine than with risperidone

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs risperidone vs quetiapine vs haloperidol	diagnosis of schizophrenia who initiated or changed antipsychotic treatment		menstrual irregularities Secondary: Not reported	and haloperidol (*P*≤0.001). Reported menstrual irregularities were as follows: olanzapine 14%, quetiapine 8%, risperidone 23%, and haloperidol 29% (*P* value not reported). Secondary: Not reported
Suicidal Risk/Behavior				
Hennen et al[244] Clozapine 12.5-450 mg daily	MA Published studies with contrasting rates of suicides or attempts by psychotic patients treated with clozapine vs other agents (with the exception of olanzapine no other agents were specified)	N=240,564 104,796 person-years of exposure to clozapine	Primary: Attempted or completed suicide Secondary: Not reported	Primary: Among chronically psychotic patients, treatment with clozapine was associated with variably lower rates of suicides-plus-attempts (by a computed, pooled value of 3.3-fold) and of completed suicides (by 2.9-fold) compared to other treatments. Secondary: Not reported
Therapeutic Duplication/Polypharmacy				
Kreyenbuhl et al[245] Clozapine, olanzapine, quetiapine, risperidone, chlorpromazine, chlorprothixene*, fluphenazine, haloperidol,	MA Veterans Affair patients with schizophrenia and schizoaffective disorder	N=61,257 1 year	Primary: Prevalence of polypharmacy Secondary: Not reported	Primary: Rate of overlapping use of ≥2 antipsychotic agents was 20.0% for ≥30 days, 13.1% for ≥60 days, and 9.5% for ≥90 days. The rate of prescription fills for ≥2 antipsychotic agents proximal to hospital discharge (within one week) was 14.0%.

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
loxapine, mesoridazine*, molindone, perphenazine, pimozide, thioridazine, thiothixene, and trifluoperazine of varying doses				Of the polypharmacy uses, 74.1% were one second generation agent plus one first generation agent, 18.2% was for two second generation agents, 1.3% was for combinations of three antipsychotic agents, and 0.03% was for combinations of four antipsychotic agents. Secondary: Not reported
Correll et al[246] Monotherapy vs polypharmacy with second generation antipsychotic agents (aripiprazole, clozapine, olanzapine, quetiapine, risperidone, ziprasidone) and first generation antipsychotic agents of varying doses	Cross-sectional study Adult psychiatric inpatients treated with at least one second generation antipsychotics at the time of admission to a psychiatric hospital	N=364 24 hours	Primary: Presence of metabolic syndrome and insulin resistance (defined as triglyceride/HDL ratio>3.5) Secondary: Not reported	Primary: The overall rate of polypharmacy was 19.2% (71 patients out of 364), of which 70.0% was with combinations of two second generation antipsychotics, 22.9% were with combinations of a first and a second generation antipsychotic, 4.3% was with combinations of three second generation antipsychotics, and 2.9% was with two second generation antipsychotics and one first generation antipsychotic. Patients on polypharmacy was more likely to have metabolic syndrome (50.0% vs 34.3%; *P*=0.015) and insulin resistance (50.7% vs 35.0%; *P*=0.016) than patients on monotherapy. Individual metabolic variables did not significantly differ between patients in the monotherapy group and patients in the polypharmacy group, except for higher waist circumference (*P*=0.028) and lower high-density lipoprotein (*P*=0.026) which was observed with the polypharmacy group. Polypharmacy was significantly more common with schizophrenic patients, patients with higher body mass index, and patients concurrently on anticholinergic treatment (*P*≤0.05 for all), while monotherapy was significantly more common in patients with bipolar disorder, patients with depressive disorder, and patients concurrently on antihypertensive drug treatment (*P*≤0.05 for all). Quetiapine, risperidone, ziprasidone, clozapine, and first generation antipsychotic agents had higher rates of polypharmacy (*P*≤0.05 for all).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Ganguly et al[247] Conventional antipsychotic agents (chlorpromazine, fluphenazine, haloperidol, loxapine, mesoridazine*, molindone, perphenazine, pimozide, prochlorperazine, promazine*, thioridazine, thiothixene, trifluoperazine, chlorprothixene*) and atypical antipsychotic agents (clozapine, olanzapine, quetiapine, risperidone, ziprasidone) of varying doses	MC, OS, RETRO, cohort study California and Georgia Medicaid recipients ≥16 years of age with schizophrenia	N=31,435 2 years	Primary: Prevalence, frequency, and mean duration of antipsychotic polypharmacy Secondary: Not reported	Primary: The prevalence of antipsychotic polypharmacy was 40% (12,549 patients out of 31,435). The mean duration of polypharmacy was 149 days. The prevalence of long-term polypharmacy (defined as >2 months) was 23%, with the average duration of 236 days. California Medicaid recipients had a higher prevalence of polypharmacy compared with Georgia Medicaid recipients (46% vs 35%; *P*<0.0001). The odds ratio of long-term antipsychotic polypharmacy was 11.77 with clozapine, 14.45 with olanzapine, 9.18 with risperidone, 18.32 with quetiapine, 6.53 with oral haloperidol, 5.43 with injectable haloperidol, 5.50 with oral fluphenazine, 5.13 with injectable fluphenazine, 18.61 with thioridazine, 28.87 with chlorpromazine, and 8.44 with thiothixene (*P*<0.0001 for all). Secondary: Not reported
Kogut et al[248] Aripiprazole, clozapine, olanzapine, quetiapine, risperidone, ziprasidone, and conventional antipsychotics at varying doses	Cross-sectional, RETRO study Rhode Island Medicaid enrollees in a fee-for-service program, with ≥3 pharmacy claims for oral solid antipsychotic medications	N=8,616 1 year	Primary: Frequency of use of polytherapy with multiple antipsychotic medications, frequency of prescribing of off-label dosages of atypical antipsychotic agents Secondary:	Primary: Of the Rhode Island Medicaid fee-for-service program enrollees who have ≥3 pharmacy claims for oral solid antipsychotic medications, approximately 90.0% (7,748 patients out of 8,616) were receiving monotherapy with an oral antipsychotic medication, 2.1% were receiving polytherapy with an atypical and a conventional antipsychotic medication, and 8.0% were receiving polytherapy with two atypical antipsychotic medications. Approximately 33.0% of the patients, who were prescribed an atypical antipsychotic medication, received a dosage that was not within the recommended range according to the product labeling (27.0% received medication below the recommended range and 6.0% received medication above the recommended range).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Frequency of prescribing of off-label dosages of atypical antipsychotic agents stratified by gender and age group	Secondary: Patients who received dosages above the recommended range were more frequently male (*P*<0.001) and younger than 65 years of age (*P*<0.001). Olanzapine (*P*<0.05) and quetiapine (*P*<0.05) were more frequently administered above the recommended range compared with the other atypical antipsychotic medications. Quetiapine was most frequently prescribed below the recommended range compared with the other atypical antipsychotic medications (*P* value not reported).
Ziegenbein et al[249] Clozapine plus ziprasidone of varying doses	Open study Outpatients or inpatients with treatment-resistant schizophrenia, who were unresponsive or partially responsive to a stable dose of clozapine monotherapy for ≥6 months	N=9 6 months	Primary: Clinical status assessed with the BPRS Secondary: Side effects	Primary: At 6 months, the combination of clozapine plus ziprasidone significantly reduced the total BPRS score from baseline (*P*=0.013), with a mean improvement of 28.0%. Seven out of the nine patients (77.8%) responded to the combination treatment regimen. At 6 months, the dose of ziprasidone remained unchanged, but the dose of clozapine was reduced by 18.0% (*P*=0.057). Secondary: At 6 months, no increase in side effects was observed.
Patrick et al[250] Monotherapy of antipsychotics vs combination of antipsychotics	MA (including DB studies, OL studies, and case reports) Demographics not defined	N=not specified Duration not specified	Primary: Efficacy of combination therapy Secondary: Not reported	Primary: Most frequent combination was clozapine and risperidone. Seventy five percent of double-blinded studies and 69% of open-label trials found that combination treatment was effective at reducing symptoms. Thirty seven percent of case reports found that combination treatment produced positive outcomes (*P* values not reported).

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<table>
<tr><th>Study and Drug Regimen</th><th>Study Design and Demographics</th><th>Sample Size and Study Duration</th><th>End Points</th><th>Results</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Secondary:
Not reported</td></tr>
<tr><td>Josiassen et al[251]

Clozapine steady dose plus risperidone up to 6 mg/day

vs

clozapine steady dose plus placebo</td><td>DB, MC, PC, RCT

Inpatients or outpatients with schizophrenia who were unresponsive or partially responsive to clozapine monotherapy for ≥3 months of ≥600 mg/day</td><td>N=40

12 weeks</td><td>Primary:
Clinical status assessed with the BPRS, CGI, and SANS, movement disorders assessed with SAS

Secondary:
Adverse events</td><td>Primary:
More patients in the clozapine/risperidone group (7/20 or 35%) than in the clozapine/placebo group (2/20 or 10%) achieved a treatment response (P<0.01).

Clozapine/risperidone treatment resulted in a greater reduction in BPRS total scores (P<0.04), BPRS positive symptom subscale scores (P<0.05), and SANS scores (P<0.05) than treatment with clozapine/placebo.

The SAS scores were lower with clozapine/risperidone group than clozapine/placebo group throughout the 12 weeks (P value not reported).

Secondary:
No significant between group differences in weight gain, agranulocytosis, and seizures were observed.</td></tr>
<tr><td>Glick et al[252]

Clozapine 12.5-450 mg daily

vs

olanzapine 5-20 mg daily</td><td>MC, RCT

Male and female patients aged 18-65 years with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder considered to be at a high risk for committing suicide</td><td>N=956

2 years</td><td>Primary:
Usage patterns of concomitant psychotropic medications

Secondary:
Not reported</td><td>Primary:
92.4% of the clozapine group and 91.8% of the olanzapine group received at least one concomitant psychotropic medications during the study.

The mean±SD number of concomitant psychotropic medications per patient was 3.80±2.90 in the clozapine group and 4.20±3.16 in the olanzapine group.

For each class of concomitant psychotropic medications, the mean daily dose was lower in the clozapine group vs the olanzapine group:

<table><tr><td></td><td colspan="2">Clozapine</td><td colspan="2">Olanzapine</td><td></td></tr><tr><td>Medication Class</td><td>N</td><td>Mean Daily Dose, mg (SD)</td><td>N</td><td>Mean Daily Dose, mg (SD)</td><td>P value</td></tr><tr><td>anti-</td><td>410</td><td>2.10 (0.33)</td><td>390</td><td>3.80</td><td><0.001</td></tr></table></td></tr>
</table>

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<table>
<tr><th>Study and Drug Regimen</th><th>Study Design and Demographics</th><th>Sample Size and Study Duration</th><th>End Points</th><th>Results</th></tr>
<tr><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>psychotics</td><td></td><td></td><td></td><td>(0.34)</td><td></td></tr>
<tr><td>anti-depressants</td><td>241</td><td>16.70 (1.05)</td><td>270</td><td>20.70 (0.97)</td><td><0.01</td></tr>
<tr><td>sedatives/ anxiolytics</td><td>284</td><td>6.30 (0.64)</td><td>315</td><td>10.10 (0.61)</td><td><0.001</td></tr>
<tr><td>mood stabilizers</td><td>120</td><td>487.3 (43.2)</td><td>144</td><td>620.6 (39.9)</td><td><0.05</td></tr>
</table>
Secondary:
Not reported</td></tr>
<tr><td>Faries et al[253]

Olanzapine of varying doses

vs

quetiapine of varying doses

vs

risperidone of varying doses</td><td>MC, OS, PRO

Inpatient and outpatients with schizophrenia, who were initiated on olanzapine, quetiapine, or risperidone</td><td>N=796

1 year</td><td>Primary:
Rate and duration of antipsychotic monotherapy, rate and duration of antipsychotic polypharmacy

Secondary:
Not reported</td><td>Primary:
More than 300 days of therapy were predominately with monotherapy in 35.7% of the patients, polypharmacy in 26.9% of the patients, mix of monotherapy and polypharmacy in 30.2% of the patients, and no treatment in 0.6% of the patients.

Overall, the average number of days was 195.5 (54.0% of the year) on monotherapy, 155.7 (43.0% of the year) on polypharmacy, and 13.9 (3.0% of the year) on no antipsychotic therapy.

Patients on olanzapine were more likely to be on monotherapy than quetiapine (OR, 2.08; 95% CI, 1.30 to 3.31; P=0.002) and risperidone (OR, 1.36; 95% CI, 1.01 to 1.84; P=0.043).

Secondary:
Not reported</td></tr>
<tr><td colspan="5">Miscellaneous</td></tr>
<tr><td>Harrington et al[254]

Paliperidone

vs

placebo</td><td>MA

Adults receiving paliperidone or placebo who had experienced an adverse event</td><td>N=3,779

Study duration not reported</td><td>Primary:
Adverse events

Secondary:
Not reported</td><td>Primary:
Adverse events with the greatest incidence in the paliperidone population were any treatment emergent adverse event (68%), extra-pyramidal symptoms (23%), headache (14%), insomnia (11%), somnolence (9%), tachycardia (9%) and weight gain (8%).

Adverse events with highest risk of being caused by paliperidone and not placebo, evaluated by using the attributable risks (AR) summary statistic,</td></tr>
</table>

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				were extra-pyramidal symptoms (AR, 10), reduction in acute psychosis (AR, 8), any treatment emergent adverse event (AR, 6), tachycardia (AR, 4), and weight gain (AR, 4). Adverse events entirely attributed to paliperidone (incidence equals AR) included hypersalivation (3), dysarthria (2), and sexual dysfunction (1). Reported events unrelated to paliperidone (AR=0) included anxiety, asthenia, constipation, depression, dyspepsia, glucose related events, and vomiting. Secondary: Not reported
Harrington et al[255] Ziprasidone 10 mg to 200 mg daily vs placebo	MA Adults taking oral ziprasidone or placebo who had experienced an adverse event	N=4,132 <3 months (most); 1 study was 52 weeks and 1 study was 26 weeks	Primary: Adverse events Secondary: Not reported	Primary: Ziprasidone was associated with a significantly greater overall rate of treatment-emergent adverse events compared with placebo (73% vs. 60%; *P*<0.0001). Adverse events with the greatest frequency included somnolence (21%), extrapyramidal symptoms (13%), headache (13%), insomnia (11%) and respiratory disorders (10%). Adverse events with highest risk of being caused by ziprasidone and not placebo, evaluated by using the risk difference (RD) summary statistic, were sedation/somnolence (RD, 14), extrapyramidal symptoms (RD, 6), asthenia (RD, 5), weight gain of >7% from baseline (RD, 4), dizziness (RD, 4), and dyspepsia (RD, 4). Adverse events reported but unlikely to be caused by ziprasidone included headache (RD, 0), QTc interval greater than 480 msec (RD, 0), diarrhea (RD, 0), and abdominal pain (RD, 0). Secondary: Not reported

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Study abbreviations: AC=active-controlled, CC=case control, CS=cross sectional, DB=double-blind, I=international, MA=meta-analysis, MC=multicenter, NAT=naturalistic, OL=open-label, OS=observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective, QE=quasi-experimental design, R=randomized, RCT=randomized controlled trial, RETRO=retrospective, SB=single-blind, XO=crossover
Miscellaneous abbreviations: AIMS= Abnormal Involuntary Movement Scale, APO_B=apolipoprotein B, ASEX=Arizona Sexual Experience Scale, ASFQ=Antipsychotics and Sexual Functioning Questionnaire, BAS=Barnes Akathisia rating Scale, BMI=body mass index, BBMI= baseline body mass index, BPRS= Brief Psychiatric Rating Scale, CGI=Clinical Global Impression Scale, CI=confidence interval, DSM-III R=Diagnostic and Statistical Manual of Mental Disorders 3rd revised edition, DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th edition, EPS=extrapyramidal syndromes, ESRS=Extrapyramidal Symptom Rating Scale, HDL=high-density lipoproteins, HR=hazard ratio, IRR=incidence rate ratio, LDL=low-density lipoprotein, OR=odds ratio, MD=mean difference, NNH=number needed to harm, NNT=number needed to treat, PANSS=Positive and Negative Syndrome Scale, QLS=quality of life scale, RD-Risk Difference, RR=rate ratio, RSSE=Rating Scale for Side Effects, SAS=Simpson-Angus Scale, SANS=Scale for the Assessment of Negative Symptoms, SD=standard deviation, VLDL/VLDL-C=very low density lipoprotein cholesterol, WHR=waist to hip ratio, WMD=weighted mean difference

Table 9. Safety Clinical Trials Using the Antipsychotics in Children and Adolescents

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Diabetes				
Baker et al[256] Atypical antipsychotics (olanzapine, risperidone, quetiapine, clozapine, ziprasidone, aripiprazole) or haloperidol	RETRO, SBSDA Data relating to diabetes-related adverse events (DRAEs) was extracted from the FDA Adverse Event Reporting System (AERS), evaluated for patients under 18 years of age, 18 to 64 years of age, and for patients over 65 years of age	N=8,032 cases of DRAEs Duration of therapy not reported	Primary: Cases of DRAEs across age groups Secondary: Not reported	Primary: A total of 258 cases of DRAEs were identified for children and adolescents receiving atypical antipsychotics or haloperidol. Among the study drugs, olanzapine and risperidone were associated with the highest incidence of DRAEs (82 and 56 cases, respectively). Of the DRAEs identified, hyperglycemia was the most frequently reported event (61 cases) in this age group, followed by diabetes (58 cases), and increased blood glucose (37 cases). A total of 5,764 cases of DRAEs were identified for adults, aged 18 to 65 years, who received either an atypical antipsychotic or haloperidol. Olanzapine and clozapine were associated with the highest incidence of DRAEs (2,500 and 1,115 cases, respectively), followed by risperidone. Of the DRAEs, diabetes (1,825 cases) and hyperglycemia (955 cases) were the most frequently reported events in this age group. A total of 529 cases of DRAEs were identified for patients over the age of 65, who received either an atypical antipsychotic or haloperidol. Olanzapine and risperidone were associated with the highest frequency of DRAEs. Of the DRAEs, diabetes (176 cases), followed by hyperglycemia (122 cases) and increased blood glucose (116 cases) were the most frequently reported event in this age group.

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Across all age groups, the following reporting ratios for diabetes were found with the evaluated atypical antipsychotics: olanzapine (9.6; 95%CI, 9.2 to 10.0; 1306 cases), risperidone (3.8; 95%CI, 3.5 to 4.1; 447 cases), quetiapine (3.5; 95%CI, 3.2 to 3.9; 283 cases), clozapine (3.1; 95%CI, 2.9 to 3.3; 464 cases), ziprasidone (2.4; 95%CI, 2 to 2.9; 74 cases), aripiprazole (2.4; 95%CI, 1.9 to 2.9; 71 cases). Secondary: Not reported
Guo et al[257] Atypical antipsychotics (clozapine, olanzapine, quetiapine, risperidone, or ziprasidone) vs conventional antipsychotics (chlorpromazine, fluphenazine, haloperidol, loxapine, molindone, perphenazine, pimozide thioridazine, thiothixene, or trifluoperazine) Doses for all regimens not reported	CC, RETRO Medicaid claims from 7 states were analyzed for 283 patients with diabetes (cases) and 1,134 controls matched by age, sex, and date when bipolar disorder was diagnosed, all patients had at least a 3-month exposure to either conventional or atypical antipsychotics or three prescriptions related to treatment of bipolar disorder.	N=1,417 4 years	Primary: Risk of developing diabetes Secondary: Not reported	Primary: Compared with patients receiving conventional antipsychotics, the risk of diabetes was greatest with risperidone (HR 3.8, 95% CI: 2.7 to 5.3), olanzapine (HR 3.7, 95% CI: 2.5 to 5.3), and quetiapine (HR 2.5, 95% CI: 1.4 to 4.3). The risk for developing diabetes was associated with weight gain (HR 2.5, 95% CI: 1.9 to 3.4), hypertension (HR 1.6, 95% CI: 1.2 to 2.2), and substance abuse (HR 1.5, 95% CI: 1.0 to 2.2). Secondary: Not reported
Metabolic				
Calarge et al[258] Risperidone	PRO Children and	N=99 2.9 years	Primary: Change in weight and difference in	Primary: Over the course of the study, patients experienced a mean gain of 0.6 BMI z-score point from baseline.

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	adolescents 7 to 17 years of age receiving risperidone for at least 6 months		metabolic metrics between obese/ overweight and lean patients Secondary: Not reported	A negative correlation was identified between the patient's baseline BMI z-score and gain in BMI z-score following risperidone initiation (P<0.0001). Concomitant therapy with psychostimulants did not attenuate weight gain secondary to risperidone. Obese or overweight patients had a 14% lower mean HDL cholesterol concentration compared to lean children (P<0.05). Obese or overweight patients were also more likely than lean patients to have higher insulin and triglyceride levels (P<0.05). The odds of having at least one laboratory metabolic abnormality was approximately 12 times greater in the obese/overweight group (P<0.0001). The odds of meeting at least one metabolic syndrome criteria was seven times higher among obese/overweight patients (P=0.0002). However, the prevalence of metabolic syndrome was low in both groups. Secondary: Not reported
Maayan et al[259] Risperidone 0.25 mg to 4.0 mg daily	NAT Children and adolescents between the ages of 11 and 17 years diagnosed with psychotic or mood disorders, initiated on risperidone therapy in the 4	N=8 8 weeks	Primary: Weight gain, BMI, hip and waist circumference, waist-to-height ratio, waist-to-hip ratio, leptin, glucose, insulin, triglycerides, total cholesterol, HDL, LDL, hemoglobin A1c, and cortisol	Primary: At 8 weeks, patients gained an average of 4.16 kg from baseline (P=0.03), with 62.5% of patients (6/8) experiencing a clinically significant weight gain, defined as a gain of more than 7% of baseline body weight. An increase in BMI from baseline was also statistically significant among patients taking risperidone for 8 weeks (P=0.03). At 8 weeks, patients were observed to have larger waist circumference and hip circumference from baseline (P=0.02 and P=0.01, respectively).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	weeks prior to study onset		levels Secondary: Not reported	The waist-to-height ratio was also increased from 0.47 to 0.50 during the 8 week treatment course (*P*=0.01). Risperidone 9-week treatment was not associated with significant changes in waist-to-hip ratio, leptin, glucose, insulin, triglycerides, total cholesterol, HDL, LDL, hemoglobin A1c, and cortisol levels (*P*>0.05). Secondary: Not reported
Correll et al[260] SATIETY Study Aripiprazole vs olanzapine vs quetiapine vs risperidone vs untreated control	PRO, O, CS Children and adolescents between the ages of 4 and 19, with a history of 1 week or less of antipsychotic therapy, psychiatric illness requiring antipsychotic therapy; patients receiving more than one antipsychotic were excluded	N=272 Up to 12 weeks	Primary: Absolute and relative weight change Secondary: BMI, waist circumference, plasma glucose, insulin, homeostasis model assessment of insulin resistance (HOMA-IR), ratio of triglycerides to HDL cholesterol, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides	Primary: After a median of 10.8 weeks, weight increased by 8.5 kg with olanzapine (*P*<0.001), by 6.1 kg with quetiapine (*P*<0.001), by 5.3 kg with risperidone (*P*<0.001), and by 4.4 kg with aripiprazole (*P*<0.001); while the untreated control group experienced a minimal weight change from baseline of 0.2 kg (*P*=0.77). After a median of 10.8 weeks, weight increased by 15.20% with olanzapine (*P*<0.001), by 10.42% with quetiapine (*P*<0.001), by 10.37% with risperidone (*P*<0.001), and by 8.14% with aripiprazole (*P*<0.001); while the untreated control group experienced a non-significant weight change from baseline of 0.65% (*P*=0.39). Secondary: After a median of 10.8 weeks, BMI increased by 14.04% with olanzapine (*P*<0.001), by 9.29% with quetiapine (*P*<0.001), by 9.12% with risperidone (*P*<0.001), and by 7.20% with aripiprazole (*P*<0.001); while the untreated control group experienced a non-significant change from baseline of 0.05% (*P*=0.96). After a median of 10.8 weeks, BMI z scores increased by 0.93 with olanzapine (*P*<0.001), by 0.44 with quetiapine (*P*<0.001), by 0.60 with risperidone (*P*<0.001), and by 0.37 with aripiprazole (*P*<0.001); while the untreated control group experienced a reduction in BMI z scores from baseline of 0.003 (*P*=0.96).

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				After a median of 10.8 weeks, waist circumference increased by 8.55 cm with olanzapine (*P*<0.001), by 5.27 cm with quetiapine (*P*<0.001), by 5.10 with risperidone (*P*<0.001), and by 5.40 with aripiprazole (*P*=0.001); while the untreated control group experienced a non-significant change from baseline of 0.70 (*P*=0.40). After a median of 10.8 weeks, olanzapine-treated patients experienced a statistically significant increase in plasma glucose level (3.14 mg/dl; 95%CI, 0.69 to 5.59; *P*=0.02). Statistically significant changes in plasma glucose were not observed in association with aripiprazole, quetiapine, and risperidone (*P*>0.05). After a median of 10.8 weeks, olanzapine-treated patients experienced statistically significant increases in plasma insulin level (2.71 mIU/ml mg/dl; 95%CI, 0.42 to 5.00; *P*=0.02) and HOMA-IR (0.62; 95%CI, 0.07 to 1.17; *P*=0.03). Statistically significant changes in plasma insulin level and HOMA-IR were not observed in association with aripiprazole, quetiapine, and risperidone (*P*>0.05). After a median of 10.8 weeks, statistically significant change in the ratio of triglycerides to HDL cholesterol was observed in association with quetiapine (1.22 mg/dl; *P*=0.004), olanzapine (0.59 mg/dl; *P*=0.002), and risperidone (0.20 mg/dl; *P*=0.05). The ratio of triglycerides to HDL cholesterol decreased in the aripiprazole and untreated control groups (*P*>0.05). Olanzapine was associated with the greatest increase in total cholesterol from baseline (15.58 mg/dl; *P*<0.001). Patients receiving quetiapine also experienced a significant increase in total cholesterol levels (9.05 mg/dl; *P*<0.46). The other groups did not exhibit significant changes from baseline in total cholesterol level (*P*>0.05). Olanzapine was associated with the greatest increase in LDL cholesterol

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				from baseline (11.54 mg/dl; *P*=0.004). Patients receiving aripiprazole experienced a marginally significant increase in LDL cholesterol levels (3.75 mg/dl; *P*=0.05). The other groups did not exhibit significant changes from baseline in LDL cholesterol level (*P*>0.05). Changes in HDL cholesterol from baseline were not significant in any of the study groups (*P*>0.05). After a median of 10.8 weeks, triglycerides increased by 36.96 mg/dl with quetiapine (*P*=0.01), by 24.36 mg/dl with olanzapine (*P*=0.002) and by 9.74 mg/dl with risperidone (*P*=0.04). The changes from baseline were non-significant in the aripiprazole and untreated control groups (*P*>0.05).
Fleischhaker et al [261] Olanzapine, average dose 10.2 mg/day vs risperidone, average dose 2.6 mg/day vs clozapine, average dose 311.7 mg/day	OL, PRO Children and adolescents, aged 9 to 21.3 years, treated with olanzapine, risperidone, or clozapine	N=33 45 weeks	Primary: Weight gain Secondary: Not reported	Primary: The absolute weight gain from baseline was higher among patients receiving olanzapine compared to clozapine, though the difference did not reach statistical significance (16.2 kg vs. 9.5 kg; *P*=0.10). The percentage average weight gain was significantly higher among patients receiving olanzapine compared to clozapine (30.1% vs. 14.8%; *P*<0.05). The absolute weight gain was higher among patients receiving olanzapine compared to risperidone, though the difference did not reach statistical significance (16.2 kg vs. 7.2 kg; *P*=0.10). The percentage average weight gain was significantly higher among patients receiving olanzapine compared to risperidone (30.1% vs. 11.5%; *P*<0.05). The change in weight from baseline was statistically significant in all three groups (*P*<0.05). Secondary: Not reported

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Fraguas et al[262] Risperidone of varying doses vs olanzapine of varying doses vs quetiapine of varying doses	NAT Children and adolescents (mean age, 15.2 years), treatment naïve or taking the study antipsychotic for <30 days	N=66 6 months	Primary: Weight gain, blood pressure, thyroxin level, plasma glucose, LDL cholesterol, HDL cholesterol, triglycerides, and HbA1c, risk for adverse health outcome (defined as at least 1 of the following:1) $\geq 85^{th}$ BMI percentile plus presence of at least 1 negative weight-related clinical outcome, or 2) $\geq 95^{th}$ BMI percentile) Secondary: Not reported	Primary: At 6 months, there was a statistically significant increase in BMI z scores in patients receiving olanzapine (*P*<0.001) or risperidone (*P*=0.008), but not in patients receiving quetiapine (*P*=0.137). Patients in the olanzapine group had significantly higher BMI z scores at endpoint compared to patients in the quetiapine group (*P*=0.001). There was no statistically significant difference in BMI z scores between risperidone and either olanzapine (P=0.09) or quetiapine (*P*=0.49). At 6 months, there was a statistically significant weight gain in patients receiving olanzapine (11.1 kg; *P*<0.01) or risperidone (5 kg; *P*=0.01), but not in patients receiving quetiapine (2.5 kg; *P*>0.05). At 6 months, there was a statistically significant increase in total cholesterol in patients receiving olanzapine (*P*=0.047) or quetiapine (P=0.016), but not in patients receiving risperidone (*P*=0.813). At 6 months, quetiapine therapy was associated with a statistically significant decrease in free thyroxin level from baseline (*P*=0.011). The reduction in free thyroxin levels observed in association with quetiapine was significantly greater than that seen with risperidone (*P*<0.001). At 6 months, olanzapine group exhibited a greater increase in systolic blood pressure from baseline compared with the risperidone group (7.4 mm Hg vs. 1.3 mm Hg; P=0.011). None of the three studied antipsychotics had a significant impact on plasma glucose, LDL cholesterol, HDL cholesterol, triglycerides, and HbA1c within the evaluated time period. At 6 months, the number of patients at risk for adverse health outcome increased from 16.7% to 37.9% (P=0.001). This increase was significant only in the olanzapine group (*P*=0.012). The risk of adverse health outcome was significantly greater in patients receiving olanzapine than

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				those using quetiapine (*P*=0.022) and in patients receiving olanzapine compared to those in the risperidone group (*P*=0.016). Secondary: Not reported
Hrdlicka et al[263] Atypical antipsychotics (risperidone, olanzapine, ziprasidone, clozapine) vs typical antipsychotics (haloperidol, perphenazine, sulpiride*)	RETRO Children and adolescents with a mean age of 15.8 years diagnosed with early onset schizophrenia or other related psychotic disorder	N=109 6 weeks	Primary: Change in weight at 6 weeks after starting antipsychotic therapy Secondary: Not reported	Primary: Patients receiving atypical antipsychotics and those receiving typical antipsychotics gained an average of 3.4 kg and 2.0 kg, respectively, after 6 weeks of therapy (P=0.334). At 6 weeks, patients receiving risperidone experienced a weight gain of 3.6 kg from baseline. At 6 weeks, patients receiving olanzapine experienced a weight gain of 4.4 kg from baseline. At 6 weeks, patients receiving clozapine experienced a weight gain of 2.1 kg from baseline. The difference in weight gain among the three atypical antipsychotic groups (with enough patients to allow for a valid comparison) was not statistically significant at study endpoint (P=0.286). Secondary: Not reported
Khan et al[264] Olanzapine of varying doses vs risperidone of varying doses	RETRO, CR Hospitalized patients aged <18 years (mean age, 13 years) treated with olanzapine or risperidone	N=49 Mean duration of therapy=27 days	Primary: Secondary: Not reported	Primary: Both treatment groups experienced a statistically significant increase in BMI from baseline to endpoint (P<0.001). The difference between the two treatment groups in BMI change from baseline was not statistically significant (P=0.425). While risperidone therapy was associated with 4 (17%) new cases of patients meeting criteria for being overweight or at risk for being

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				overweight, olanzapine therapy was associated with seven (28%) such new cases. Over the course of treatment, olanzapine therapy was associated with a statistically significant increase in risk factors for developing diabetes (P=0.008) and in overall risk factors for metabolic syndrome (P=0.013). Over the course of treatment, risperidone therapy was not associated with a statistically significant change in risk factors for diabetes or metabolic syndrome. Compared to risperidone therapy, olanzapine was associated with a statistically significant increase in mean systolic blood pressure (-3.2 mm Hg vs. 5.4 mm Hg; P=0.044). In contrast, there was no statistically significant difference between the groups in the change in diastolic blood pressure from baseline. Secondary: Not reported
Moreno et al[265] Atypical antipsychotics (olanzapine, risperidone, quetiapine)	NAT Children and adolescents naïve to antipsychotics or with a maximum exposure of 30 days; patients were divided into the following 3 diagnosis groups: bipolar, other psychotic disorder, and nonpsychotic disorder	N=90 3 months	Primary: Changes in weight, BMI, cholesterol, triglycerides, plasma glucose, TSH, T4 Secondary: Not reported	Primary: Antipsychotic therapy was associated with a statistically significant 5.5 kg weight gain, assessed at 3 months of study initiation, in all patients, regardless of the diagnosis (P<0.001). There was no statistically significant difference in weight gain among the three diagnostic groups (P=0.06). Significant weight gain was found in 71.1% of patients after 3 months of therapy. Antipsychotic therapy was associated with a statistically significant increase in BMI z-scores from baseline in all three treatment groups (P<0.001). A statistically significant increase in LDL-cholesterol from baseline was only seen in patients with bipolar disorder (P=0.02). In other diagnostic groups the change was not statistically significant.

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				Total cholesterol increased significantly in patients with bipolar and psychotic disorders (P<0.05). HDL-cholesterol and triglycerides did not change significantly in any of the three diagnostic groups (P>0.05). Plasma glucose, blood pressure, and thyroid-stimulating hormone (TSH) were not significantly changed from baseline at the 3-month follow-up. Free thyroxin (T4) level was significantly decreased in patients with psychotic disorders (other than bipolar) (P=0.05). Secondary: Not reported
Patel et al[266] Quetiapine at an average daily dose of 510.9 mg vs olanzapine at an average daily dose of 13.9 mg	RETRO Children and adolescents younger than 18 years of age, hospitalized and receiving either olanzapine or quetiapine at baseline, with at least one measurement of weight and height obtained ≥14 days after baseline	N=100 ≥2 weeks	Primary: Weight gain, changed in BMI Secondary: Not reported	Primary: Patients receiving quetiapine gained an average of 0.03 kg (P>0.05); while, olanzapine-treated patients gained an average of 3.8 kg from baseline (*P*<0.001). After controlling for differences in race/ethnicity and baseline weight, the mean weight gain from baseline was significantly greater in the olanzapine group, compared to the quetiapine group (a difference of 3.4 kg; *P*<0.001). Patients receiving quetiapine experienced a reduction in BMI of 0.2 kg/m^2 (P>0.05); while, olanzapine-treated patients exhibited an increase in BMI of 1.3 kg/m^2 from baseline (*P*<0.001). After controlling for differences in race/ethnicity and baseline BMI, the increase in BMI from baseline was significantly greater in the olanzapine group, compared to the quetiapine group (a difference of 0.9 kg/m^2; *P*=0.008).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Correll et al[267] Atypical antipsychotic (olanzapine, aripiprazole, quetiapine, risperidone, clozapine) vs mood stabilizers vs two mood stabilizers vs mood stabilizer with atypical antipsychotic	SR, MA Children and adolescents (mean age, 12.3 years) with bipolar disorder	N=683 (19 studies) up to 48 weeks	Primary: Change in weight, plasma glucose, lipid levels Secondary: Not reported	Primary: Patients receiving a mood stabilizer, other than topiramate, exhibited a weight gain of 1.8 kg from baseline. Patients receiving a mood stabilizer, including topiramate, exhibited a weight gain of 1.2 kg from baseline. Patients receiving monotherapy with an atypical antipsychotic exhibited a weight gain of 3.4 kg from baseline. Patients receiving combination therapy with two different mood stabilizers exhibited a weight gain of 2.1 kg from baseline. Patients receiving combination therapy with a mood stabilizer and an atypical antipsychotic exhibited the greatest weight gain of 5.5 kg from baseline. The weight gain experienced by this combination treatment group was statistically greater than the weight gain observed in either the mood stabilizer monotherapy group or the two mood stabilizer combination group (P<0.05). Glucose and lipid values were only evaluated in two eight-week, open-label studies. Nonfasting lipid and glucose values did not significantly change from baseline in 16 and 15 preschoolers treated with risperidone and olanzapine, respectively. In the second study, risperidone therapy was not associated with a significant change from baseline in lipid and glucose values in 30 children and adolescents. Secondary: Not reported
Fedorowicz et al[268] Atypical antipsychotics	SR Children and	N=2,979 up to 3.6	Primary: Change in weight, blood glucose, LDL	Primary: Risperidone was associated with a significantly greater weight gain compared to placebo in 2 double-blind, randomized controlled trials of 5

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(risperidone, olanzapine, clozapine, quetiapine, ziprasidone)	adolescents <18 years of age (mean age, 13 years) receiving atypical antipsychotic therapy	years	cholesterol, prolactin level Secondary: Not reported	and 8 weeks in duration, respectively. Weight gain was more common with atypical antipsychotics compared to typical antipsychotics, with the greatest weight gain associated with clozapine and olanzapine (data from 3 studies). A double-blind, randomized controlled study did not find a statistically significant difference between ziprasidone and placebo at 8 weeks. One double-blind randomized controlled study reported a non-statistically significant increase in blood glucose with olanzapine but not with risperidone or haloperidol, while 2 case series reported some hyperglycemia with risperidone, quetiapine and olanzapine. One double-blind, randomized controlled study reported a non-statistically significant increase in LDL cholesterol with olanzapine but not with risperidone or haloperidol. Six studies found non-statistically significant increases in prolactin level in association with risperidone. Three open-label comparative studies reported increased prolactin with haloperidol, clozapine, and olanzapine. Two small, open-label studies reported no change in prolactin level with quetiapine use. In contrast, another study reported cases of transient hyperprolactinemia with ziprasidone use. Secondary: Not reported
De Hart et al[269] Atypical antipsychotics (aripiprazole, ziprasidone, quetiapine, risperidone, olanzapine)	MA Children and adolescents <18 years of age	N=3,595 Study durations varied	Primary: Change in weight from baseline Secondary: Not reported	Primary: Ziprasidone was associated with the lowest weight gain (-0.04 kg; 95% CI, -0.38 to 0.30), followed by aripiprazole (0.79 kg; 95% CI, 0.54 to 1.04), quetiapine (1.43 kg; 95%CI, 1.17 to 1.69) and risperidone (1.76 kg; 95%CI, 1.27 to 2.25). Olanzapine was association with the greatest weight gain compared to

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				the other agents included in the meta-analysis (3.45 kg; 95% CI, 2.93 to 3.97). Significant weight gain was observed in children with autism, who were also younger and less likely to have been previously exposed to antipsychotics. Secondary: Not reported
Safer et al[270] Risperidone of varying doses	SR Studies of youths and adults over the age of 65 with risperidone-induced weight gain data; the treatment and weight gain data were pooled by age group and by duration of therapy	N=2,692 (36 studies) 4-56 weeks	Primary: Weight gain for patients aged 5-11 years, 12-17 years, 33-45 years, and 71-83 years Secondary: Not reported	Primary: Total weight gain for children between the ages of 5 and 11 years was 2.1 kg, 3.4 kg, and 5.8 kg after the following durations of therapy: 6-8 weeks, 11-14 weeks, and 46-78 weeks, respectively. Total weight gain for children between the ages of 12 and 17 years was 2.6 kg, 2.6 kg, and 4.2 kg after the following durations of therapy: 6-8 weeks, 11-14 weeks, and 26-28 weeks, respectively. Total weight gain for adults between the ages of 33 and 45 years was 1.6 kg, 2.1 kg, 2.4 kg, and 3.3 kg after the following durations of therapy: 6-8 weeks, 11-14 weeks, 26-28 weeks, and 46-78 weeks, respectively. Total weight gain for older adults between the ages of 71 and 83 years was 0.30 kg, -0.006 kg, and 0.65 kg after the following durations of therapy: 6-8 weeks, 26-28 weeks, and 46-78 weeks, respectively. Children between the ages of 5 and 11 years experienced the greatest percentage of weight gain from baseline (5.6%, 7.4%, and 16.3%), compared to other age groups, when assessed after the following durations of therapy: 4-8 weeks, 9-16 weeks, and 17-56 weeks, respectively. Adolescents between the ages of 12 and 17 years experienced less weight gain compared to pre-adolescents but twice that of adults in their

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				early 30s and 40s. Adolescents experienced an increase in weight of 4.1%, 6.3%, and 8.1% from baseline, when assessed after the following durations of therapy: 4-8 weeks, 9-16 weeks, and 17-56 weeks, respectively. Adults between the ages of 33 and 44 years experienced a weight gain of 2.1%, 2.9%, and 3.4% from baseline after 4-8 weeks, 9-16 weeks, and 17-56 weeks of therapy, respectively. Older adults between the ages of 71 and 83 years experienced a weight gain of 0.5%, 0.2%, and 0.3% from baseline after 4-8 weeks, 9-16 weeks, and 17-56 weeks of therapy, respectively. The following average mg/kg doses were administered to pre-adolescents, adolescents, adults, and older adults: 0.04 mg/kg, 0.05 mg/kg, 0.08 mg/kg, and 0.03 mg/kg, respectively. Pre-adolescents (children between the ages of 5 and 11 years) exhibited consistently larger increases in BMI (5.6%-15%) compared to middle-aged adults (2.7%-5.9%). In middle-aged adults and youths, risperidone was associated with the greatest weight gain during the first few months of therapy; though, weight gain could persist beyond the first year. Secondary: Not reported Conclusion: risperidone-induced weight gain is greater in children than in adults.
Prolactin Levels				
Saito et al[271] Risperidone at a mean daily	PRO Children and	N=40 4 to 15	Primary: Prolactin level	Primary: A significantly greater percentage of patients in the risperidone group exhibited hyperprolactinemia compared to patients in the olanzapine and

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dose of 2.2 mg vs olanzapine at a mean daily dose of 7.8 mg vs quetiapine at a mean daily dose of 282.3 mg	adolescents, aged 5 to 18 years, who were initiated on an atypical antipsychotic	weeks	Secondary: Not reported	quetiapine groups (71% vs. 38% vs.17%; *P*=0.031). Endpoint prolactin levels were significantly higher among patients receiving risperidone compared to patients in the olanzapine group (46.8 ng/ml vs. 24.5 ng/ml; *P*=0.027). Endpoint prolactin levels were significantly higher among patients receiving risperidone compared to patients in the quetiapine group (46.8 ng/ml vs. 16.7 ng/ml; *P*=0.008). Secondary: Not reported
Staller et al[272] Risperidone (median dose 15 mg/day), or olanzapine (median dose 10 mg/day), or quetiapine (median dose 200 mg/day) vs control (no antipsychotic medication)	NAT Children aged 5-17 years receiving one of the specified antipsychotics for at least 6 months	N=50 Not specified	Primary: Average of 2 fasting prolactin levels taken one month apart Secondary: Side effects associated with sustained prolactin elevation defined as changes in sexual functioning or menstrual or breast problems	Primary: Mean prolactin level among all patients receiving risperidone, olanzapine, and quetiapine were greater than those of the control group (*P*<0.05). The mean prolactin level for males in the risperidone treatment group was elevated above upper limit of standard normal values (*P* value not provided) and risperidone treatment was associated with greater prolactin levels in comparison to the three other treatment groups (*P*=0.05). Secondary: Side effects possibly associated with sustained prolactin elevation were reported in 12% of patients; 2 male patients receiving risperidone and 1 male patient receiving olanzapine indicated breast problems, 1 male on olanzapine indicated a change in sexual functioning, and 2 female patients receiving quetiapine reported menstrual or breast problems.
Metabolic and Neurological				
Pringsheim et al[273] Atypical antipsychotics (risperidone, olanzapine, quetiapine, aripiprazole, clozapine, ziprasidone,	MA Double blind, randomized-controlled studies in children and	35 studies (number of patients not provided) ≤12 weeks	Primary: Weight gain, cholesterol, blood pressure, prolactin, blood glucose, triglycerides, liver	Primary: Compared with placebo, mean weight gain was highest for olanzapine at 3.47 kg, followed by risperidone at 1.72 kg, quetiapine at 1.41 kg and aripiprazole at 0.85 kg (*P*<0.00001). In one study, olanzapine and clozapine were associated with comparable weight gain and BMI increase from baseline (*P*=0.96; *P*=0.76, respectively). According to the

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
paliperidone)	adolescents up to 18 years of age on atypical antipsychotics for the treatment of a mental health disorder Note: none of the paliperidone studies met inclusion criteria and were hence excluded from MA		enzymes, ECG changes, neurological adverse events Secondary: Not reported	only pediatric study with ziprasidone, weight gain was comparable to placebo (*P* value not reported). Prolactin levels were significantly increased from baseline by 44.57 ng/mL in association with risperidone therapy (*P*<0.00001). Olanzapine therapy was likewise associated with a statistically significant prolactin elevation compared to placebo (OR, 30.52; P<0.00001). In contrast, aripiprazole therapy was associated with a significantly greater decrease in prolactin levels after treatment compared with placebo (-5.03 ng/ml; 95%CI, -7.80 to -2.26). Quetiapine was not associated with a significant change in prolactin levels (*P* value not reported)/ Risperidone-treated children had significantly greater odds of experiencing extrapyramidal symptoms (EPS) compared to placebo-treated patients (OR, 3.35; *P* <0.00001). Aripiprazole therapy was also associated with a statistically significant increase in the odds of extrapyramidal symptoms compared to placebo (OR, 3.70; *P*<0.00001). Risperidone was associated with a higher risk of requiring anti-cholinergic therapy for the treatment of EPS compared to olanzapine, though the difference did not reach statistical significant (*P* value not reported). Olanzapine and clozapine were associated with the greatest increases in cholesterol and triglycerides compared to placebo. The odds of high triglycerides after receiving olanzapine were higher compared to placebo, with an OR of 5.13. Cholesterol increased by a mean of 3.67 mg/dl (*P*=0.001) from baseline. Risperidone was not associated with significant changes in cholesterol, triglycerides, or glucose plasma levels compared to baseline. Quetiapine was associated with a significant increase in triglycerides levels compared to placebo (30 mg/dl vs. -14 mg/dl; *P*=0.003). Aripiprazole was not associated with significant changes in cholesterol, triglycerides, blood pressure or blood glucose compared to placebo (*P* value not reported). Olanzapine, aripiprazole, ziprasidone and quetiapine were not associated

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				with significant changes in QTc interval from baseline. Olanzapine was associated with a statistically significant increase in systolic blood pressure compared to placebo (3.61 mmHg vs. -2.28 mmHg; *P*=0.001). Quetiapine was also associated with significantly higher blood pressure compared to placebo (6 mmHg vs. -6 mmHg; *P* value not reported). Heart rate was also significantly higher in the quetiapine-treated patients compared to placebo (11 beats per minute vs. -3 bpm; *P* value not reported). Compared to placebo, olanzapine was associated with a significantly greater risk of ALT elevation from baseline (*P*=0.0005). Secondary: Not reported
Neurological				
Jerrell et al[274] Antipsychotics (aripiprazole 5-30 mg, ziprasidone 20-80 mg, quetiapine 25-300 mg, risperidone 0.25-4 mg, olanzapine 2.5-20 mg, haloperidol [doses not reported], fluphenazine [doses not reported]) vs controls (no history of antipsychotic medications)	RETRO Medicaid data was used to identify patients (0-17 years of age) who developed neurological adverse events subsequent to exposure to at least one antipsychotic (aripiprazole, ziprasidone, quetiapine, risperidone, olanzapine, haloperidol,	N=8,649 8 years Treatment duration: 1-5 months (35% of children); 6-90 months (65% of children)	Primary: Involuntary movements/ extrapyramidal symptoms, convulsions/ seizures, sedation/ somnolence Secondary: Not reported	Primary: The odds of being diagnosed with involuntary movements/ extrapyramidal symptoms were significantly increased for those taking aripiprazole (OR, 6.04), risperidone (OR, 1.85), and haloperidol (OR, 15.98) as monotherapy, those taking multiple antipsychotics (OR, 3.35), or those with preexisting central nervous system disorders (OR, 3.89), organic brain disorders/mental retardation (OR, 1.56), or cardiovascular disorders (OR, 2.02; *P*<0.05 for all). The odds of developing convulsions or seizures were increased among patients receiving risperidone (OR, 1.62), multiple antipsychotics (OR, 3.41), serotonin-specific reuptake inhibitors (OR, 1.46), those with preexisting central nervous system (OR, 3.71) or organic brain disorders/mental retardation (OR, 1.39; *P*<0.05 for all). The odds of experiencing sedation/somnolence were significantly greater among patients receiving ziprasidone (OR, 2.05), risperidone (OR, 1.28), and quetiapine (OR, 1.68) as monotherapy, those requiring multiple

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	fluphenazine)			antipsychotic use (OR, 2.20), serotonin-specific reuptake inhibitors (OR, 1.78), or those with preexisting central nervous system (OR, 1.99), cardiovascular disorders (OR, 1.52) and obstructive sleep apnea (OR, 1.96; *P*<0.05 for all). The odds of sedation/ somnolence were lower among males (OR, 0.75) and children 12 years and under (OR, 0.79; *P*<0.05 for all). Secondary: Not reported
Correll et al[275] Atypical antipsychotics (amisulpride*, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, sertindole*, sulpiride, ziprasidone, and zotepine*)	SR Prospective and retrospective studies with a duration of at least 11 months, conducted in children, 4-18 years of age, treated with any atypical antipsychotic and who had developed tardive dyskinesia (TD) or dyskinesia	N=783 ≥11 months (Treatment duration= mean of 329.6 days)	Primary: 1-year risk of tardive dyskinesia in children with assumed minimal past exposure to first-generation antipsychotics Secondary: Not reported	Primary: Three new cases of TD were associated with during treatment with atypical antipsychotics of up to 3 years (1 with quetiapine and 2 with risperidone). The crude and annualized TD rates associated with atypical antipsychotics were 0.38% (95%CI, 0.079 to 1.11) and 0.42% (95%CI, 0.087 to 1.24), respectively. The crude and annualized TD rates associated with risperidone use were 0.27% (95%CI, 0.033 to 0.97) and 0.30% (95%CI, 0.037 to 1.10), respectively. TD resolved within a few weeks after risperidone discontinuation. Secondary: Not reported
Cardiovascular				
De Castro et al[276] Atypical antipsychotics (olanzapine, quetiapine, risperidone) vs	RETRO Children and adolescents (mean age, 15.1 years) who received a new prescription for olanzapine,	N=52 6 months	Primary: Change from baseline in QTc Secondary: Not reported	Primary: Mean QTc durations at baseline and at 6 months were 387.29 msec and 393.63 msec, respectively (*P*=0.134). QTc interval duration at baseline was inversely related to QTc change in controls at endpoint (*P*<0.001). The difference in QTc change from baseline between the two groups was

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
matched healthy controls	quetiapine, or risperidone and who took the prescribed antipsychotic without interruptions for 6 months			not statistically significant (*P*=0.364). Secondary: Not reported
Growth and Development				
Calarge et al[277] Risperidone 0.03 mg/kg	NAT Male patients between the ages of 7 and 17, treated with risperidone for at least 6 months	N=83 Average of 2.9 years	Primary: Prolactin level, serum testosterone, BMD	Primary: Hyperprolactinemia was found in 49% of children treated with risperidone for an average of 2.9 years. Serum testosterone level increased with sexual development (P<0.0001) but was not affected by hyperprolactinemia (*P*>0.07). Volumetric BMD significantly increased with sexual maturity (*P*=.002). After adjustment for the stage of sexual development, height and BMD z scores, serum prolactin was negatively associated with trabecular volumetric BMD at the ultra-distal radius (*P*<0.03). Prolactin level was also negatively associated with total volumetric BMD (*P*<0.04) Treatment with SSRIs was associated with lower trabecular BMD at the radius (*P*=0.03) and BMD z score at the lumbar spine (*P*<0.05). Secondary: Not reported
Liver Function Tests				
Erdogan et al[278] Risperidone 0.25 to 6 mg daily (or 0.01 to 0.32 mg/kg daily)	O, OL Children and adolescents, aged 2 to 18 years,	N=102 6 months	Primary: Changes from baseline in alanine aminotransferase (ALT), aspartate	Primary: At 6 months, patients exhibited statistically significant increases in ALT levels from baseline (17.21 vs. 12.34; *P*=0.0001). At 6 months, patients exhibited statistically significant increases in AST

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	treated with risperidone (new starts) for any psychiatric problem (diagnoses included ADHD, anxiety, tic disorder, psychotic disorder), drug-free for at least two weeks prior to study onset		aminotransferase (AST), gamma glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), direct and indirect bilirubin levels, weight	levels from baseline (28.27 vs. 17.06; *P*=0.0001). At 6 months, patients exhibited statistically significant increases in GGT levels from baseline (12.75 vs. 9.28; *P*=0.0001). At 6 months, patients exhibited statistically significant increases in ALP levels from baseline (310.54 vs. 229.83; *P*=0.0001). At 6 months, patients exhibited statistically significant increases in direct bilirubin levels from baseline (0.17 vs. 0.09; *P*=0.0001). At 6 months, patients exhibited statistically significant increases in indirect bilirubin levels from baseline (0.38 vs. 0.27; *P*=0.0001). At 6 months, patients exhibited statistically significant increases in weight from baseline (37.50 vs. 31.98; *P*=0.002). There was no significant association between weight gain and changes in liver function tests (*P* value not reported). Secondary: Not reported
Usage and Safety				
Harrison-Woolrych et al[279] Atypical antipsychotics (clozapine, olanzapine, risperidone, quetiapine)	I, O, PRO Children and adolescents, aged 2 to 15 years, who were prescribed an atypical antipsychotic, identified through a post-marketing Prescription Event	N=420 641.2 patient-years	Primary: Usage, safety Secondary: Not reported	Primary: During the study period, 93% of patients included in the study received a prescription for risperidone, followed by 8%, 2%, and 0.2% of patients with a prescription for quetiapine, olanzapine, and clozapine, respectively. Total exposure to atypical antipsychotics was 7694 patient-months, with the majority of exposure (94%) being to risperidone. The most common indications for prescribing an antipsychotic were disruptive disorders (conduct disorder, ADHD) reported in 43% of patients, pervasive developmental disorders (34%), and cognitive impairment (17%). Aggression was the most common target symptom

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	Monitoring system in Australia			among pediatric patients treated by an antipsychotic, reported in 43% of the study sample. Other common target symptoms for antipsychotic therapy included behavioral difficulties (26%), anxiety (17%), hyperactivity (10%) and mood disturbances (9%). Mood disturbances were identified as a target symptom in 3% of pediatric patients prescribed an atypical antipsychotic. The most commonly reported adverse events in patients receiving risperidone were weight gain, dental caries, dental extractions, and somnolence. Six patients in the risperidone group experienced dystonic reactions. The estimated incidence of new-onset diabetes among risperidone recipients was 4 cases per 1000 patient-years of therapy. The estimated incidence of depression among risperidone recipients was 8 cases per 1000 patient-years of therapy. Secondary: Not reported

Study abbreviations: AC=active-controlled, CC=case control, CR=Chart Review, CS=cross sectional, DB=double-blind, I=international, MA=meta-analysis, MC=multicenter, NAT=naturalistic, OL=open-label, OS=observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective, R=randomized, RCT=randomized controlled trial, RETRO=retrospective, SB=single-blind, SBSDA=Systematic Bayesian Signal Detection Analysis, SR=systematic review, XO=crossover
Miscellaneous abbreviations: AERS=Adverse Event Reporting System, AIMS= Abnormal Involuntary Movement Scale, ALP=Alkaline phosphatase, ALT=Alanine aminotransferase, AST=aspartate aminotransferase, APO_B=apolipoprotein B, BAS=Barnes Akathisia rating Scale, BMI=body mass index, BBMI= baseline body mass index, BPRS= Brief Psychiatric Rating Scale, CGI=Clinical Global Impression Scale, CI=confidence interval, DSM-III R=Diagnostic and Statistical Manual of Mental Disorders 3rd revised edition, DRAEs=Diabetes Related Adverse Events, DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th edition, EPS=extrapyramidal syndromes, ESRS=Extrapyramidal Symptom Rating Scale, GGT=Gamma glutamyl transpeptidase, HOMA-IR=Homeostatic Model Assessment of Insulin Resistance, HDL=high-density lipoproteins, HR=hazard ratio, IRR=incidence rate ratio, LDL=low-density lipoprotein, OR=odds ratio, MD=mean difference, NNH=number needed to harm, NNT=number needed to treat, PANSS=Positive and Negative Syndrome Scale, QLS=quality of life scale, RD-Risk Difference, RR=rate ratio, RSSE=Rating Scale for Side Effects, SAS=Simpson-Angus Scale, SANS=Scale for the Assessment of Negative Symptoms, SD=standard deviation, VLDL/VLDL-C=very low density lipoprotein cholesterol, WHR=waist to hip ratio, WMD=weighted mean difference

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Special Populations

Table 11. Special Populations[6-11,13-19,21-22]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Aripiprazole	No dosage adjustment is recommended for elderly patients. The safety and effectiveness in pediatric patients with schizophrenia less than 13 years of age have not been established. The safety and effectiveness in pediatric patients with bipolar mania less than 10 years of age have not been established. Safety and effectiveness in pediatric patients with other conditions have not been established.	No dosage adjustment is required in subjects with renal function impairment.	No dosage adjustment is required in subjects with hepatic function impairment.	C	Unknown; women receiving aripiprazole should not breastfeed.
Asenapine	Clinical studies did not include sufficient numbers of patients aged 65 and over to determine whether or not they respond differently than younger patients. Not approved for the treatment of patients with dementia-related psychosis. Safety and effectiveness in pediatric patients have not been established.	No dosage adjustment is required in subjects with renal function impairment.	Not recommended in patients with severe hepatic impairment.	C	Unknown; women receiving asenapine should not breastfeed.
Clozapine	Dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic,	Caution is advisable in patients with renal disease.	Caution is advised in patients who have concurrent	B	Unknown; women receiving clozapine should not

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Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	renal, or cardiac function, and of concomitant disease or other drug therapy. Safety and effectiveness in pediatric patients have not been established.		hepatic disease.		breastfeed.
Iloperidone	Clinical studies did not include sufficient numbers of patients aged 65 and over to determine whether or not they respond differently than younger patients. Safety and effectiveness in pediatric patients have not been established.	Renal impairment (creatinine clearance <30 mL/min) had minimal effect on maximum plasma concentrations of iloperidone and its metabolites.	Not recommended for patients with hepatic impairment.	C	Unknown; women receiving iloperidone should not breastfeed.
Lurasidone	No dosage adjustment is recommended for elderly patients. The safety and effectiveness in pediatric patients have not been established.	Dosage adjustment is recommended in patients with moderate/ severe renal impairment (dose should not exceed 40 mg daily).	Dosage adjustment is recommended in patients with moderate/ severe hepatic impairment (dose should not exceed 40 mg daily).	B	Unknown; women receiving lurasidone should not breastfeed.
Olanzapine	Consider a lower starting dose for any elderly patient if factors are present that might decrease pharmacokinetic clearance or increase the pharmacodynamic response. The safety and effectiveness in pediatric patients with schizophrenia or manic/mixed bipolar I disorder less than 13 years of age have not been established.	Dosage adjustment based upon the degree of renal function impairment is not required.	Exercise caution in patients with signs and symptoms of hepatic function impairment, preexisting conditions associated with limited hepatic functional reserve, or being treated with potentially hepatotoxic drugs.	C	Women receiving olanzapine should not breastfeed.

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Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	Safety and effectiveness in pediatric patients with other conditions have not been established.				
Paliperi-done/ paliperidone palmitate	Because elderly patients may have diminished renal function, dose adjustments may be required according to their renal function status. In general, the recommended dosing for elderly patients with healthy renal function is the same as for younger adult patients with healthy renal function. The safety and effectiveness in pediatric patients with schizophrenia less than 12 years of age have not been established. Safety and effectiveness in pediatric patients with other conditions have not been established.	Dose according to the patient's renal function. For mild renal impairment (creatinine clearance 50 to <80 mL/ minute), the recommended initial dosage is 3 mg daily; dose may then be increased to a maximum recommended dosage of 6 mg once daily based on clinical response and tolerability. For moderate to severe renal impairment (creatinine clearance 10 to <50 mL/ minute), the recommended initial dosage is 1.5 mg once daily, which may be increased to a maximum recommended dosage of 3 mg once daily after clinical reassessment.	For patients with mild to moderate hepatic impairment no dose adjustment is recommend-ed. Not studied in patients with severe hepatic impairment.	C.	The known benefits of breast-feeding should be weighed against the known risks of infant exposure.
Quetiapine	For elderly patients, consider a slower rate of dose titration and a	Dosage adjustment not needed.	Dosage adjustment may be	C	Women receiving quetiapine

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Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	lower target dose; when indicated, dose escalation should be performed with caution in these patients. The safety and effectiveness in pediatric patients with schizophrenia less than 13 years of age have not been established. The safety and effectiveness in pediatric patients with bipolar mania less than 10 years of age have not been established. Safety and effectiveness in pediatric patients with other conditions have not been established.		needed.		should not breastfeed.
Risperidone	Clinical studies in the treatment of schizophrenia did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. The safety and effectiveness in pediatric patients with schizophrenia less than 13 years of age have not been established.	Reduce dose in patients with renal disease; for patients with severe renal impairment, the initial dosage is 0.5 mg twice daily; dosage increases should be in increments of no more than 0.5 mg twice daily.	Reduce dose in patients with hepatic /disease; for patients with severe hepatic impairment, the initial dosage is 0.5 mg twice daily; dosage increases should be in increments of no more than 0.5 mg twice daily.	C	Women receiving risperidone should not breastfeed.

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Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	The safety and effectiveness in pediatric patients with bipolar disorder less than 10 years of age have not been established. The safety and effectiveness in pediatric patients with autistic disorder less than 5 years of age have not been established.				
Ziprasidone	Consider a lower starting dose, slower titration, and careful monitoring during the initial dosing period for some elderly patients. Safety and effectiveness in pediatric patients have not been established.	Dosage adjustments are generally not required on the basis of renal impairment.	Dosage adjustments are generally not required on the basis of hepatic impairment.	C	Unknown; women receiving ziprasidone should not breastfeed.

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Adverse Drug Events

Table 11. Adverse Drug Events (%)[6-11,13-19,21-22]

Adverse Event	Aripiprazole	Asenapine	Clozapine	Iloperidone	Lurasidone	Olanzapine	Olanzapine Pamoate	Paliperidone/ paliperidone palmitate	Quetiapine	Risperidone Oral	Risperidone Intramuscular	Ziprasidone Oral	Ziprasidone Intramuscular
Cardiovascular													
Angina	-	-	-	-	✔	-	-	-	-	-	✔	-	-
Atrioventricular block	-	-	-	✔	✔	-	-	>2	-	-	✔	-	-
Bradycardia	-	-	-	-	✔	-	-	✔	-	-	✔	-	-
Bundle branch block	-	-	-	-	-	-	-	>2	-	-	✔	-	-
Electrocardiogram changes	-	-	1	-	-	-	-	>2	-	-	-	✔	✔
Hypertension	2	2	4	-	✔	2	0-3	>2	✔	0.1-1.0	>2	>1	≤2
Hypotension	>1	✔	9	1-5	✔	3-5*	-	>2	7*	0.1-1.0	✔	1*	≤5
Myocardial infarction	0.1-1.0	-	✔	-	-	-	-	-	-	0.1-1.0	-	-	-
Palpitation	0.1-1.0	-	-	✔	-	0.1-1.0	-	✔	>1	0.1-1.0	✔	-	-
Phlebitis	0.1-1.0	-	✔	-	-	-	-	-	-	<0.1	-	<0.1	<0.1
Pulmonary embolus	<0.1	-	✔	-	-	<0.1	-	-	-	✔	-	<0.1	<0.1
Q- and T-wave distortions	-	-	-	-	-	-	-	>2	-	-	-	-	-
QTc interval prolongation	0.1-1.0	✔	-	✔	-	-	0-2	>2	0.1-1.0	-	-	✔	✔
Sinus arrhythmia	-	-	-	-	-	-	-	>2	-	-	-	-	-
T-wave flattening	-	-	✔	-	-	-	-	-	0.1-1.0	-	-	-	-
T-wave inversion	-	-	✔	-	-	-	-	-	0.1-1.0	<0.1	✔	-	-
Tachycardia	>1	-	25	3-12	✔	3	-	>2	7	3-5	-	2	2
Thrombophlebitis	<0.1	-	✔	-	-	-	-	-	0.1-1.0	-	-	<0.1	<0.1
Twitch	0.1-1.0	-	✔	-	-	-	-	-	0.1-1.0	-	-	-	-
Vasodilation	0.1-1.0	-	-	-	-	0.1-1.0	-	-	0.1-1.0	-	-	-	≤1
Central Nervous System													
Agitation	25	-	4	-	6	-	-	-	-	22-26	✔	>1	≤2
Akathisia	15-17	4-6	3	1.7-2.3	15	3	-	>2	-	-	>5	8	≤2
Akinesia	0.1-1.0	-	4	-	-	<0.1	-	-	-	-	-	>1	>1
Amnesia	0.1-1.0	-	✔	✔	-	0.1-1.0	-	-	0.1-1.0	0.1-1.0	✔	>1	>1
Anxiety	20	4	1	-	6	-	-	>2	-	12-20	✔	-	≤2
Apathy	0.1-1.0	-	-	-	-	-	-	-	0.1-1.0	0.1-1.0	✔	-	-
Asthenia	8	-	-	-	-	10-15	-	>2	4	-	✔	5	≤2
Ataxia	0.1-1.0	-	1	-	-	0.1-1.0	-	-	0.1-1.0	-	✔	>1	>1
Catatonic-like states	-	-	-	✔	-	-	-	-	0.1-1.0	0.1-1.0	-	-	-

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Adverse Event	Aripiprazole	Asenapine	Clozapine	Iloperidone	Lurasidone	Olanzapine	Olanzapine Pamoate	Paliperidone/ paliperidone palmitate	Quetiapine	Risperidone Oral	Risperidone Intramuscular	Ziprasidone Oral	Ziprasidone Intramuscular
Cerebrovascular accident	-	-	-	-	✔	-	-	-	-	-	-	-	-
Confusion	>1	-	3	✔	-	-	-	✔	0.1-1.0	0.1-1.0	✔	>1	>1
Convulsions†	✔	✔	3	-	-	-	-	-	-	-	✔	-	-
Delirium	0.1-1.0	-	✔	✔	-	0.1-1.0	-	-	<0.1.0	<0.1	✔	>1	>1
Dementia	-	-	-	-	-	-	-	-	-	-	✔	-	-
Depersonalization	-	-	-	-	-	-	-	-	-	-	✔	-	-
Depression	>1	-	1	✔	-	-	-	-	-	0.1-1.0	✔	-	-
Dizziness	-	5-11	19	10-20	5	11-18	1-4	>2	10	4-7	>2	8	3-10
Dreams, abnormal/ bizarre/increased	≥1	-	✔	-	✔	>1	0-2	-	0.1-1.0	≥1	>2	-	-
Drowsiness/sedation/ somnolence	7.5-15.3	13-24	39-46	9-15	22	29-35	8-13	>2	12-18	3-8	>5	14	8-20
Dysarthria	0.1-1.0	-	✔	-	✔	0.1-1.0	0-2	-	>1	0.1-1.0	-	>1	>1
Dyskinesia	0.1-1.0	-	-	1.0-1.7	-	≤2	-	-	0.1-1.0	-	✔	>1	>1
Dystonia	0.1-1.0	-	-	0.8-1.0	5	2-3	-	>2	-	-	✔	4	4
Euphoria	<0.1	-	-	-	-	>1	-	-	<0.1	0.1-1.0	✔	-	-
Extrapyramidal symptoms	6	7-10	-	4-5	-	-	-	>2	✔	17-34	-	5	≤2
Fatigue	-	3-4	2	4-6	4	-	2-4	>2	-	>1	>5	-	-
Gait abnormal	>1	-	-	-	-	6	-	✔	0.1-1.0	-	✔	>1	>1
Hallucinations	≥1	-	✔	-	-	-	0-3	-	0.1-1.0	-	>2	-	-
Headache	31	12	7	-	-	-	13-18	>2	19	12-14	>2	-	3-13
Hostility	>1	-	-	-	-	-	-	-	✔	-	-	>1	>1
Hyperactivity	0.1-1.0	-	-	-	-	-	-	-	-	-	-	-	-
Hyperkinesia	0.1-1.0	-	1	-	-	-	-	-	0.1-1.0	-	-	>1	>1
Hyperreflexia	0.1-1.0	-	-	-	-	-	-	-	-	<0.1	-	<0.1	<0.1
Hypertonia	-	-	-	-	-	-	-	>2	-	-	✔	-	-
Hypesthesia	0.1-1.0	-	-	-	-	0.1-1.0	-	-	-	<0.1	-	>1	>1
Hypoaesthesia	-	-	-	-	-	-	-	-	-	-	>2	-	-
Hypokinesia	0.1-1.0	-	4	-	-	0.1-1.0	-	-	-	-	✔	>1	>1
Impaired concentration	-	-	-	-	-	-	-	-	-	-	✔	-	-
Impaired thinking	-	-	-	-	-	-	0-3	-	-	-	-	-	-
Incoordination	<0.1	-	-	-	-	0.1-1.0	-	-	0.1-1.0	-	-	>1	>1
Insomnia	20	6-15	2	-	8	12	-	-	✔	23-26	>2	<3	<3
Lethargy	-	-	1	1-3	-	-	-	-	-	-	-	-	-

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Adverse Event	Aripiprazole	Asenapine	Clozapine	Iloperidone	Lurasidone	Olanzapine	Olanzapine Pamoate	Paliperidone/ paliperidone palmitate	Quetiapine	Risperidone Oral	Risperidone Intramuscular	Ziprasidone Oral	Ziprasidone Intramuscular
Libido increased	0.1-1.0	-	✔	-	-	0.1-1.0	-	-	0.1-1.0	0.1-1.0	-	-	-
Libido loss of/decreased	0.1-1.0	-	✔	✔	-	-	-	-	<0.1	≥5	✔	-	-
Lightheadedness	11	-	-	-	-	-	-	-	-	-	-	-	-
Malaise	0.1-1.0	-	-	-	-	0.1-1.0	-	-	0.1-1.0	0.1-1.0	✔	-	-
Manic reaction	-	-	-	✔	-	-	-	-	-	-	✔	-	-
Migraine	0.1-1.0	-	-	-	-	0.1-1.0	-	-	0.1-1.0	<0.1	✔	-	-
Nervousness	>1	-	-	-	-	-	-	-	✔	≥1	✔	-	-
Neuroleptic malignant syndrome	✔	✔	✔	✔	✔	✔	-	✔	✔	✔	✔	✔	✔
Neuropathy	0.1-1.0	-	-	-	-	<0.1	-	-	-	-	-	>1	>1
Panic attack					✔		-						
Paranoid reaction	-	-	-	-	-	-	-	-	-	-	✔	-	-
Paresthesia	0.1-1.0	-	-	✔	-	>1	-	-	✔	0.1-1.0	✔	>1	≤2
Parkinsonism	-	-	-	0.2-0.3	11	-	-	>2	-	-	>5	-	-
Pseudoparkinsonism	-	-	<1	-	-	✔	-	-	-	✔	-	-	-
Psychosis	✔	-	✔	✔	-	-	-	-	0.1-1.0	-	✔	-	≤1
Restlessness	-	-	4	✔	3	-	1-3	-	-	-	-	-	-
Seizure	✔	✔	✔	✔	✔	✔	-	✔	✔	✔	✔	✔	✔
Sleep disorder					✔		0-2						
Speech slurred	-	-	1	-	-	-	-	-	-	-	-	-	-
Suicide attempt/thought	0.1-1.0	✔	-	✔	✔	>1	-	✔	0.1-1.0	✔	>2	✔	✔
Stupor	0.1-1.0	-	-	-	-	-	-	-	0.1-1.0	0.1-1.0	-	-	-
Syncope	-	-	6	✔	✔	-	-	✔	-	-	>2	-	-
Tardive dyskinesia	0.1-1.0	✔	✔	✔	✔	0.1-1.0	-	✔	0.1-1.0	✔	✔	>1	>1
Tardive dystonia	4-9	-	-	-	-	-	-	-	-	-	-	-	-
Tremor	-	-	6	2.5-3.1	-	4-6	0-3	>2	✔	-	>2	>1	>1
Vertigo	0.1-1.0	-	19	-	✔	0.1-1.0	-	-	0.1-1.0	0.1-1.0	✔	>1	>1
Weakness	-	-	1	-	-	-	-	-	-	-	-	-	-
Dermatological													
Acne	0.1-1.0	-	-	-	-	0.1-1.0	0-2	-	0.1-1.0	0.1-1.0	>2	-	-
Alopecia	0.1-1.0	-	-	-	-	0.1-1.0	-	-	-	0.1-1.0	✔	0.1-1.0	0.1-1.0
Angioedema	-	-	-	-	✔	-	-	-	-	-	-	-	-
Dermatitis	<0.1‡	-	✔	-	-	0.1-1.0	-	-	0.1-1.0	0.1-1.0	✔	0.1-2.0‡,§,‖	0.1-2.0‡,§,‖

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Adverse Event	Aripiprazole	Asenapine	Clozapine	Iloperidone	Lurasidone	Olanzapine	Olanzapine Pamoate	Paliperidone/ paliperidone palmitate	Quetiapine	Risperidone Oral	Risperidone Intramuscular	Ziprasidone Oral	Ziprasidone Intramuscular
Dry skin	-	-	-	-	-	-	-	-	-	-	>2	-	-
Ecchymosis	>1	-	✔	-	-	5	-	-	0.1-1.0	-	-	0.1-1.0	0.1-1.0
Eczema	0.1-1.0	-	✔	-	-	0.1-1.0	-	-	0.1-1.0	2-4	✔	0.1-1.0	0.1-1.0
Erythema	-	-	✔	-	-	-	-	-	-	-	✔	-	-
Increased sweating	-	-	-	-	-	-	-	-	-	-	✔	-	-
Maculopapular skin reactions	<0.1	-	-	-	-	0.1-1.0	-	-	✔	-	-	0.1-1.0	0.1-1.0
Pallor	0.1-1.0	-	-	-	-	0.1-1.0	-	-	-	<0.1	-	-	-
Photosensitivity	0.1-1.0	-	✔	-	-	0.1-1.0	-	-	0.1-1.0	>1	✔	>1	>1
Pruritus	0.1-1.0	-	-	-	✔	0.1-1.0	-	-	0.1-1.0	0.1-1.0	✔	-	-
Psoriasis	0.1-1.0	-	-	-	-	-	-	-	<0.1	<0.1	-	-	-
Rash	✔	-	2	2-3	✔	-	-	-	4	2-5	-	4	4
Rash, vesiculobullous	0.1-1.0	-	-	-	-	0.1-1.0	-	-	-	-	-	0.1-1.0	0.1-1.0
Seborrhea	0.1-1.0	-	-	-	-	0.1-1.0	-	-	0.1-1.0	≤1	✔	-	-
Urticaria	<0.1	-	✔	-	-	<0.1.0	-	-	-	<0.1	-	0.1-1.0	0.1-1.0
Gastrointestinal													
Abdominal discomfort/pain	✔	2	4	1-3	✔	-	3	>2	3	1-4	✔	>1	≤2
Abdominal distention/ enlargement	0.1-1.0	-	-	-	-	0.1-1.0	-	-	<0.1	<0.1	-	-	-
Anorexia	✔	-	1	-	-	-	-	-	>1	>1	✔	2	≤2
Appetite decreased	-	-	-	-	✔	-	-	-	-	-	-	-	-
Appetite increased	0.1-1.0	2-4	✔	✔	-	3-6	1-6	-	0.1-1.0	0.1-1.0	✔	-	-
Colitis	-	-	-	-	-	-	-	-	-	-	✔	-	-
Constipation	13	5	14	-	-	9-11	-	-	6-9	7-13	>5	9	≤2
Diarrhea	✔	-	2	5-7	✔	-	2-7	-	✔	≥5	>2	5	≤3
Diverticulitis	-	-	-	-	-	-	-	-	-	<0.1	-	-	-
Dry mouth	✔	2-3	6	8-10	-	9-22	2-6	>2	7-12	≥5	>5	4	≤1
Dyspepsia	15	4	14	-	8	7-11	-	>2	5-6	5-10	>5	8	1-3
Dysphagia	0.1-1.0	-	✔	-	✔	0.1-1.0	-	✔	0.1-1.0	0.1-1.0	✔	0.1-1.0	0.1-1.0
Eructation	0.1-1.0	-	✔	-	-	0.1-1.0	-	-	-	<0.1	-	-	-
Esophageal ulcer/esophagitis	<0.1	-	-	-	-	<0.1	-	-	-	<0.1	-	-	-
Fecal impaction	0.1-1.0	-	✔	-	-	0.1-1.0	-	-	-	-	-	<0.1	<0.1
Flatulence	0.1-1.0	-	-	-	-	0.1-1.0	1-2	-	0.1-1.0	0.1-1.0	✔	-	-

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Gastric ulcer	-	-	-	-	-	-	-	-	-	-	✔	-	-
Gastritis	0.1-1.0	-	-	-	✔	0.1-1.0	-	-	0.1-1.0	0.1-1.0	✔	-	-
Gastroenteritis	0.1-1.0	-	✔	-	-	0.1-1.0	-	-	0.1-1.0	<0.1	-	-	-
Gastroesophageal reflux	0.1-1.0	-	4	-	-	-	-	-	0.1-1.0	<0.1	✔	-	-
Gingivitis	0.1-1.0	-	-	-	-	0.1-1.0	-	-	0.1-1.0	<0.1	✔	-	-
Glossitis	<0.1	-	-	-	-	<0.1	-	-	<0.1	-	-	-	-
Gum hemorrhage	<0.1	-	-	-	-	-	-	-	0.1-1.0	-	-	<0.1	<0.1
Hematemesis	<0.1	-	✔	-	-	-	-	-	<0.1	<0.1	-	<0.1	<0.1
Hemorrhoids	0.1-1.0	-	-	-	-	-	-	-	0.1-1.0	0.1-1.0	✔	-	-
Incontinence, fecal	0.1-1.0	-	-	-	-	0.1-1.0	-	-	0.1-1.0	<0.1	✔	-	-
Intestinal obstruction	0.1-1.0	-	✔	-	-	<0.1	-	-	<0.1	✔	-	-	-
Irritable bowel syndrome	-	-	-	-	-	-	-	-	-	-	✔	-	-
Melena	<0.1	-	-	-	-	0.1-1.0	-	-	0.1-1.0	0.1-1.0	✔	<0.1	<0.1
Mouth ulceration	0.1-1.0	-	-	-	-	0.1-1.0	-	-	0.1-1.0	-	-	-	-
Nausea	16	-	5	7-10	12	0.1-1.0	4-5	>2	✔	4-6	✔	10	4-12
Paralytic ileus	-	-	-	-	-	<0.1	-	-	-	-	-	-	-
Polydipsia	0.1-1.0	-	-	-	-	>1	-	-	0.1-1.0	>1	-	0.1-1.0	≤2
Rectal hemorrhage	0.1-1.0	-	✔	-	-	0.1-1.0	-	-	0.1-1.0	-	✔	<2	<2
Salivation	3	2	31	-	2	>1	-	>2	0.1-1.0	≤2	>2	✔	✔
Stomatitis	0.1-1.0	-	-	-	-	0.1-1.0	-	-	0.1-1.0	0.1-1.0	✔	0.1-1.0	0.1-1.0
Taste altered	0.1-1.0	3	-	-	-	-	-	-	0.1-1.0	-	-	-	-
Tongue discoloration	-	-	-	-	-	<0.1	-	-	-	<0.1	-	-	-
Tongue swollen	-	-	-	-	-	-	-	✔	-	-	-	-	-
Tooth caries/ toothache	0.1-1.0	-	-	-	-	0.1-1.0	3-4	-	0.1-1.0	-	>2	-	-
Tooth infection	-	-	-	-	-	-	0-4	-	-	-	-	-	-
Vomiting	11	5	3	-	8	4	1-6	-	✔	5-7	✔	>1	<3
Weight gain	3-8¶	3-5	4	1-9	-	5-6	5-7	-	2	18	>5	10¶	10¶
Weight loss	>1	-	✔	-	-	-	-	-	0.1-1.0	0.1-1.0	>2	-	-
Genitourinary													
Albuminuria	0.1-1.0	-	-	-	-	<0.1	-	-	-	-	-	0.1-1.0	0.1-1.0
Amenorrhea	0.1-1.0	-	-	✔	✔	>1	-	-	0.1-1.0	0.1-1.0	-	0.1-1.0	0.1-1.0
Breast enlargement	-	-	-	-	✔	-	-	-	-	-	-	-	-
Breast pain	-	-	-	✔	✔	-	-	-	-	-	✔	-	-
Dysmenorrhea	-	-	✔	-	✔	-	-	-	0.1-1.0	0.1-1.0	✔	-	≤2

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Dysuria	-	-	-	-	✔	-	-	-	-	-	-	-	-
Erectile dysfunction	-	-	-	-	✔	-	-	-	-	-	-	-	-
Ejaculation disorders	0.1-1.0	-	1	2	-	0.1-1.0	-	-	0.1-1.0	≥5	-	0.1-1.0	0.1-1.0
Galactorrhea	-	-	-	-	✔	0.1-1.0	-	-	0.1-1.0	0.1-1.0	-	0.1-1.0	0.1-1.0
Glycosuria	<0.1	-	-	-	-	0.1-1.0	-	-	<0.1	-	✔	0.1-1.0	0.1-1.0
Gynecomastia	0.1-1.0	-	-	✔	-	<0.1	-	-	<0.1	<0.1	-	<0.1	<0.1
Hematuria	0.1-1.0	-	-	-	-	>1	-	-	-	0.1-1.0	✔	0.1-1.0	0.1-1.0
Impotence	0.1-1.0	-	✔	-	-	0.1-1.0	-	-	0.1-1.0	≥5	✔	0.1-1.0	0.1-1.0
Incontinence, urinary	>1	-	-	✔	-	2	-	-	0.1-1.0	0.1-1.0	✔	-	-
Mastalgia	0.1-1.0	-	✔	-	-	0.1-1.0	-	-	-	0.1-1.0	-	-	-
Menorrhagia	<0.1	-	-	✔	-	0.1-1.0	-	-	-	≥5	-	0.1-1.0	0.1-1.0
Metrorrhagia	-	-	-	-	-	>1	-	-	0.1-1.0	-	-	0.1-1.0	0.1-1.0
Nocturia	<0.1	-	-	-	-	-	-	-	<0.1	-	-	<0.1	<0.1
Polyuria	<0.1	-	-	-	-	0.1-1.0	-	-	<0.1	>1	-	0.1-1.0	0.1-1.0
Priapism	<0.1	-	✔	✔	-	0.1-1.0	-	✔	-	✔	✔	✔	≤1
Renal failure	-	-	-	-	✔	-	-	-	-	-	-	-	-
Urinary frequency/urgency increased	0.1-1.0	-	1	-	-	0.1-1.0	-	-	0.1-1.0	-	✔	-	-
Urinary retention	0.1-1.0	-	1	✔	-	0.1-1.0	-	-	0.1-1.0	>1	✔	0.1-1.0	0.1-1.0
Vaginal hemorrhage	0.1-1.0	-	-	-	-	0.1-1.0	-	-	0.1-1.0	0.1-1.0	-	<0.1	<0.1
Vaginal discharge	-	-	-	-	-	-	0-4	-	-	-	-	-	-
Vaginitis	-	-	-	-	-	-	-	-	-	-	✔	-	-
Hematologic													
Agranulocytosis	-	✔	1	✔	-	-	-	-	✔	-	-	-	-
Anemia	>1	-	✔	✔	✔	0.1-1.0	-	-	0.1-1.0	0.1-1.0	✔	0.1-1.0	0.1-1.0
Anemia, hypochromic	0.1-1.0	-	-	-	-	-	-	-	0.1-1.0	0.1-1.0	-	<0.1	<0.1
Edema	0.1-1.0	-	✔	-	-	-	-	✔	-	0.1-1.0	-	-	-
Edema, facial	0.1-1.0	-	-	-	-	0.1-1.0	-	-	0.1-1.0	-	-	>1	>1
Edema, peripheral	2	-	-	-	-	3	-	-	>1	-	>2	0.1-1.0	0.1-1.0
Eosinophilia	<0.1	-	1	-	-	-	-	-	0.1-1.0	-	-	0.1-1.0	0.1-1.0
Hemorrhage	0.1-1.0	-	-	-	-	0.1-1.0	-	-	-	<0.1	-	-	-
Hypoproteinemia	-	-	-	-	-	<0.1	-	-	-	<0.1	-	<0.1	<0.1
Leukocytosis	0.1-1.0	-	✔	-	-	0.1-1.0	-	-	0.1-1.0	<0.1	✔	0.1-1.0	0.1-1.0
Leukopenia	0.1-1.0	✔	3	✔	✔	>1	-	-	>1	<0.1.0	✔	0.1-1.0	0.1-1.0

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Lymphadenopathy	0.1-1.0	-	-	-	-	0.1-1.0	-	-	0.1-1.0	-	✔	0.1-1.0	0.1-1.0
Neutropenia	-	-	-	✔	✔	-	-	-	✔	-	-	-	-
Pancytopenia	-	-	-	-	-	-	-	-	-	-	-	<0.1	<0.1
Thrombocythemia	<0.1	-	✔	-	-	0.1-1.0	-	-	-	-	-	<0.1	<0.1
Thrombocytopenia	<0.1	-	✔	-	-	0.1-1.0	-	✔	<0.1	✔	✔	<0.1	<0.1
Laboratory Test Abnormalities													
Alanine aminotransferase/aspartate aminotransferase elevation	0.1-1.0	-	-	-	-	-	✔	-	✔	0.1-1.0	✔	0.1-1.0	0.1-1.0
Alkaline phosphatase increased	0.1-1.0	-	-	-	-	0.1-1.0	✔	-	0.1-1.0	-	✔	0.1-1.0	0.1-1.0
Cholecystitis	0.1-1.0	-	-	-	-	-	-	-	-	<0.1	-	-	-
Cholelithiasis	0.1-1.0	-	✔	-	-	-	-	-	-	<0.1	-	-	-
Creatine phosphokinase elevated	>1	-	✔	-	✔	-	-	-	-	-	-	0.1-1.0	0.1-1.0
Creatinine increased	0.1-1.0	-	-	-	-	-	-	-	0.1-1.0	0.1-1.0	✔	<0.1	<0.1
Hepatitis	<0.1	-	✔	-	-	0.1-1.0	-	-	-	<0.1	✔	<0.1	<0.1
Hypercholesterolemia	0.1-1.0	-	-	-	-	0.1-1.0	✔	-	✔	-	✔	0.1-1.0	0.1-1.0
Hyperglycemia	0.1-1.0	✔	✔	✔	-	0.1-1.0	-	>2	0.1-1.0	✔	✔	0.1-1.0	0.1-1.0
Hyperkalemia	0.1-1.0	-	-	-	-	<0.1	-	-	-	-	-	<0.1	<0.1
Hyperlipemia	0.1-1.0	-	-	-	-	0.1-1.0	-	-	0.1-1.0	-	✔	<0.1	<0.1
Hyperprolactinemia	-	-	-	-	-	✔	-	✔	✔	✔	✔	✔	✔
Hyperthyroidism	<0.1	-	-	-	-	-	-	-	<0.1	-	-	<0.1	<0.1
Hypertonia	✔	-	-	-	-	3	-	-	>1	-	-	3	3
Hyperuricemia	0.1-1.0	-	✔	-	-	-	-	-	-	-	✔	<0.1	<0.1
Hypoglycemia	0.1-1.0	-	-	-	-	0.1-1.0	-	-	0.1-1.0	<0.1	-	<0.1	<0.1
Hypokalemia	0.1-1.0	-	-	-	-	0.1-1.0	-	-	<0.1	<0.1	✔	0.1-1.0	0.1-1.0
Hyponatremia	0.1-1.0	-	✔	-	-	0.1-1.0	-	-	-	0.1-1.0	✔	<0.1	<0.1
Hypothyroidism	0.1-1.0	-	-	✔	-	-	-	-	0.1-1.0	-	-	<0.1	<0.1
Liver function impaired	-	-	1	-	-	-	1-4	-	-	-	✔	-	-
Renal failure, acute	0.1-1.0	-	-	-	-	-	-	-	<0.1	-	-	-	-
Musculoskeletal													
Arthralgia/joint pain	0.1-1.0	3	✔	3	-	5	3	-	0.1-1.0	2-3	✔	✔	✔
Arthritis	0.1-1.0	-	-	-	-	0.1-1.0	-	-	0.1-1.0	<0.1	✔	-	-

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Adverse Event	Aripiprazole	Asenapine	Clozapine	Iloperidone	Lurasidone	Olanzapine	Olanzapine Pamoate	Paliperidone/ paliperidone palmitate	Quetiapine	Risperidone Oral	Risperidone Intramuscular	Ziprasidone Oral	Ziprasidone Intramuscular
Bone pain	0.1-1.0	-	-	-	-	<0.1	-	-	0.1-1.0	-	✔	-	-
Bursitis	0.1-1.0	-	-	-	-	0.1-1.0	-	-	-	<0.1	-	-	-
Leg cramps	-	-	-	-	-	-	-	-	-	-	✔	-	-
Injection site pain	-	-	-	-	-	-	2-3	-	-	-	-	-	-
Injection site reactions	-	-	-	-	-	-	3.6	-	-	-	✔	-	-
Muscle rigidity	-	-	✔	1-3	-	-	-	-	-	-	✔	-	-
Muscle spasms	-	-	-	-	-	-	1-3	-	-	-	-	-	-
Muscle stiffness	-	-	-	-	-	-	1-4	-	-	-	-	-	-
Muscle weakness	0.1-1.0	-	1	-	-	-	-	-	0.1-1.0	-	✔	-	-
Myalgia	4	-	1	-	-	-	-	-	✔	0.1-1.0	>2	1	1
Myoclonus	0.1-1.0	-	1	-	-	-	-	-	0.1-1.0	-	-	<0.1	<0.1
Myopathy	0.1-1.0	-	-	-	-	<0.1	-	-	-	-	-	<0.1	<0.1
Opisthotonos	-	-	-	-	-	-	-	-	-	-	-	<0.1	<0.1
Rhabdomyolysis	-	-	-	-	✔	-	-	-	-	-	-	-	-
Rigidity	-	-	5	-	-	-	-	-	-	0.1-1.0	-	-	-
Tendinitis	-	-	-	-	-	-	-	-	-	-	✔	-	-
Tetany	-	-	-	-	-	-	-	-	-	-	✔	-	-
Torticollis	-	-	-	-	-	-	-	-	-	<0.1	✔	<0.1	<0.1
Respiratory													
Apnea	<0.1	-	-	-	-	0.1-1.0	-	-	-	✔	✔	-	-
Aspiration	-	-	✔	-	-	-	-	-	-	<0.1	-	-	-
Asthma	≥1	-	-	✔	-	0.1-1.0	-	-	0.1-1.0	<0.1	-	-	-
Cough, increased	3	-	✔	-	-	6	3-9	>2	>1	3	>2	3	3
Dyspnea	>1	-	1	2	-	>1	-	✔	>1	≤1	-	>1	>1
Epistaxis	0.1-1.0	-	✔	✔	-	0.1-1.0	-	-	0.1-1.0	0.1-1.0	-	0.1-1.0	0.1-1.0
Hemoptysis	<0.1	-	-	-	-	0.1-1.0	-	-	-	-	✔	<0.1	<0.1
Hyperventilation	-	-	✔	-	-	-	-	-	<0.1	0.1-1.0	-	-	-
Nasal congestion	-	-	1	5-8	-	-	1-7	-	-	-	-	-	-
Pharyngitis	4	-	-	3-4	-	4	-	-	>1	2-3	-	-	-
Pharyngolaryngeal pain	-	-	-	-	-	-	2-3	-	-	-	-	-	-
Pneumonia	>1	-	✔	-	-	0.1-1.0	-	-	0.1-1.0	0.1-1.0	✔	0.1-1.0	0.1-1
Pulmonary edema/embolus	-	-	✔	-	-	-	-	✔	-	-	✔	-	-
Rhinitis	4	-	-	✔	-	7	-	-	3	8-10	>2	4	≤1
Sinusitis	-	-	-	✔	-	-	-	-	-	-	>2	-	-

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Adverse Event	Aripiprazole	Asenapine	Clozapine	Iloperidone	Lurasidone	Olanzapine	Olanzapine Pamoate	Paliperidone/ paliperidone palmitate	Quetiapine	Risperidone Oral	Risperidone Intramuscular	Ziprasidone Oral	Ziprasidone Intramuscular
Stridor	-	-	-	-	-	-	-	-	-	-	✔	-	-
Upper respiratory tract infection	-	-	-	2-3	-	-	1-4	-	✔	-	>2	-	-
Other													
Accidental injury	6	-	-	-	-	12	-	-	✔	-	-	4	4
Allergic reaction	✔	-	✔	-	-	✔	-	✔	-	<0.1	✔	-	-
Anaphylactoid reactions	-	-	-	-	-	✔	-	✔	-	✔	✔	-	-
Back pain	✔	-	1	-	4	5	3-5	>2	2	≤2	✔	-	≤1
Blepharitis	0.1-1.0	-	-	✔	-	0.1-1.0	-	-	0.1-1.0	<0.1	-	0.1-1.0	0.1-1.0
Cataracts	0.1-1.0	-	-	-	-	0.1-1.0	-	-	✔	-	-	0.1-1.0	0.1-1.0
Chest pain	>1	-	1	-	-	3	-	-	✔	2-3	✔	-	-
Chills	0.1-1.0	-	✔	-	-	0.1-1.0	-	-	0.1-1.0	-	-	>1	>1
Choreoathetosis	-	-	-	-	-	-	-	-	<0.1	<0.1	-	>1	>1
Cogwheel rigidity	0.1-1.0	-	-	-	-	0.1-1.0	-	-	-	-	-	>1	≤1
Conjunctivitis	>1	-	✔	✔	-	>1	-	-	0.1-1.0	-	✔	0.1-1.0	0.1-1.0
Death, sudden	-	-	-	-	✔	-	-	-	-	-	-	-	-
Dehydration	≥1	-	-	-	-	0.1-1.0	-	-	0.1-1.0	<0.1	✔	0.1-1.0	0.1-1.0
Diabetes	✔	✔	✔	✔	-	✔	-	✔	✔	✔	✔	✔	✔
Diaphoresis	>1	-	6	-	-	>1	-	-	>1	0.1-1.0	-	-	≤2
Diplopia	<0.1	-	-	-	-	0.1-1.0	-	-	-	<0.1	-	>1	>1
Dry eyes	0.1-1.0	-	-	✔	-	0.1-1.0	-	-	0.1-1.0	-	-	0.1-1.0	0.1-1.0
Ear disorder	-	-	-	✔	-	-	-	-	-	-	>2	-	-
Ear pain	-	-	-	-	-	-	1-4	-	-	-	-	-	-
Edema, tongue	0.1-1.0	-	-	-	-	0.1-1.0	-	-	0.1-1.0	<0.1	-	0.1-1.0	0.1-1.0
Eye hemorrhage	0.1-1.0	-	-	-	-	0.1-1.0	-	-	-	-	-	<0.1	<0.1
Eye pain	-	-	-	-	-	-	-	-	-	-	✔	-	-
Fever	≥1	-	5	-	-	6	-	-	2	2-3	>2	>1	>1
Flu syndrome	>1	-	-	-	-	>1	-	-	>1	0.1-1.0	-	>1	≤1
Glaucoma	-	-	✔#	-	-	<0.1	-	-	<0.1	-	-	-	-
Gout	<0.1	-	-	-	-	<0.1	-	-	<0.1	-	-	<0.1	<0.1
Hypertonia	✔	-	-	-	-	3	-	-	>1	-	-	3	3
Hypotonia	<0.1	-	-	-	-	0.1-1.0	-	-	-	<0.1	-	>1	>1
Moniliasis	-	-	-	-	-	0.1-1.0	-	-	0.1-1.0	-	-	-	-
Mydriasis	-	-	-	-	-	<0.1	-	-	-	-	-	-	-

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Adverse Event	Aripiprazole	Asenapine	Clozapine	Iloperidone	Lurasidone	Olanzapine	Olanzapine Pamoate	Paliperidone/ paliperidone palmitate	Quetiapine	Risperidone Oral	Risperidone Intramuscular	Ziprasidone Oral	Ziprasidone Intramuscular
Nasopharyngitis	-	-	-	-	-	-	1-6	-	-	-	-	-	-
Neck pain/rigidity	>1	-	1	-	-	0.1-1.0	-	-	0.1-1.0	-	-	-	-
Obesity	-	-	-	-	-	-	-	-	-	-	✔	-	-
Oculogyric crisis	<0.1	-	-	-	-	-	-	-	-	-	-	>1	>1
Pain	≥1	2	-	-	-	0.1-1.0	0-3	>2	0.1-1.0	-	>2	-	-
Parotid swelling	-	-	✔	-	-	-	-	-	-	-	-	-	-
Photophobia	<0.1	-	-	-	-	-	-	-	-	<0.1	-	0.1-1.0	0.1-1.0
Pyrexia	-	-	-	-	-	-	0-2	-	-	-	-	-	-
Tinnitus	0.1-1.0	-	-	✔	-	0.1-1.0	-	-	0.1-1.0	-	-	0.1-1.0	0.1-1.0
Viral infection	-	-	-	-	-	-	0-2	-	-	-	-	-	-
Vision abnormal	-	-	-	-	-	-	-	-	0.1-1.0	1-2	>2	3	3
Vision blurred	3	-	-	1-3	✔	-	-	>2	-	-	-	-	-
Visual disturbances	-	-	5	-	-	-	-	-	-	-	-	-	-
Withdrawal syndrome	-	-	-	-	-	1	-	-	-	<0.1	-	>1	>1

✔ Percent not specified.
- Event not reported or incidence <1%.
*Includes orthostatic.
†Includes petit and grand mal seizures.
‡Exfoliative dermatitis included.
§Contact dermatitis included.
‖Fungal dermatitis.
¶Gained at least 7% body weight.
#Narrow-angle glaucoma.

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Contraindications/Precautions

Atypical antipsychotics have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk.[6-11,13-19,21-22] These metabolic changes include weight gain, hyperglycemia, and hyperlipidemia. While all the drugs in the class exhibit some metabolic changes, specific risk profile varies with each individual drug. Recently, the prescribing information for olanzapine, quetiapine, risperidone, paliperidone, iloperidone, aripiprazole, and lurasidone has been adjusted to include new warnings for metabolic adverse events. Olanzapine is noted to be associated with greater weight gain and hyperglycemia than the other SGAs.[13] In addition, the prescribing information for quetiapine has recently been adjusted to include warnings about the risk of QT prolongation and hypothyroidism. While quetiapine has not been associated with a persistent increase in QT intervals, this effect was not systematically evaluated in a thorough QT study.[15] Hypersensitivity reactions, including anaphylaxis and angioedema, have been observed in patients treated with asenapine. Consequently, asenapine is contraindicated in patients with a known hypersensitivity to the product.[7]

Several black box warnings have been designated to atypical antipsychotics; some affecting the class as a whole, while others applying to individual agents.

The treatment of elderly patients with behavioral disturbances, specifically dementia, with the SGAs is not approved by the Food and Drug Administration (FDA) and the use of these agents in this patient population has been associated with an increased risk of death. For this reason the FDA issued an alert and asked the manufacturers to include a black box warning (outlined below) on April 11, 2005.[23] In response to the FDA's concerns, in 2005 and 2006 the black box warning was added to product labeling for the following agents: aripiprazole, clozapine, olanzapine, quetiapine, risperidone and ziprasidone. Since then, it has been added to the product labeling for newly-approved agents (asenapine, iloperidone, lurasidone, paliperidone, paliperidone palmitate, and quetiapine extended-release).[6-11,13-19,21-22]

Aripiprazole should be used with caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure, or conduction abnormalities), cerebrovascular disease, or conditions that would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications). Additionally, the risk of suicidality in children and adolescents has led to a black box warning (outlined below) being assigned to aripiprazole, quetiapine, quetiapine XR, and olanzapine (when used in combination with fluoxetine).[6,13,15-16] Data has shown that the use of antidepressant drugs (selective serotonin- reuptake inhibitors and others) in children and adolescents with major depressive disorder, obsessive-compulsive disorder or other psychiatric disorders has resulted in a greater risk of adverse events representing suicidal thinking or behavior during the first few months of treatment.[280] Although olanzapine (in combination with fluoxetine) is not FDA approved for use in pediatric patients, this warning is important to note due to potential off-label use. Olanzapine pamoate has been associated with a post-injection delirium/sedation syndrome, necessitating close observation of patients for at least 3 hours post administration.[13]

Clozapine, the first SGA that was approved by the FDA, has also been associated with serious adverse events and carries a number of black box warnings which are outlined below. The association of clozapine with agranulocytosis is one of the boxed warnings and requires routine monitoring which has hindered the use of this agent. In May 2005, following recommendations issued in June 2003 by the FDA Psychopharmacologic Drugs Advisory Committee, product labeling for clozapine was changed to reflect a decrease in the required monitoring interval from every two weeks to every four weeks; this change applies only to patients who have had normal white blood cell counts (WBCs), (defined as ≥3,500/mm^3) and normal absolute neutrophil counts (ANCs), (defined as ≥2,000/mm^3) for one year.[8-9, 281,] At that time, the "warnings" section of the clozapine package insert was reorganized and this section of the agranulocytosis warnings was retained as a black box warning. As part of this revision a new table was added, which appears below; this table and the figure below, also from the package insert, outline the FDA-approved algorithms for monitoring WBC and ANC in various circumstances.[8-9] In addition to the warning for agranulocytosis, clozapine also has black box warnings due to its association with seizures, myocarditis and other adverse cardiovascular and respiratory effects.[8-9]

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Ziprasidone is contraindicated in patients with a known history of QT prolongation (including congenital long QT syndrome), recent acute myocardial infarction or uncompensated heart failure.[22] Lurasidone is contraindicated in combination with a strong CYP3A4 inhibitor (e.g. ketoconazole) and inducer (e.g. rifampin).[11]

Black Box Warning for the Use of Antipsychotics in Elderly Patients with Behavioral Disturbances[6-11,13-19,21-22]

WARNING
Increased mortality in elderly patients with dementia-related psychosis: Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear.

Black Box Warning Regarding the Risk of Suicidality in Children and Adolescents Treated with Aripiprazole[6]

WARNING
Suicidality and antidepressant drugs: Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder and other psychiatric disorders. Anyone considering the use of adjunctive aripiprazole or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared with placebo in adults older than 24 years of age; there was a reduction in risk with antidepressants compared with placebo in adults 65 years of age and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Aripiprazole is not approved for use in children with depression.

Black Box Warnings for Clozapine[8-9]

WARNING
Agranulocytosis: Because of a significant risk of agranulocytosis, a potentially life-threatening adverse reaction, reserve clozapine for use in the treatment of severely ill patients with schizophrenia who fail to show an acceptable response to adequate courses of standard antipsychotic drug treatment or for use in reducing the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder who are judged to be at risk of reexperiencing suicidal behavior. Patients being treated with clozapine must have a baseline white blood cell (WBC) count and absolute neutrophil count (ANC) before initiation of treatment, as well as regular WBC counts and ANCs during treatment and for at least 4 weeks after discontinuation of treatment. Clozapine is available only through a distribution system that ensures monitoring of WBC counts and ANCs according to the following schedule prior to delivery of the next supply of medication.

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WARNING
Seizures: Seizures have been associated with the use of clozapine. Dose appears to be an important predictor of seizure, with a greater likelihood at higher clozapine doses. Use caution when administering clozapine to patients who have a history of seizures or other predisposing factors. Advise patients not to engage in any activity in which sudden loss of consciousness could cause serious risk to themselves or others. **Myocarditis:** Analyses of postmarketing safety databases suggest that clozapine is associated with an increased risk of fatal myocarditis, especially during, but not limited to, the first month of therapy. In patients in whom myocarditis is suspected, promptly discontinue clozapine treatment. **Other adverse cardiovascular and respiratory reactions:** Orthostatic hypotension, with or without syncope, can occur with clozapine treatment. Rarely, collapse can be profound and be accompanied by respiratory and/or cardiac arrest. Orthostatic hypotension is more likely to occur during initial titration in association with rapid dose escalation. In patients who have had even a brief interval off clozapine (2 or more days since the last dose), start treatment with 12.5 mg once or twice daily. Because collapse, respiratory arrest, and cardiac arrest during initial treatment have occurred in patients who were being administered benzodiazepines or other psychotropic drugs, caution is advised when clozapine is initiated in patients taking a benzodiazepine or any other psychotropic drug. (See group monograph.) Antipsychotic Agents.

Frequency of Monitoring Based on Stage of Clozapine Therapy or Results from White Blood Cell Count and Absolute Neutrophil Count Monitoring Tests[8-9]

Situation	Hematological Values for Monitoring	Frequency of White Blood Cell and Absolute Neutrophil Count Monitoring
Initiation of therapy	WBC ≥3,500/mm^3 ANC ≥2,000/mm^3 Do not initiate in patients with history of myeloproliferative disorder or clozapine-induced agranulocytosis or granulocytopenia	Weekly for 6 months
6 to 12 months of therapy	All results for WBC ≥3,500/mm^3 and ANC ≥2,000/mm^3	Every 2 weeks for 6 months
12 months of therapy	All results for WBC ≥3,500/mm^3 and ANC ≥2,000/mm^3	Every 4 weeks ad infinitum
Immature forms present	N/A	Repeat WBC and ANC
Discontinuation of therapy	N/A	Weekly for at least 4 weeks from day of discontinuation or until WBC ≥3,500/mm^3 and ANC >2,000/mm^3
Substantial drop in WBC or ANC	Single drop or cumulative drop within 3 weeks of WBC ≥3,000/mm^3 and ANC ≥1,500/mm^3	1. Repeat WBC and ANC 2. If repeat values are 3,000/mm^3 ≤ WBC ≤3,500/mm^3 and ANC >2,000/mm^3, then monitor twice weekly
Mild leukopenia Mild granulocytopenia	3,500/mm^3 > WBC ≥3,000/mm^3 and/or 2,000/mm^3 > ANC ≥1,500/mm^3	Twice weekly until WBC >3,500/mm^3 and ANC >2,000/mm^3, then return to previous monitoring frequency

Situation	Hematological Values for Monitoring	Frequency of White Blood Cell and Absolute Neutrophil Count Monitoring
Moderate leukopenia Moderate granulocytopenia	3,000/mm^3 > WBC ≥2,000/mm^3 and/or 1,500/mm^3 > ANC ≥1,000/mm^3	1. Interrupt therapy 2. Daily until WBC >3,000/mm^3 and ANC >1,500/mm^3 3. Twice weekly until WBC >3,500/mm^3 and ANC >2,000/mm^3 4. May rechallenge when WBC >3,500/mm^3 and ANC >2,000/mm^3 5. If rechallenged, monitor weekly for 1 year before returning to the usual monitoring schedule of every 2 weeks for 6 months and then every 4 weeks ad infinitum
Severe leukopenia Severe granulocytopenia	WBC <2,000/mm^3 and/or ANC <1,000/mm^3	1. Discontinue treatment and do not rechallenge patient 2. Monitor until normal and for at least 4 weeks from day of discontinuation as follows: • Daily until WBC >3,000/mm^3 and ANC >1,500/mm^3 • Twice weekly until WBC >3,500/mm^3 and ANC >2,000/mm^3 • Weekly after WBC >3,500/mm^3
Agranulocytosis	ANC ≤500/mm^3	1. Discontinue treatment and do not rechallenge patient 2. Monitor until normal and for at least 4 weeks from day of discontinuation as follows: • Daily until WBC >3,000/mm^3 and ANC >1,500/mm^3 • Twice weekly until WBC >3,500/mm^3 and ANC >2,000/mm^3 • Weekly after WBC >3,500/mm^3

ANC=absolute neutrophil count, N/A=not applicable, WBC=white blood cell count

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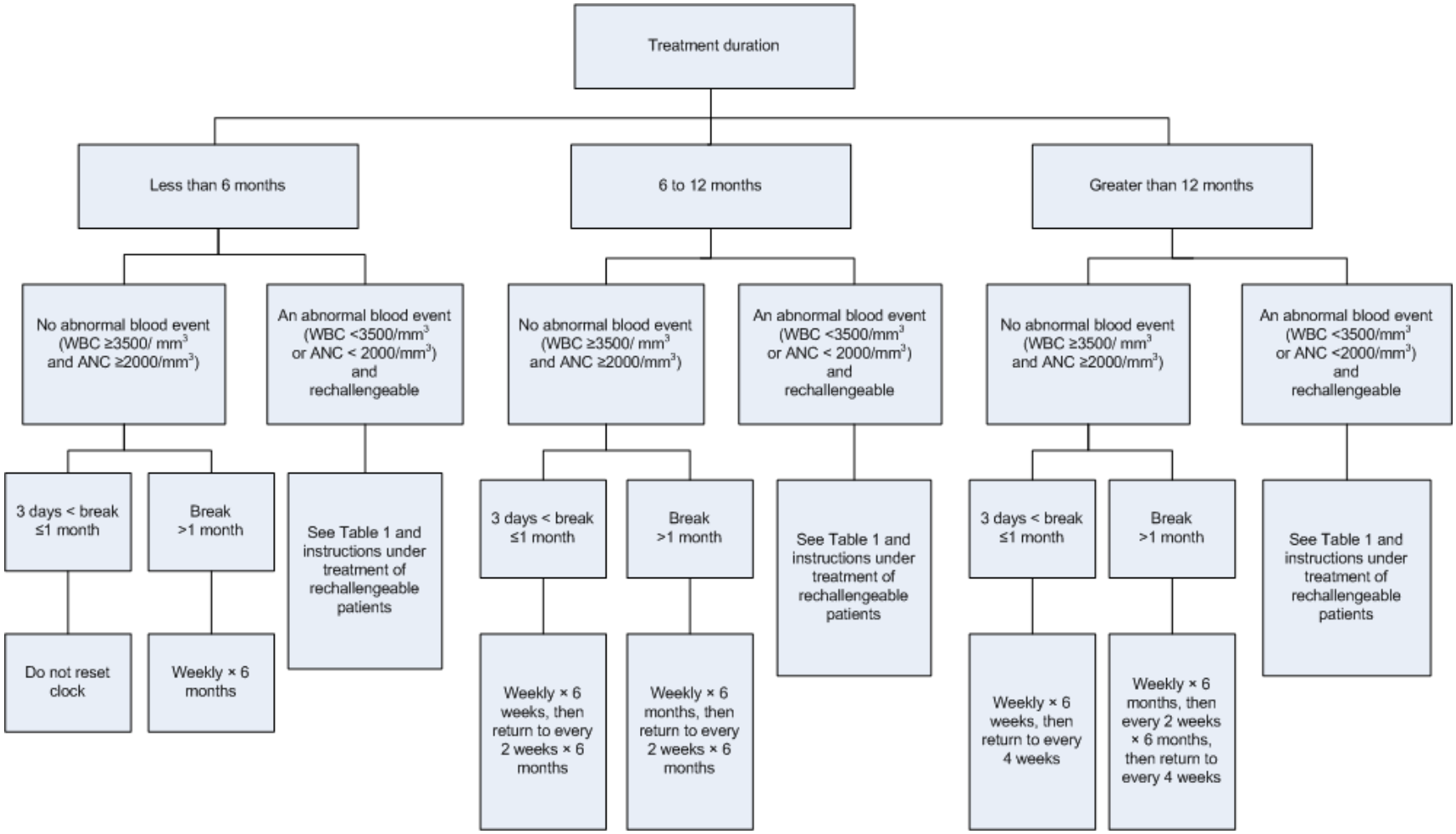
Resuming Monitoring Frequency for Clozapine Treatment after an Interruption in Therapy[8-9]



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Black Box Warning Regarding the Risk of Suicidality in Children and Adolescents Treated with Quetiapine[15-16]

WARNING
Suicidality and antidepressant drugs: Antidepressants increased the risk compared with placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of quetiapine or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared with placebo in adults older than 24 years of age; there was a reduction in risk with antidepressants compared with placebo in adults 65 years of age and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Monitor patients of all ages who are started on antidepressant therapy appropriately and observe them closely for clinical worsening, suicidality, or unusual changes in behavior. Advise families and caregivers of the need for close observation and communication with the prescriber. Quetiapine is not approved for use in children.

Black Box Warning Regarding the Risk of Suicidality in Children and Adolescents Treated with Olanzapine/fluoxetine[282]

WARNING
Suicidality and antidepressant drugs: Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of Symbyax or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Symbyax is not approved for use in pediatric patients.

Black Box Warning Regarding the Risk of Suicidality in Children and Adolescents Treated with Olanzapine pamoate[14]

WARNING
Post-Injection Delirium/Sedation Syndrome: Adverse events with signs and symptoms consistent with olanzapine overdose, in particular, sedation (including coma) and/or delirium, have been reported following injections of Zyprexa Relprevv. Zyprexa Relprevv must be administered in a registered healthcare facility with ready access to emergency response services. After each injection, patients must be observed at the healthcare facility by a healthcare professional for at least 3 hours. Because of this risk, Zyprexa Relprevv is available only through a restricted distribution program called Zyprexa Relprevv Patient Care Program and requires prescriber, healthcare facility, patient, and pharmacy enrollment.

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Drug Interactions

Table 12. Significant Drug-Drug Interactions[25]

Drug(s)	Interacting Medication or Disease	Mechanism
Aripiprazole, iloperidone, quetiapine, risperidone	Azole antifungals	Inhibition of metabolism through CYP3A4 by azole antifungals may result in increased concentrations. When the azole antifungal is discontinued, adjust the dose.
Aripiprazole, quetiapine, risperidone	Carbamazepine	Induction of metabolism through CYP3A4 by carbamazepine may result in decreased concentrations, decreasing the pharmacologic effects. When carbamazepine is discontinued, adjust the dose.
Clozapine, iloperidone, risperidone	Serotonin-reuptake inhibitors	Serum levels may be elevated, resulting in increased pharmacologic and toxic effects. Monitor serum levels, observe clinical response and adjust the dose as needed.
Aripiprazole	Quinidine	Inhibition of aripiprazole metabolism through CYP2D6 by quinidine may result in increased aripiprazole concentrations, increasing the pharmacologic and adverse effects. When quinidine is discontinued, adjust the dose of aripiprazole.
Clozapine	Barbiturates	Induction of clozapine metabolism by barbiturates may result in decreased clozapine concentrations, decreasing the pharmacologic effects of clozapine. Observe the patient for clozapine toxicity when phenobarbital is stopped.
Clozapine	Benzodiazepines	The pharmacologic or toxic effects of certain benzodiazepines may be increased with concomitant administration. Consider monitoring vital signs and observing patients for excessive adverse reactions.
Clozapine	Quinolones	Clozapine plasma concentrations may be elevated due to inhibition of metabolism (CYP1A2) by certain quinolone antibiotics, increasing the risk of adverse reactions. Observe the clinical response of the patient and adjust the dose of clozapine as needed.
Clozapine	Ritonavir	Inhibition of clozapine metabolism through CYP2D6 by ritonavir may result in increased clozapine concentrations, increasing risk of toxicity. Coadministration is contraindicated.
Iloperidone	Agents that prolong the QT interval	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation. Coadministration is contraindicated.
Lurasidone	Strong CYP3A4 inhibitors (i.e. ketoconazole)	Concomitant administration is contraindicated. Coadministration has resulted in significant increases in lurasidone Cmax and AUC, via inhibition of CYP3A4-mediated lurasidone metabolism.
Lurasidone	Strong CYP3A4 inducers (i.e. rifampin)	Concomitant administration is contraindicated. Coadministration has resulted in significant increases in lurasidone Cmax and AUC, via induction of CYP3A4-mediated lurasidone metabolism.
Lurasidone	Moderate CYP3A4 inhibitor (diltiazem)	Concomitant use of diltiazem and lurasidone has resulted in significant increases in lurasidone Cmax and AUC, via inhibition of CYP3A4-mediated lurasidone metabolism. Therefore, the lurasidone dose should not exceed 40 mg/day when coadministered with diltiazem.
Lurasidone	Lithium	Concomitant use of lithium and lurasidone has resulted in increases in lurasidone Cmax and AUC. However, no lurasidone dose adjustments are required with concomitant use.
Olanzapine	Protease inhibitors	Increased metabolism of olanzapine through CYP1A2 by protease inhibitors may result in decreased olanzapine concentrations, decreasing the therapeutic effects. Adjust the dose of olanzapine as

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Drug(s)	Interacting Medication or Disease	Mechanism
		needed.
Quetiapine	Hydantoins	Increased metabolism of quetiapine through CYP3A4 by hydantoins may result in decreased quetiapine concentrations, decreasing pharmacologic effects.
Quetiapine	Valproic acid	Quetiapine plasma concentrations may be elevated due to inhibition of metabolism (CYP3A4) by valproic acid, increasing the pharmacologic and adverse effects. Closely monitor patients and be prepared to change the quetiapine dose as needed.
Ziprasidone	Antiarrhythmics	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation. Coadministration is contraindicated.
Ziprasidone	Cisapride	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation. Coadministration is contraindicated.
Ziprasidone	Dofetilide	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation. Coadministration is contraindicated.
Ziprasidone	Dolasetron	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation. Coadministration is contraindicated.
Ziprasidone	Droperidol	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation. Coadministration is contraindicated.
Ziprasidone	Halofantrine	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation. Coadministration is contraindicated.
Ziprasidone	Mefloquine	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation. Coadministration is contraindicated.
Ziprasidone	Pentamidine	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation. Coadministration is contraindicated.
Ziprasidone	Phenothiazines	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation. Coadministration is contraindicated.
Ziprasidone	Pimozide	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation. Coadministration is contraindicated.
Ziprasidone	Quinolones	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation. Coadministration is contraindicated.
Ziprasidone	Tacrolimus	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation. Coadministration is contraindicated.

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Dosage and Administration

Table 13. Dosing and Administration[6-11,13-19,21-22]

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Aripiprazole	Adjunctive treatment of major depressive disorder: Orally disintegrating tablet, oral solution, tablet: initial, 2-5 mg PO daily; target dose, 5-10 mg PO daily; maximum, 15 mg PO daily Agitation associated with schizophrenia or bipolar mania: Injection: initial, 5.25 mg IM up to every 2 hours; recommended dose, 9.75 mg IM daily; maximum, 30 mg IM daily; 15 mg IM daily was not shown to be more efficacious than 9.75 mg IM daily Bipolar disorder: Orally disintegrating tablet, tablet: initial, 15 mg PO daily; recommended dose, 15 mg PO daily; maximum, 30 mg PO daily; if used in adjunction with lithium or valproate, initial dose may range from 10 mg to 15 mg PO daily Oral solution: initial, 15 mg PO daily; maintenance, 15 mg PO daily, maximum, 25 mg PO daily Schizophrenia: Orally disintegrating tablet, tablet: initial, 10-15 mg PO daily; maintenance, 10-15 mg PO daily; maximum, 30 mg PO daily Oral solution: initial, 15-25 mg PO daily; maintenance, 15-25 mg PO daily; maximum, 25 mg PO daily	Schizophrenia, adolescents (13 to 17 years): Orally disintegrating tablet, oral solution, tablet: initial, 2 mg PO daily; target dose, 10 mg PO daily; maximum, 30 mg PO daily tablet or 25 mg PO daily solution; 30 mg PO daily was not shown to be more efficacious than 10 mg PO daily Bipolar mania, children and adolescents (10 to 17 years): Orally disintegrating tablet, oral solution, tablet: initial, 2 mg PO daily; target dose, 10 mg PO daily; maximum, 30 mg PO daily tablet or 25 mg PO daily solution Autistic disorder with irritability , children and adolescents (6 to 17 years): Orally disintegrating tablet, oral solution, tablet: initial, 2 mg PO daily; target dose, 5 to 10 mg PO daily; maximum, 15 mg PO daily tablet or PO daily solution The safety and effectiveness in pediatric patients with schizophrenia less than 13 years of age or in pediatric patients with bipolar mania less than 10 years of age have not been established. Safety and effectiveness in pediatric patients with other conditions have not been established.	Injection: 7.5 mg/mL Orally disintegrating tablet: 10 mg 15 mg Oral solution: 1 mg/mL Tablet: 2 mg 5 mg 10 mg 15 mg 20 mg 30 mg
Asenapine	Bipolar disorder: Acute treatment: initial, 10 mg PO twice daily; dose can be decreased to 5 mg PO twice daily if adverse effects occur; target dose, 5 to 10 mg PO twice daily; maximum dose, 10 mg PO twice daily	Safety and effectiveness in pediatric patients have not been established.	Sublingual tablet: 5 mg 10 mg

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Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
	Schizophrenia: Acute treatment: initial, 5 mg PO twice daily; target dose, 5 to 10 mg PO twice daily; maximum dose, 10 mg PO twice daily; safety of doses above 10 mg PO twice daily have not been evaluated		
Clozapine	Treatment-resistant schizophrenia: Orally disintegrating tablet, tablet: initial, 12.5 mg PO every 12-24 hours;* maximum, 900 mg PO daily	Safety and effectiveness in pediatric patients have not been established.	Orally disintegrating tablet: 12.5 mg 25 mg 100 mg Tablet: 12.5 mg 25 mg 50 mg 100 mg 200 mg
Iloperidone	Schizophrenia: Tablet: initial, 1 mg PO twice daily; increases to reach the target dose range of 6-12 mg PO twice daily with daily dosage adjustments; maximum, 12 mg PO twice daily Dose should be reduced by one-half when administered concomitantly with strong CYP2D6 inhibitors.	Safety and effectiveness in pediatric patients have not been established.	Tablet: 1 mg 2 mg 4 mg 6 mg 8 mg 10 mg 12 mg
Lurasidone	Schizophrenia: Tablet: initial, 40 mg PO once daily†; maximum, 80 mg PO once daily Dose should not exceed 40 mg daily if administered concomitantly with a moderate CYP3A4 inhibitor (i.e. diltiazem). Use with strong CYP3A4 inhibitors/inducers is contraindicated.	Safety and effectiveness in pediatric patients have not been established.	Tablet: 20 mg 40 mg 80 mg
Olanzapine	Agitation associated with schizophrenia and bipolar I mania: Injection: initial, 2.5-10 mg IM up to every 2 hours; target dose, 10 mg IM; maximum, 30 mg IM daily Bipolar disorder: Orally disintegrating tablet, tablet: initial, 10 mg or 15 mg PO daily; maintenance, 5-20 mg PO daily; maximum, 20 mg PO daily Depressive episodes associated with bipolar disorder:	Bipolar disorder, adolescents (13 to 17 years): Orally disintegrating tablet, tablet: initial, 2.5mg or 5mg PO daily; target, 10 mg PO daily; maximum, 20 mg PO daily Schizophrenia, adolescents (13 to 17 years): Orally disintegrating tablet, tablet: initial, 2.5mg or 5mg PO daily; target, 10 mg PO daily; maximum, 20 mg PO	Injection: 10 mg vials Orally disintegrating tablet: 5 mg 10 mg 15 mg 20 mg Tablet: 2.5 mg 5 mg

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Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
	Tablet: initial, 5 mg PO daily in combination with fluoxetine 20 mg PO daily; maintenance, 5-12.5 mg PO daily in combination with fluoxetine 20-50 mg PO daily Schizophrenia: Orally disintegrating tablet, tablet: initial, 5-10 mg PO daily; maintenance, 10-15 mg PO daily; maximum, 20 mg PO daily Treatment resistant depression: Tablet: initial, 5 mg PO daily in combination with fluoxetine 20 mg PO daily; maintenance, 5-20 mg PO daily in combination with fluoxetine 20-50 mg PO daily	daily The safety and effectiveness in pediatric patients with schizophrenia or bipolar disorder less than 13 years of age have not been established. Safety and effectiveness in pediatric patients with other conditions have not been established.	7.5 mg 10 mg 15 mg 20 mg
Olanzapine pamoate	Schizophrenia: Long-acting IM injection: 150 mg, 210 mg or 300 mg administered every 2 weeks or 405 mg administered every 4 weeks via deep IM gluteal injection	Safety and effectiveness in pediatric patients have not been established.	Long-acting Injection: 210 mg vial 300 mg vial 405 mg vial
Paliperidone	Schizophrenia: Extended-release tablet†: initial, 6 mg PO daily; maintenance, 3-12 mg PO daily*; maximum, 12 mg PO daily Schizoaffective disorder: Extended-release tablet†: initial, 6 mg PO daily; maintenance, 3-12 mg PO daily*; maximum, 12 mg PO daily	Schizophrenia, adolescents (13 to 17 years) weighing <51 kg: Extended-release tablet†: initial, 3 mg PO daily; maintenance, 3-6 mg PO daily; maximum, 6 mg PO daily Schizophrenia, adolescents (13 to 17 years) weighing =/>51 kg: Extended-release tablet†: initial, 3 mg PO daily; maintenance, 3-12 mg PO daily; maximum, 12 mg PO daily The safety and effectiveness in pediatric patients with schizophrenia less than 12 years of age have not been established. Safety and effectiveness in pediatric patients with other conditions have not been established.	Extended-release tablet: 1.5 mg 3 mg 6 mg 9 mg
Paliperidone palmitate	Schizophrenia: Suspension for IM injection: initial, 234	Safety and effectiveness in patients <18 years of age	Suspension for IM

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Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
	mg on treatment day 1 and 156 mg one week later, both administered in the deltoid muscle; following the second dose, monthly maintenance is 117 mg and can be given in either the deltoid or gluteal muscle; some patients may benefit from lower or higher doses within the recommended range of 39-234 mg based on individual patient tolerability and/or efficacy	have not been established.	injection: 39 mg 78 mg 117 mg 156 mg 234 mg
Quetiapine	Bipolar disorder (depression): Tablet: initial, 50 mg PO once daily at bedtime; maintenance, 300-600 mg PO daily*; maximum, 600 mg PO daily Extended-release tablet: initial, 50 mg PO once daily; maintenance, 300 mg once PO daily* Bipolar disorder (mania): Tablet: initial, 50 mg PO every 12 hours; maintenance, 400-800 mg PO daily*; maximum, 800 mg PO daily Extended-release tablet: initial, 300 mg PO once daily; maintenance, 400-800 mg PO once daily* Major depressive disorder: Extended-release tablet: initial, 50 mg PO once daily; maintenance, 150-300 mg PO once daily* Schizophrenia: Tablet: initial, 25 mg PO every 12 hours; maintenance, 150-750 mg PO daily*; maximum, 800 mg PO daily Extended-release tablet: initial, 300 mg PO once daily; maintenance, 400-800 mg PO once daily*	Bipolar mania, children and adolescents (10 to 17 years): Tablet: initial, 25 mg PO twice daily; maintenance, 200-300 mg PO twice daily* Schizophrenia, adolescents (13 to 17 years): Tablet: initial, 25 mg PO twice daily; maintenance, 200-400 mg PO twice daily* The safety and effectiveness in pediatric patients with bipolar disorder less than 10 years of age or schizophrenia less than 13 years of age have not been established. Safety and effectiveness in pediatric patients with other conditions have not been established.	Extended-release tablet: 50 mg 150 mg 200 mg 300 mg 400 mg Tablet: 25 mg 50 mg 100 mg 200 mg 300 mg 400 mg
Risperidone	Bipolar mania‡: Orally disintegrating tablet, oral solution, tablet: initial, 2-3 mg PO daily; maximum, 6 mg PO daily Schizophrenia: Injection: initial, 25 mg IM every 2 weeks; maintenance, 25-50 mg IM every 2 weeks; maximum, 50 mg IM every 2 weeks	Bipolar mania, children and adolescents aged 10 to 17 years: Orally disintegrating tablet, oral solution, tablet: initial, 0.5 mg PO once daily; dosage adjustments, if indicated, at intervals not less than 24 hours, in increments of 0.5 mg or 1 mg PO daily, as tolerated, to a recommended	Injection: 12.5 mg 25 mg 37.5 mg 50 mg Orally disintegrating tablet: 0.5 mg 1 mg

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Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
	Orally disintegrating tablet, oral solution, tablet: initial, 1 mg PO every 12 hours; maintenance, 4-16 mg PO daily dosed every 12-24 hours; maximum, 16 mg PO daily	dose of 2.5 mg PO daily; no additional benefit was seen above 2.5 mg PO daily; doses higher than 6 mg PO daily were not studied Irritability associated with autistic disorder, children and adolescents aged 5 to 16 years§: Orally disintegrating tablet, oral solution, tablet: initial, 0.25 mg PO daily for patients <20 kg and 0.5 mg daily for patients ≥20 kg; maximum, 1 mg PO daily in patients <20 kg, 2.5 mg in patients ≥20 kg Schizophrenia, adolescents aged 13 to 17 years: Orally disintegrating tablet, oral solution, tablet: initial, 0.5 mg PO once daily; dosage adjustments, if indicated, at intervals not less than 24 hours, in increments of 0.5 mg or 1 mg PO daily, as tolerated, to a recommended dose of 3 mg PO daily; maximum, 6 mg PO daily	2 mg 3 mg 4 mg Oral solution: 1 mg/mL Tablet: 0.25 mg 0.5 mg 1 mg 2 mg 3 mg 4 mg
Ziprasidone	Acute agitation in schizophrenia: Injection: initial, 10 mg IM every 2 hours or 20 mg IM every 4 hours; maximum, 40 mg IM daily¶ Bipolar mania: Capsule: initial, 40 mg PO every 12 hours; maintenance, 40-80 mg PO every 12 hours Schizophrenia: Capsule: initial, 20 mg PO every 12 hours; maintenance, 20-80 mg PO every 12 hours; maximum, 100 mg PO every 12 hours; no additional benefit was demonstrated for doses above 20 mg twice daily	Safety and effectiveness in pediatric patients have not been established.	Capsule: 20 mg 40 mg 60 mg 80 mg Injection: 20 mg/mL

IM=intramuscular, PO=by mouth
*Please refer to individual package insert for titration of dose information.
†Initial dose titration is not required.
‡There is no clinical data supporting maintenance dosing.
§No dosing data is available for children who weighed less than 15 kg.
¶Administration for more than three consecutive days has not been studied.

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Clinical Guidelines

Table 14. Clinical Guidelines in Adults

Guideline	Recommendations
Anxiety Disorder	
National Collaborating Centre for Mental Health, National Institute for Health and Clinical Excellence (NICE): **Generalised Anxiety Disorder and Panic Disorder (with or without agoraphobia) in Adults: Management in Primary Secondary and Community Care (update) (2011)**[283]	High-intensity psychological interventions: • If a patient with GAD chooses a high-intensity psychological intervention, cognitive behavioral therapy (CBT) or applied relaxation may be offered. Pharmacotherapy: • If pharmacotherapy is chosen, selective serotonin reuptake inhibitors (SSRIs) are preferred. Sertraline is the most cost-effective treatment option and may be used first-line. • If sertraline is ineffective, either an alternative SSRI or a serotonin-norepinephrine reuptake inhibitor (SNRI) may be offered. • If a patient cannot tolerate either a SSRI or a SNRI, pregabalin may be tried. • Benzodiazepines or antipsychotics should not be used for the treatment of GAD in primary care. • Efficacy and safety should be evaluated every 2-4 weeks during the first 3 months of therapy and every 3 months subsequently. • If a drug is effective, therapy should continue for at least one year as the risk of relapse is high. Complex, treatment-refractory GAD: • Combination of psychological and pharmacotherapy may be offered. Alternatively, combinations of antidepressants or augmentation of antidepressants with other drugs may be tried. However, the evidence for the effectiveness of combination treatments is lacking and side effects and interactions are more likely when combining and augmenting antidepressants. • Combination therapy should only be initiated by practitioners with expertise in the psychological and drug treatment of complex, treatment-refractory anxiety disorders and after full discussion with the patients about the benefits and risks of therapy.
American Psychiatric Association (APA): **Practice guideline for the treatment of patients with panic disorder (2009)**[312]	Initial therapy: • The use of a selective serotonin reuptake inhibitor (SSRI), serotonin-norepinephrine reuptake inhibitor (SNRI), tricyclic antidepressant (TCA), benzodiazepine (appropriate as monotherapy only in the absence of a co-occurring mood disorder), or cognitive-behavioral therapy (CBT) as the initial treatment for panic disorder is strongly supported by demonstrated efficacy in numerous randomized controlled trials [I]. • There is insufficient evidence to recommend any of these pharmacological or psychosocial interventions as superior to the others, or to routinely recommend a combination of treatments over monotherapy [II]. • Considerations that guide the choice of an initial treatment modality include patient preference, the risks and benefits for the particular patient, the patient's past treatment history, the presence of co-occurring general medical and other psychiatric conditions, cost, and treatment availability [I].

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Guideline	Recommendations
	• Psychosocial treatment (i.e.CBT) is recommended for patients who prefer non-pharmacological treatment and are able to commit to weekly sessions and complete between-session practices [I]. • Pharmacotherapy (SSRI or SNRI) is recommended for patients who prefer this modality or who do not have sufficient time or other resources to engage in psychosocial treatment [I]. • Adding psychosocial treatment to pharmacotherapy either from the start, or at some later point in treatment, may enhance long-term outcomes by reducing the likelihood of relapse when pharmacological treatment is stopped [II]. Treatment of Refractory Patients: • Patients who have failed first-line therapy may either augment the current treatment by adding another agent or another modality (i.e.CBT), or add pharmacotherapy if the patient is already receiving CBT [I], or they can switch to a different medication or treatment modality [I]. • If one first-line treatment (e.g., CBT, SSRI, or SNRI) has failed, adding or switching to another first-line treatment is recommended [I]. • Adding a benzodiazepine to an antidepressant is a common augmentation strategy to target residual symptoms [II]. • After first- and second-line treatments and augmentation appraches have failed (either due to lack of efficacy or intolerance), less well-supported treatment approaches may be considered [III]. These include monotherapy or augmentation with gabapentin or a second-generation antipsychotic or with a psychotherapeutic intervention other than CBT or panic-focused psychodynamic psychotherapy [III].
Bipolar Disorder	
Veterans Affairs/Department of Defense (VA/DoD): **Clinical Practice Guideline for Management of Bipolar Disorder in Adults (2010)**[284]	Bipolar Mania or Mixed Bipolar Disorder: • Pharmacotherapy for bipolar mania or mixed episode should start with initiation or optimization of a medication that has been shown to be the most effective in treating bipolar manic episodes while minimizing the potential risks. Agents that are most likely to be beneficial for mania are the following: lithium, valproate, carbamazepine, aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone. In addition, lithium or valproate may be combined with an atypical antipsychotic. [Level A Recommendation] • Agents most likely to be beneficial for the treatment of a mixed bipolar episode are valproate, carbamazepine, aripiprazole, olanzapine, risperidone, or ziprasidone [A]. • Agents that are unlikely to be beneficial either for bipolar mania or mixed bipolar are lamotrigine, topiramate, or gabapentin. • Clozapine, haloperidol and oxcarbazepine may be considered in patients with mania or mixed episode. [I] Lithium or quetiapine may be considered in patients with mixed episode. [I]. • Treatment response should be evaluated at 4 to 8 weeks after initiation of treatment, after each change in treatment, and periodically until full remission is achieved. In patients who reach full remission, assessment of symptoms should be continued periodically to monitor for relapse or recurrence. [B] • Patients who have failed monotherapy may consider switching to another monotherapy, combining a non-antipsychotic mood stabilizer

Guideline	Recommendations
	(lithium or valproate) with a second generation antipsychotic • Clozapine, with its more serious side effect profile, may be combined with valproate or lithium as a treatment of severe mania or mixed episode, if it has been successful in the past or if other antipsychotics have failed. [I] <u>Pharmacotherapy for Bipolar Depression</u> • Pharmacotherapy for bipolar depression should start with initiation or optimization of a medication that has been shown to be the most effective in treating bipolar depressive episodes, while minimizing the potential risks. [B] • Quetiapine, [A], lamotrigine [B], or lithium [B] monotherapy should be considered as first-line treatment for adult patients with bipolar depression. • Olanzapine/fluoxetine combination should be considered for treatment of bipolar depression, but its adverse effects (weight gain, risk of diabetes, hypertriglyceridemia) places this combination as a second-line treatment. [B] Olanzapine alone may also be considered for bipolar depression, but adverse effects require caution. [C] • Agents that had been effective in treating prior episodes of depression should be considered. • There is insufficient evidence to recommend for or against the use of valproate, carbamazepine, topiramate, risperidone, ziprasidone, or clozapine for BD depression. [I] • Aripiprazole is not recommended for monotherapy in the treatment of acute bipolar depression, unless there is a history of previous good response during depression without switch to mania or a history of treatment refractory depression. [D] • Combining lithium with lamotrigine can be considered for patients with bipolar depression who do not respond to monotherapy. [A] • When patients do not respond to treatment options that have shown better efficacy, antidepressant augmentation with SSRI, SNRI, bupropion, and monoamine oxidase inhibitor (MAOI) can be considered for short-term treatment, monitoring closely for triggering of manic symptoms. [C] • Clozapine may be considered for augmentation, using caution regarding metabolic or other adverse effects. [I] • There is insufficient evidence to recommend for or against use of augmentation with aripiprazole, olanzapine, risperidone, haloperidol, oxcarbazepine, topiramate, ziprasidone, valproate, or carbamazepine for the treatment of bipolar depression. [I] • Gabapentin and the tricyclic antidepressants (TCAs) are not recommended for monotherapy or augmentation in the treatment of acute bipolar depression, unless there is a history of previous good response during depression without switch to mania or a history of treatment refractory depression. [D] • If there is no response within 2 to 4 weeks on an adequate dose of medication, therapy should be adjusted by either augmenting with additional agents, discontinuing switching to another effective medication or electroconvulsive therapy if multiple medication trials have been ineffective.
National Collaborating	<u>Acute manic episode in adults</u>

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Guideline	Recommendations
Centre for Mental Health, National Institute for Health and Clinical Excellence (NICE): **Bipolar Disorder: The Management of Bipolar Disorder in Adults, Children and Adolescents, in Primary And Secondary Care (2006)**[285]	• An antipsychotic or valproate should be used for severe manic symptoms marked by a behavioral disturbance. Lithium may be used if symptoms are not severe due to its slower onset of action. • For an acute manic episode while on lithium or valproate, dose should be optimized, then olanzapine, quetiapine or risperidone should be added on if there are no signs of improvement. Acute depressive episode in adults • Patients with an incomplete response to antidepressant monotherapy may be managed by increasing the dose, switching antidepressants (e.g., mirtazapine or venlafaxine), adding an antipsychotic (olanzapine or quetiapine) or adding lithium. • Patients with concurrent depressive and psychotic symptoms may be managed with olanzapine, quetiapine, or risperidone if the depressive illness is severe. Long-term management • Lithium, olanzapine, or valproate should be considered for long-term treatment of bipolar disorder. • Long-acting intramuscular antipsychotic injections should not be used routinely. • Quetiapine or lamotrigine can be considered for the management of patients with chronic and recurrent depressive symptoms.
The Texas Medication Algorithm Project (TMAP): **Texas Implementation of Medication Algorithms (TIMA) Procedural Manual: Bipolar Disorder Algorithms (2007)**[286]	Treatment of hypomanic or manic episodes • Stage 1 treatment options for euphoric symptoms include: lithium, valproate, aripiprazole, quetiapine, risperidone, and ziprasidone. • Stage 1 treatment options for mixed symptoms include: valproate, aripiprazole, risperidone, and ziprasidone. • Stage 1b, olanzapine and carbamazepine are potential alternatives to stage 1 agents. • Stage 2 treatment options include a combination with two of the following: lithium, valproate, olanzapine, quetiapine, risperidone, or ziprasidone (not 2 antipsychotics). • Stage 3 treatment options include a different combination than that tried in Stage 2, with additional options including carbamazepine, oxcarbazepine, aripiprazole, and a typical antipsychotic. • Stage 4 treatment options include clozapine or 3-drug combinations (include lithium, an anticonvulsant mood stabilizer [valproate, carbamazepine, or oxcarbazepine], plus an atypical antipsychotic). Treatment of depression • Stage 1 recommended treatment is lamotrigine monotherapy for those patients without a recent and/or severe history of manic symptoms. Others should receive lamotrigine plus a mood stabilizer. • Stage 2 treatment options include quetiapine monotherapy or the olanzapine/fluoxetine combination treatment. • For Stage 3 and beyond, evidence-based medicine is limited to case series, open-label studies and expert clinical consensus. A variety of treatment options are suggested. • For intolerance or unresponsiveness to agents used in a particular Stage, it is recommended to try an alternative mood stabilizer within that Stage.
American Psychiatric	Treatment of acute manic or mixed episodes

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Guideline	Recommendations
Association (APA): **Practice Guideline for the Treatment of Patients with Bipolar Disorder (2002)**[†287]	• Adjunctive antipsychotic treatment is recommended for manic or mixed manic episodes with psychotic features. • Second generation antipsychotics are preferable over first generation antipsychotics because of their side effect profile. Treatment of acute depressive episodes • Patients presenting with psychotic features would require adjunctive treatment with an antipsychotic medication or electroconvulsive therapy. Treatment of acute rapid cycling • A combination regimen containing a second generation antipsychotic may also be used. Maintenance treatment for manic/depressive episode • Ongoing adjunctive antipsychotic therapy should be reassessed, and slowly tapered, unless required for control of persistent psychosis or prophylaxis against recurrence.
Dementia	
American Psychiatric Association (APA): **Practice Guideline for the Treatment of Patients with Alzheimer's Disease and Other Dementias (2007)**[288]	Treatment of Cognitive Symptoms • Cholinesterase inhibitors should be offered to patients with mild to moderate Alzheimer's disease after a thorough discussion of their potential risks and benefits [I], and they may be helpful for patients with severe Alzheimer's disease [II]. • Cholinesterase inhibitors should be considered for patients with mild to moderate dementia associated with Parkinson's disease [I]. • Cholinesterase inhibitors can be considered for patients with dementia with Lewy bodies [II]. • Memantine, a noncompetitive N-methyl-D-aspartate (NMDA) antagonist, may provide modest benefits and has few adverse effects; thus, it may be considered [I]. There is some evidence of its benefit in mild Alzheimer's disease [III] and very limited evidence of its benefit in vascular dementia [I]. Treatment of Psychosis and Agitation • Psychosis, aggression, and agitation are common in patients with dementia and may respond to similar therapies. • On the basis of good evidence, antipsychotic medications are recommended for the treatment of psychosis in patients with dementia [II] and for the treatment of agitation [II]. • These medications have also been shown to provide modest improvement in behavioral symptoms in general [I]. • Evidence for a difference in efficacy and safety among antipsychotic medications is limited. • Antipsychotic medications as a group are associated with a number of severe adverse events, including increased risks for death, cerebrovascular accidents, tardive dyskinesia, neuroleptic malignant syndrome, hyperlipidemia, weight gain, diabetes mellitus, sedation, parkinsonism, and worsening of cognition. Thus, they must be used with caution and at the lowest effective dosage [I], after considering the risks of not treating the psychiatric symptoms [I]. • Data demonstrating benefit from benzodiazepines are modest, but

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Guideline	Recommendations
	benzodiazepines occasionally have a role in treating patients with prominent anxiety [III] or on an as-needed basis for patients with infrequent episodes of agitation or for those who require sedation for a procedure [II]. Lorazepam and oxazepam, which have no active metabolites, are preferable to agents with a longer half-life such as diazepam or clonazepam [III]. • There is minimal evidence for the efficacy of anticonvulsants, lithium, and beta-blockers for the treatment of psychosis or agitation in dementia, and these medications have significant adverse effects; therefore, they are generally not recommended except for patients for whom other treatments have failed [III]. • The antidepressant trazodone and the SSRIs are not well studied but may be appropriate for nonpsychotic patients with agitation [III]. <u>Treatment of Depression:</u> • Clinical consensus supports a trial of an antidepressant to treat clinically significant, persistent depressed mood [II]. • SSRIs may be preferred because they appear to be better tolerated than other antidepressants [II]. Bupropion, venlafaxine, and mirtazapine may also be effective [II]. • Agents with substantial anticholinergic effects (e.g., amitriptyline, imipramine) should be avoided [I]. • Psychostimulants, bupropion, bromocriptine, and amantadine may be helpful for apathy [III]. Psychostimulants are also sometimes useful in the treatment of depression in patients with significant general medical illness [III]. <u>Treatment of Sleep Disturbances:</u> • If a patient requires medication for another psychiatric condition, an agent with sedating properties, given at bedtime, is preferred [I]. • For primarily sleep disturbance, medications with possible effectiveness include trazodone, zolpidem, or zaleplon [III], but there are few data on the efficacy of specific agents. • Benzodiazepines are not recommended for other than brief use because of risks of daytime sedation, tolerance, rebound insomnia, worsening cognition, falls, disinhibition, and delirium [II]. • Diphenhydramine is not recommended because of its anticholinergic properties [II]. • Antipsychotic medications should not be used solely for the purpose of treating sleep disturbances [I].
Eating Disorder	
World Federation of Societies of Biological Psychiatry (WFSBP): **Guidelines for the Pharmacological Treatment of Eating Disorders (2011)**[289]	Anorexia Nervosa: • Zinc supplementation has a grade B evidence for use. • Olanzapine has a grade B evidence for weight gain. • The other atypical antipsychotics have an evidence grade of C. • Antidepressants are not associated with weight gain, but can improve depressive symptoms. Bulimia Nervosa: • Imipramine, desipramine, fluoxetine, and topiramate may be used to reduce bulimic behavior (Evidence A). • Fluvoxamine and sertraline may reduce bulimic behavior (Evidence

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Guideline	Recommendations
	B). Binge Eating Disorder: • Imipramine, citalopram, escitalopram, sertraline, topiramate, and sibutramine may be used to reduce binge eating behavior (Evidence A). • Zonisamide may reduce binge eating behavior (Evidence B).
American Psychiatric Association: **Practice Guideline for the Treatment of Patients with Eating Disorders (2010)**[290]	Anorexia Nervosa: • The limited empirical data on SSRIs do not suggest a role in weight gain. • Atypical antipsychotics, especially olanzapine, risperidone, and quetiapine, have been studied in small case series and case studies. These agents may be useful in patients with severe, unremitting resistance to gaining weight, severe obsessional thinking, and denial that assumes delusional proportions. Ziprasidone has not been studied in patients with anorexia nervosa; hence, patients who are using this agent should be monitored for ECG changes and serum potassium abnormalities. Bulimia Nervosa: • Antidepressants are effective as one component of an initial treatment program for most patients, with SSRIs having the most evidence for efficacy and the fewest difficulties with adverse effects. Of the SSRIs, fluoxetine is the best studied agent. • Lithium is ineffective and should not be used. Binge Eating Disorder: • Antidepressants, particularly SSRIs, are associated with a short-term reduction in binge eating behavior, but not with substantial weight loss. • Topiramate is effective in binge reduction and weight loss, although adverse effects may limit its use. • Zonisamide is another option for patients with binge eating disorder.
Major Depressive Disorder (MDD)	
Institute for Clinical Systems Improvement (ICSI): **Major Depression in Adults in Primary Care (2011)**[291]	Pharmacotherapy: • SSRIs, venlafaxine, duloxetine, desvenlafaxine, mirtazapine and bupropion are recommended as first-line antidepressant treatment options [R]. Side effects may include headache, nervousness, insomnia, and sexual side effects. • Secondary Amine Tricyclics (TCAs) are effective for the treatment of MDD. However, they are used less frequently as first-line agents due to their safety profile. Secondary amine tricyclics cause less orthostatic hypotension and sedation than do tertiary amine tricyclics. Monitoring blood levels and electrocardiogram (EKG) may be advised. • Monoamine Oxidase Inhibitors (MAOIs) should only be used in patients who do not respond to other treatments because of their potential for serious side effects and the necessity of dietary restrictions. • Augmentation therapy is used in patients whose depression is either treatment-resistant or partially responsive to treatment. Consultation with a behavioral health specialist is advised. The following agents

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	may be added to antidepressant therapy: bupropion, buspirone, mirtazapine, triiodothyronine (T3), stimulants, TCA-SSRI combination, lithium, and atypical antipsychotics.
American Psychiatric Association: **Practice Guideline for the Treatment of Patients With Major Depressive Disorder (2010)**[292]	Acute phase • Pharmacotherapy: o An antidepressant medication is recommended as an initial treatment choice for patients with mild to moderate major depressive disorder (MDD) and definitely should be provided for those with severe MDD. o Due to the fact that the effectiveness of antidepressant medications is generally comparable between classes and within classes of medications, the initial selection of an antidepressant medication will largely be based on the anticipated side effects; the safety or tolerability of these side effects; pharmacological properties of the medication and additional factors such as medication response in prior episodes, cost and patient preference. o For the majority of patients, a selective serotonin reuptake inhibitor (SSRI), serotonin norepinephrine reuptake inhibitor (SNRI), bupropion or mirtazapine is optimal. o In general, the use of nonselective monoamine oxidase inhibitors (MAOIs) should be restricted to patients who do not respond to other treatments. o In patients who prefer complementary and alternative therapies, *S*-adenosyl methionine or St John's Wort might be considered. o Once an antidepressant has been initiated, the rate at which it is titrated to a full therapeutic dose should depend upon the patient's age, the treatment setting and the presence of co-occurring illnesses, concomitant pharmacotherapy or medication side effects. o During the acute phase of treatment, patients should be carefully and systematically monitored on a regular basis to assess their response to pharmacotherapy. o Determine the frequency of patient monitoring based upon the patient's symptom severity, co-occurring disorders, cooperation with treatment, availability of social supports and the frequency and severity of side effects with the chosen treatment. o If side effects do occur, an initial strategy is to lower the dose of the antidepressants or to change to an antidepressant that is not associated with those side effects. • Assessing the adequacy of treatment response: o It is important to establish that treatment has been administered for a sufficient duration and at a sufficient frequency or, in the case of medication, dose. o Generally, four to eight weeks of treatment are needed before concluding that a patient is partially responsive or unresponsive to a specific intervention. • Strategies to address non-response: o For individuals who have not responded fully to treatment, the acute phase of treatment should not be concluded prematurely, as an incomplete response to treatment is often

Guideline	Recommendations
	associated with poor functional outcomes. o If at least a moderate improvement in symptoms is not observed within four to eight weeks of treatment initiation, the diagnosis should be reappraised, side effects assessed, complicating co-occurring conditions and psychosocial factors reviewed and the treatment plan adjusted. o It is important to assess the quality of the therapeutic alliance and treatment adherence. o If medications are prescribed, the psychiatrist should determine whether pharmacokinetic or pharmacodynamic factors suggest a need to adjust medication dose. o After an additional four to eight weeks of treatment, if the patient continues to show minimal or no improvement in symptoms, the psychiatrist should conduct another thorough review of possible contributory factors and make additional changes in the treatment plan. o There are a number of strategies available when a change in treatment seems necessary. ▪ For patients treated with an antidepressant, optimizing the medication dose is a reasonable first step if the side effect burden is tolerable and the upper limit of a medication dose has not been reached. ▪ In patients who have shown minimal improvement or experienced significant medication side effects, other options include augmenting the antidepressant with a depression-focused psychotherapy or with other agents or with changing to another non-MAOI antidepressant. ▪ Patients may be changed to an antidepressant from the same pharmacological class or to one from a different class. ▪ Patients who have not responded to an SSRI, may respond to SNRI. ▪ Augmentation of antidepressant medications can utilize another non-MAOI antidepressant, generally from a different pharmacological class, or a non-antidepressant medication, such as lithium, thyroid hormone or a second generation antipsychotic. <u>Continuation phase</u> • During the continuation phase of treatment, the patient should be carefully monitored for signs of possible relapse. • Systematic assessment of symptoms, side effects, adherence and functional status is essential and may be facilitated through the use of clinician- and/or patient-administered rating scales. • To reduce the risk of relapse, patients who have been treated successfully with antidepressant medications in the acute phase should continue treatment with these agents for four to nine months. • In general, the dose used in the acute phase should be used in the continuation phase. • To prevent a relapse of depression in the continuation phase, depression-focused psychotherapy is recommended, with the best

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	evidence available for cognitive behavioral therapy (CBT). Maintenance phase • In order to reduce the risk of a recurrent depressive episode, patients who have had three or more prior MDD episodes or who have chronic MDD should proceed to the maintenance phase of treatment after completing the continuation phase. • Maintenance therapy should also be considered for patients with additional risk factors for recurrence. • Additional considerations that may play a role in the decision to use maintenance therapy include patient preference, the type of treatment received, the presence of side effects during continuation therapy, the probability of recurrence, the frequency and severity of prior depressive episodes, the persistence of depressive symptoms after recovery and the presence of co-occurring disorders. Such factors also contribute to decisions about the duration of the maintenance phase. • For many patients, some form of maintenance treatment will be required indefinitely. • An antidepressant medication that produced symptom remission during the acute phase and maintained remission during the continuation phase should be continued at a full therapeutic dose. • For patients whose depressive episodes have not previously responded to acute or continuation treatment with medications or a depression-focused psychotherapy but who have shown a response to electroconvulsive therapy (ECT), maintenance ECT may be considered. • Due to the risk of recurrence, patients should be monitored systematically and at regular intervals during the maintenance phase. Discontinuation of treatment • When pharmacotherapy is being discontinued, it is best to taper the medication over the course of at least several weeks. • To minimize the likelihood of discontinuation symptoms, patients should be advised not to stop medications abruptly and to take medications with them when they travel or are away from home. • A slow taper or temporary change to a longer half-life antidepressant may reduce the risk of discontinuation syndrome when discontinuing antidepressants or reducing antidepressant doses. • Before the discontinuation of active treatment, patients should be informed of the potential for a depressive relapse and a plan should be established for seeking treatment in the event of recurrent symptoms. • After discontinuation of medications, patients should continue to be monitored over the next several months and should receive another course of adequate acute phase treatment if symptoms recur. Clinical factors influencing treatment • Psychiatric factors: o For suicidal patients, an increase in the intensity of treatment should be considered and may include hospitalization when warranted and/or combined treatment with pharmacotherapy

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	and psychotherapy. o For patients who exhibit psychotic symptoms during an episode of MDD, treatment should include a combination of antipsychotic and antidepressant medications or ECT. o Catatonic features should be treated with a benzodiazepine or barbiturate, typically in conjunction with an antidepressant. If an antipsychotic medication is needed, it is important to monitor for signs of neuroleptic malignant syndrome, to which patients with catatonia may have a heightened sensitivity. o Benzodiazepines may be used adjunctively in MDD and co-occurring anxiety, although they do not treat depressive symptoms. o In patients who smoke, bupropion or nortriptyline may be options to simultaneously treat depression and assist with smoking cessation.
National Institute for Health and Clinical Excellence: **The Treatment and Management of Depression in Adults (2009)**[293]	<u>Persistent subthreshold depressive symptoms or mild to moderate depression with inadequate response to initial interventions, and moderate and severe depression</u> • For patients with persistent subthreshold depressive symptoms or mild to moderate depression who have not benefited from a low-intensity psychosocial intervention, discuss the relative merits of different interventions with the person and provide: o An antidepressant (normally an SSRI) or a high intensity psychosocial intervention. • For people with moderate or severe depression, provide a combination of an antidepressant medication and a high intensity psychological intervention. • The choice of intervention should be influenced by the duration of the episodes of depression and the trajectory of symptoms, previous course of depression and response to treatment, likelihood of adherence to treatment and any potential adverse effects and the patient's treatment preference and priorities. • For people with depression who decline an antidepressant, CBT, interpersonal therapy, behavioral activation and behavioral couples therapy; consider counseling for people with persistent subthreshold depressive symptoms or mild to moderate depression, short term psychodynamic psychotherapy for people with mild to moderate depression or discussing with the patient the uncertainty of the effectiveness of counseling and psychodynamic psychotherapy in treating depression. <u>Antidepressant drugs</u> • Choice of antidepressant: o Discuss the choice of antidepressant with the patient, including any anticipated adverse events and potential drug interactions, and their perception of the efficacy and tolerability of any antidepressant they have previously taken. o When an antidepressant is used, it should normally be an SSRI in a generic form. The SSRIs are equally effective as other antidepressants and have a favorable risk-benefit ratio. Fluoxetine, fluvoxamine and paroxetine are associated with a higher propensity for drug interactions than other SSRIs, and paroxetine is associated with a higher incidence of

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	discontinuation symptoms than other SSRIs. o Take into account toxicity in overdose when choosing an antidepressant for people at significant risk for suicide. Be aware that compared to other equally effective antidepressants routinely used in primary care, venlafaxine is associated with a greater risk of death from overdose, and tri-cyclic antidepressants (TCAs), except lofepramine, are associated with the greatest risk in overdose. o When prescribing drugs other than SSRIs, take the following into account: the increased likelihood of the person stopping treatment because of side effects with duloxetine, venlafaxine and TCAs, the specific cautions, contraindications and monitoring requirements for some drugs, that non-reversible MAOIs should normally be prescribed only by specialists and dosulepin should not be prescribed. • Starting and initial phase of treatment: o When prescribing antidepressants, explore any concerns the patient has. Explain the gradual development of the full antidepressant effect, the importance of taking the medication as prescribed, the need to continue treatment after remission, potential side effects, the potential for interactions with other medications, the risk and nature of discontinuation symptoms with all antidepressants and how these symptoms can be minimized and the fact that addiction does not occur with antidepressants. o If side effects develop early in antidepressant treatment, provide appropriate information and consider one of the following strategies: monitor symptoms closely where side effects are mild and acceptable to the patient, stop the antidepressant, change to a different antidepressant if the person prefers or consider short term concomitant treatment with a benzodiazepine if anxiety, agitation and/or insomnia are problematic (this should usually be for no longer than two weeks in order to prevent the development of dependence). o Patients who start on low dose TCAs and who have clear clinical response can be maintained on that dose with careful monitoring. o If the patient's depression shows no improvement after two to four weeks with the first antidepressant, check that the drug has been taken regularly and in the prescribed dose. o If response is absent or minimal after three to four weeks of treatment with a therapeutic dose of an antidepressant, increase the level of support and consider increasing the dose in line with the summary of product characteristics if there are no significant side effects or switching to another antidepressant. o If the patient's depression shows some improvement by four weeks, continue treatment for another two to four weeks. Consider switching to another antidepressant if response is still not adequate, there are side effects or the person prefers to change treatment.
Obsessive Compulsive Disorder (OCD)	
American Psychiatric	• In choosing a treatment approach, the clinician should consider the

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Association (APA): **Practice Guideline for the Treatment of Patients with Obsessive-Compulsive Disorder (2007)**[294]	patient's motivation and ability to comply with pharmacotherapy and psychotherapy [I]. • Cognitive behavioral therapy (CBT) and SSRIs are recommended as safe and effective first-line treatments for OCD [I]. Combined treatment should be considered for patients with an unsatisfactory response to monotherapy [II], for those with co-occurring psychiatric conditions for which SSRIs are effective [I], and for those who wish to limit the duration of SSRI treatment [II]. • Clomipramine, fluoxetine, fluvoxamine, paroxetine, and sertraline are recommended first-line pharmacological agents [I]. Because the SSRIs have a less troublesome side-effect profile than clomipramine, an SSRI is preferred for a first medication trial [I]. • CBT that relies primarily on behavioral techniques such as exposure and response prevention is recommended because it has the best evidentiary support [I]. • Most patients will not experience substantial improvement until 4 to 6 weeks after starting medication, and some who will ultimately respond will experience little improvement for as many as 10 to 12 weeks. • Medication doses may be increased weekly or biweekly to the maximum dose comfortably tolerated and indicated [II]. This maximum dose may exceed the manufacturer's recommended maximum dose in some cases [III]. Higher doses may be appropriate for patients who have had little response to treatment and are tolerating a medication well [I]. • When initial therapy is inadequate, augmentation strategies may be preferred to switching strategies in patients who have a partial response to the initial treatment [II]. • The psychiatrist should first consider augmentation of SSRIs with trials of different antipsychotic medications or with CBT [II]. • Patients who do not respond to one SSRI may be switched to a different SSRI [I]. A switch to venlafaxine is less likely to produce an adequate response [II]. For patients who have not benefitted from their first SSRI trial, a switch to mirtazapine can also be considered [III]. • SSRI nonresponders and partial responders may try augmentation with antipsychotic medications [II]. Available evidence does not support the use of antipsychotic monotherapy. • After first- and second-line treatments and well-supported augmentation strategies have been exhausted, less well-supported treatment strategies may be considered [III]. These include augmenting SSRIs with clomipramine, buspirone, pindolol, riluzole, or once-weekly oral morphine sulfate [III].
Post-Traumatic Stress Disorder (PTSD)	
Institute for Clinical Systems Improvement (ICSI): **Clinical Practice Guideline for the Management of Post-Traumatic Stress (2010)**[295]	Pharmacotherapy: • There is no evidence to support a recommendation for use of a pharmacological agent to prevent the development of ASD or PTSD. [I] • Benzodiazepines are not recommended for the prevention of ASD or PTSD [D] • Monotherapy should be optimized before proceeding to subsequent strategies by monitoring outcomes, maximizing dosage (medication

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	or psychotherapy), and allowing sufficient response time (for at least 8 weeks). [C] If there is some response and patient is tolerating the drug, therapy should be continued for at least another 4 weeks. • If there is no improvement at 8 weeks consider increasing the dose of the initial drug to maximum tolerated, discontinuing the current agent and switching to another effective medication or augmenting with additional agents. • Patients diagnosed with PTSD should be offered selective serotonin reuptake inhibitors (SSRIs), for which fluoxetine, paroxetine, or sertraline have the strongest support, or serotonin norepinephrine reuptake inhibitors (SNRIs), for which venlafaxine has the strongest support, for the treatment of PTSD. [A] • Mirtazapine, nefazodone, tricyclic antidepressants (TCAs) (amitriptyline and imipramine), or monoamine oxidase inhibitors (phenelzine) may also be used for the treatments for PTSD. [B] • Guanfacine and anticonvulsants (tiagabine, topiramate, or valproate) are not recommended to be used as monotherapy in the management of PTSD. [D] • The existing evidence does not support the use of bupropion, buspirone, trazodone, anticonvulsants (lamotrigine or gabapentin), or atypical antipsychotics as monotherapy in the management of PTSD. [I] • There is evidence against the use of benzodiazepines in the management of PTSD. [D] \ • There is insufficient evidence to support the use of prazosin as monotherapy in the management of PTSD. [I] • Atypical antipsychotics (risperidone or olanzapine [B] or, quetiapine [C]) are recommended as adjunctive therapy for the management of PTSD. • Prazosin is recommended as adjunctive therapy for sleep/nightmares. [B] • There is insufficient evidence to recommend a sympatholytic or an anticonvulsant as an adjunctive therapy for the treatment of PTSD. [I]
American Psychiatric Association (APA): **Practice Guideline for the Treatment of Patients with Acute Stress Disorder and Posttraumatic Stress Disorder (2004)†**[296]	Pharmacotherapy: • SSRIs are recommended as first-line pharmacotherapy option for PTSD [I]. • Other antidepressants, including tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs), may also be beneficial in the treatment of PTSD [II]. • Benzodiazepines may be useful in reducing anxiety and improving sleep [III]. Although their efficacy in treating the core symptoms of PTSD has not been established, benzodiazepines are often used in trauma-exposed individuals and patients with PTSD. However, due to the risk of dependence, increased incidence of PTSD after early treatment with these medications, or worsening of PTSD symptoms after withdrawal of these medications, benzodiazepines cannot be recommended as monotherapy in PTSD. • Second generation antipsychotic medications (e.g., olanzapine, quetiapine, risperidone) may be helpful in individual patients with PTSD [III]. • Anticonvulsant medications (e.g., divalproex, carbamazepine, topiramate, lamotrigine), alpha-2-adrenergic agonists, and beta-

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	adrenergic blockers may also be helpful in treating specific symptom clusters in individual patients [III]. Psychotherapy: • Cognitive behavior therapies may speed recovery and prevent PTSD when therapy is given over a few sessions beginning 2-3 weeks after trauma exposure [II]. • Early supportive interventions, psychoeducation, and case management appear to be helpful in acutely traumatized individuals, because these approaches promote engagement in ongoing care and may facilitate entry into evidence-based psychotherapeutic and psychopharmacological treatments [II]. Encouraging acutely traumatized persons to first rely on their inherent strengths, their existing support networks, and their own judgment may also reduce the need for further intervention [II]. • Patients with ASD may be helped by cognitive behavior therapy and other exposure-based therapies [II]. In addition, cognitive behavior therapy is an effective treatment for core symptoms of acute and chronic PTSD [I].
Schizophrenia	
National Collaborating Centre for Mental Health, National Institute for Health and Clinical Excellence (NICE): **Schizophrenia: Core Interventions in the Treatment and Management of Schizophrenia in Primary and Secondary Care (update) (2009)**[297]	• The recent update no longer prefers second generation antipsychotics and recommends selection of antipsychotics be based on patient characteristics and potential side effects. Initial episode • An antipsychotic agent should be considered at the earliest opportunity. Acute episode • A single antipsychotic agent is first line. Regular use of combination therapy should not be initiated except when changing agents. • Clinical response and side effects should be routinely monitored. • Large loading doses should not be used with antipsychotics. • Combination antipsychotic therapy should not be prescribed except for a short duration while transitioning to a different antipsychotic agent. • Due to the high risk of relapse following an acute episode, it is recommended to continue antipsychotic medications for up to 1-2 years. Recovery/relapse prevention • The goal of pharmacologic treatment is to prevent relapse and maintain the patient's quality of life. • The same considerations for drug treatment should be given as in acute episodes: potential side effects, patient characteristics and preferences. • Depot preparations should be considered when adherence to oral medication is in question. Inadequate response to treatment • Factors for inadequate response should be evaluated including diagnosis, adherence to treatment, and comorbid conditions.

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	• Consider clozapine for patients who have tried 2 antipsychotic agents (including one second generation antipsychotic) without significant improvement. • Adding a second antipsychotic to clozapine may be considered for patients who are unresponsive to clozapine alone at standard doses; however, the use of more than 1 antipsychotic is not recommended in other situations except during the conversion from one agent to another.
The Texas Medication Algorithm Project (TMAP): **Texas Implementation of Medication Algorithms (TIMA) Procedural Manual: Schizophrenia Module (2008)**[298]	Stage 1 • Second generation antipsychotics such as aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone are considered first-line and can be used short-term for agitation and excitement. • A lower dose of an antipsychotic medication is required for patients during a first episode. Stage 2 • A trial of a single second generation antipsychotic not tried in Stage 1 or first generation antipsychotics is an appropriate treatment option. • A first generation antipsychotic may be worth trying if the patient has never tried one. Stage 3 • A trial of clozapine is recommended. • Clozapine should be considered earlier if there is a history of suicidal ideation, violence, or comorbid substance abuse. Stage 4 • A trial of clozapine and a first generation antipsychotic, second generation antipsychotic or electroconvulsive therapy are considered appropriate treatment options. • Monotherapy should be exhausted before using combination therapy. Stage 5 • A trial of a single first or second generation antipsychotic not tried in Stages 1 or 2 is recommended. Stage 6 • Combination therapy (first and second generation antipsychotics, combination of second generation antipsychotics, first or second generation antipsychotics and electroconvulsive therapy, first or second generation antipsychotic and other agent-mood stabilizer) is recommended. • Little evidence supports combination therapy due to increased risk of drug interactions, side effects and decreased safety and compliance.
American Psychiatric Association (APA): **Practice Guideline for the Treatment of Patients with Schizophrenia (2004)†**[299]	Acute phase • Pharmacological treatment with aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone should begin at once with the first episode. • Patients with persistent suicidal behavior or persistent hostility and aggressive behavior should be treated with clozapine. • Patients with tardive dyskinesia should be treated with clozapine or second generation antipsychotics.

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	• Patients sensitive to extrapyramidal side effects should be treated with a second generation antipsychotics (except clozapine); if risperidone is used, high doses are not recommended. • Patients sensitive to prolactin elevations should be treated with a second generation antipsychotics (except clozapine and risperidone). • Patients sensitive to weight gain, hyperglycemia, or hyperlipidemia should be treated with either aripiprazole or ziprasidone. • Patient's nonadherent to pharmacological treatment should be treated with long-acting injectable antipsychotic agents. • Agent should be chosen based on clinical circumstances and side effects. • For intolerable side effects, one of the following should be chosen: aripiprazole, a first generation antipsychotic, olanzapine, quetiapine, risperidone or ziprasidone. • For an inadequate response, a different agent should be chosen: aripiprazole, clozapine, a first generation antipsychotic, olanzapine, quetiapine, risperidone or ziprasidone. • For an inadequate response to a second agent, a different agent should be chosen; aripiprazole, clozapine, a first generation antipsychotic, olanzapine, quetiapine, risperidone or ziprasidone. • Clozapine should be used to treat persistent psychotic symptoms. Consider electroconvulsive therapy for persistent severe psychosis, catatonia, and/or suicidal behavior in patients who failed prior treatments (including clozapine). • Clozapine has the greatest efficacy on suicidal behavior and it should be considered in patients with suicidal ideation. • Electroconvulsive therapy is used when a schizophrenic patient has not responded to antipsychotic treatment. When electroconvulsive therapy is administered in conjunction with an antipsychotic agent (either a first or second generation antipsychotic, it provides the largest benefit; however electroconvulsive therapy should not be used prior to a trial of clozapine. <u>Stabilization or maintenance phase</u> • The goal of medication in the stable phase is to minimize the risk of relapse, severity of side effects and possible residual symptoms. • Continue with acute phase treatment. Electroconvulsive therapy should be considered for maintenance therapy for patients who have used electroconvulsive therapy in acute treatment with good response and who were not controlled with medication alone. • Maintenance electroconvulsive therapy may help patients who have responded to acute electroconvulsive therapy and pharmacological prophylaxis is ineffective or intolerable. Evidence shows that antipsychotics should be used with electroconvulsive therapy maintenance. • For intolerable side effects, another agent should be chosen; aripiprazole, a first generation antipsychotic, olanzapine, quetiapine, risperidone or ziprasidone.
Metabolic Side Effects	
American Diabetes Association (ADA), American Psychiatric	• Second-generation antipsychotics are more effective than first-generation antipsychotics in the treatment of negative symptoms and have fewer or no extrapyramidal side effects at clinically effective

Guideline	Recommendations
Association (APA), American Association of Clinical Endocrinologists (AACE), North American Association for the Study of Obesity (NAASO): **Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes (2004)**[300]	doses. • The second generation antipsychotics are a widely used and they have important public health ramifications. • Whether the prevalence of metabolic disorders is increased in psychiatric patient populations independent of drug therapy is difficult to determine. • Study data suggests that the prevalence of both diabetes and obesity among individuals with schizophrenia and affective disorders is 1.5-2.0 times higher than in the general population. • Whether a function of the illness itself or from the pharmacologic treatment, the limited amount of epidemiological data suggests an increased prevalence of obesity, impaired glucose tolerance and type 2 diabetes in patients with psychiatric illness. • Treatment with a second generation antipsychotic particularly in patients with schizophrenia can cause a rapid increase in body weight that may not reach a plateau even after 1 year of treatment. • There have been numerous reports of the onset or exacerbation of diabetes following the initiation of therapy with many of the second generation antipsychotics and in some cases, hyperglycemia promptly resolved after the medication was discontinued. • According to current evidence, changes in serum lipids correspond with changes in body weight. • The benefits of first and second generation antipsychotics in certain patients could outweigh the potential risks. • Patients taking second generation antipsychotics should receive appropriate baseline screening and ongoing monitoring due to the health risks associated with these medications. • Further research is needed to better understand the relationship between first and second generation antipsychotics and significant weight gain, dyslipidemia and diabetes.

† The American Psychiatric Association (APA) provides the following statement: this guideline is more than 5 years old and has not yet been updated to ensure that it reflects current knowledge and practice. In accordance with national standards, including those of the Agency for Healthcare Research and Quality's National Guideline Clearinghouse, this guideline can no longer be assumed to be current.

Table 15. Clinical Guidelines in Children and Adolescents

Guideline	Recommendations
Anxiety Disorders	
American Academy of Child and Adolescent Psychiatry (AACAP): **Practice Parameter for the Assessment and Treatment of Children and Adolescents with Anxiety Disorders (2007)**[301]	• The psychiatric assessment should consider differential diagnosis of other physical conditions and psychiatric disorders that may mimic anxiety symptoms (MS). • Treatment planning should consider a multimodal treatment approach (CG). • Psychotherapy should be considered as part of the treatment of children and adolescents with anxiety disorders (CG). o CBT has the most empirical support for the treatment of anxiety disorders in youths. • SSRIs should be considered for the treatment of youths with anxiety disorders. • There is no empirical evidence that any one SSRI is more effective than another for the treatment of childhood anxiety disorders. • Medications other than SSRIs may be considered for the treatment of youths with anxiety disorders (OP).

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	These include venlafaxine, tricyclic antidepressants, buspirone, and benzodiazepines.
Bipolar Disorder	
American Academy of Child and Adolescent Psychiatry (AACAP): **Practice Parameter for the Assessment and Treatment of Children and Adolescents with Bipolar Disorder (2007)**[302]	• Youth with suspected bipolar disorder must also be carefully evaluated for other associated problems, including suicidality, comorbid disorders (including substance abuse), psychosocial stressors, and medical problems (MS). • The diagnostic validity of bipolar disorder in young children has yet to be established. Caution must be taken before applying this diagnosis in preschool children (MS). • For mania in well-defined DSM-IV-TR bipolar I disorder, pharmacotherapy is the primary treatment (MS). o Standard therapy, based on adult literature, includes lithium, valproate, and/or atypical antipsychotic agents, with other adjunctive medications used as indicated. o The choice of medication should be based on 1) evidence of efficacy, 2) illness phase, 3) presence of confounding symptoms, 4) side effects, 5) patient's medication response history, 6) patient and family preferences. o Clozapine is reserved for treatment-refractory cases because of its side effect profile. o Antidepressants may be used as adjunctive therapy for bipolar depression. • Most youths with bipolar I disorder will require ongoing medication therapy to prevent relapse; some individuals will need lifelong treatment (CG). • Psychopharmacological interventions require baseline and follow-up symptoms, side effect (including patient's weight), and laboratory monitoring as indicated (MS). o A 6-8 week trial of a mood-stabilizing agent is recommended, using adequate doses, before adding or substituting other mood stabilizers. • For severely impaired adolescents with manic or depressive episodes in bipolar I disorder, electroconvulsive therapy (ECT) may be used if medications either are not helpful or cannot be tolerated (OP). • Psychotherapeutic interventions are an important component of a comprehensive treatment plan for early-onset bipolar disorder (MS). • The treatment of bipolar disorder not otherwise specified (NOS) generally involves the combination of psychopharmacology with behavioral/psychosocial interventions (CG).
National Collaborating Centre for Mental Health, National Institute for Health and Clinical Excellence (NICE): **Bipolar Disorder: The Management of Bipolar Disorder in Adults, Children and Adolescents, in Primary And Secondary Care (2006)**[303]	<u>Acute manic episode in children and adolescents</u> • An antipsychotic or valproate should be used for severe manic symptoms marked by behavioral disturbance. Lithium may be used if symptoms are not severe due to its slower onset of action. • If there is an inadequate response to an antipsychotic, adding lithium or valproate should be considered. • For an acute manic episode while on lithium or valproate, dose should be optimized, then if there are no signs of improvement, olanzapine, quetiapine or risperidone may be added. • Valproate should be avoided in girls and young women because of risks during pregnancy and risk of polycystic ovary syndrome. • At the start of therapy and periodically thereafter, height, weight and

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	prolactin levels should be measured. • When considering an antipsychotic, the risk of increased prolactin levels with risperidone and weight gain with olanzapine should be considered. <u>Acute depressive episode in children and adolescents</u> • Patients with mild depressive symptoms, not requiring immediate treatment should be monitored. • Children and adolescents with depressive symptoms needing treatment should be treated by specialists. • A structured psychological therapy aimed at treating depression should be considered in addition to prophylactic medication. • When prescribing an antidepressant, an antimanic agent should also be prescribed. • Patients with an incomplete response to antidepressant therapy may be managed by increasing the dose, switching antidepressants (e.g., mirtazapine or venlafaxine), adding an antipsychotic (olanzapine or quetiapine) or adding lithium. • Patients with concurrent depressive and psychotic symptoms may be managed with olanzapine, quetiapine, or risperidone if the depressive illness is severe.
Depressive Disorder	
American Academy of Child and Adolescent Psychiatry (AACAP): **Practice Parameter for the Assessment and Treatment of Children and Adolescents With Depressive Disorders (2007)**[304]	• The clinician should maintain a confidential relationship with the child or adolescent while developing collaborative relationships with parents, medical providers, other mental health professionals, and appropriate school personnel (MS). • The psychiatric assessment of children and adolescents should routinely include screening questions about depressive symptomatology (MS). • If the screening indicates significant depressive symptomatology, the clinician should perform a thorough evaluation to determine the presence of depressive and other comorbid psychiatric and medical disorders (MS). • The evaluation must include assessment for the presence of harm to self or others (MS). • The evaluation should assess for the presence of ongoing or past exposure to negative events, the environment in which depression is developing, support and family psychiatric history (MS). • The treatment of depressive disorders should always include an acute and continuation phase; some children may also require maintenance treatment (MS). • Each phase of treatment should include psychoeducation, supportive management, and family and school involvement (MS). • Education, support, and case management appear to be sufficient treatment for the management of depressed children and adolescents with an uncomplicated or brief depression or with mild psychosocial impairment (CG). • For children and adolescents who do not respond to supportive psychotherapy or who have more complicated depressions, a trial with specific types of psychotherapy and/or antidepressants is indicated (CG). • Selective serotonin reuptake inhibitors (SSRIs) is the most commonly

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Guideline	Recommendations
	used pharmacotherapy for depression in youths. Clinical response should be assessed at 4-week intervals, and if the response is inadequate, the dose may be increased. • To consolidate the response to the acute treatment and avoid relapses, treatment should always be continued for 6 to 12 months (MS). • To avoid recurrences, some depressed children and adolescents should be maintained on treatment for longer periods of time (CG). • Depressed patients with psychosis, seasonal depression, and bipolar disorder may require specific somatic treatment. o Atypical antipsychotics, combined with SSRIs, are recommended as the treatment of choice for depressed psychotic youths. • Treatment should include the management of comorbid conditions (MS). • During all treatment phases, clinicians should arrange frequent follow-up contacts that allow sufficient time to monitor the subject's clinical status, environmental conditions, and if appropriate, medication side effects (MS).
Obsessive Compulsive Disorder (OCD)	
American Academy of Child and Adolescent Psychiatry (AACAP): **Practice Parameter for the Assessment and Treatment of Children and Adolescents Obsessive-Compulsive Disorders (2012)**[305]	• The psychiatric assessment of children and adolescents should routinely screen for the presence of obsessions and/or compulsions or repetitive behaviors (CG). • A complete psychiatric evaluation should be performed, including information from all available sources and comprising standard elements of history and a mental state examination, with attention to the presence of commonly occurring comorbid psychiatric disorders (CS). • A full medical, developmental, family, and school history should be included with the psychiatric history and examination (CG). • When possible, cognitive behavioral therapy (CBT) is the first-line treatment for mild to moderate cases of OCD in children (CS). • For moderate-severe OCD, medication is indicated in addition to CBT (CS). • SSRIs are the first-line medications recommended for OCD in children (CS). • Multimodal treatment is recommended if CBT fails to achieve a clinical response after several months or in more severe cases (CS). • For greatest efficacy, the combination of CBT and medication is the treatment of choice and should be considered the default option for first-line treatment in moderate to severe OCD. • Medication augmentation strategies are reserved for treatment-resistant cases in which impairments are deemed moderate in at least one important domain of function despite adequate monotherapy (OP). o Treatment resistance is defined as failure of adequate trials of at least two SSRIs or one SSRI and a clomipramine trial (as monotherapy) AND a failure of adequately delivered CBT (no improvement or substantial residual OCD symptoms after 8-10 total sessions). Children should have a minimum of 10 weeks of each SSRI or clomipramine at maximum recommended or maximum tolerated doses, with no change

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Guideline	Recommendations
	in dose for the preceding 3 weeks. • The most commonly used augmentation strategy is the addition of atypical antipsychotics; though, there is no controlled data for the use of these agents in children with OCD. • According to expert consensus, some children with treatment-resistant OCD may benefit from judicious antipsychotic augmentation, particularly children with tic disorders, poor insight, pervasive developmental disorder symptoms, and mood instability. Clinical experience indicates a minimum of two different adequate SSRI trials or an SSRI and clomipramine before antipsychotic augmentation. • When atypical antipsychotics are used, at a minimum, there should be regular weight, fasting lipid profile, serum glucose and adverse event monitoring. • Other augmentation strategies include addition of clomipramine to an SSRI or addition of either venlafaxine or duloxetine to an SSRI.
Oppositional Defiant Disorder (ODD)	
American Academy of Child and Adolescent Psychiatry (AACAP): **Practice Parameter for the Assessment and Treatment of Children and Adolescents with Oppositional Defiant Disorder (2007)**[306]	• Successful assessment and treatment of oppositional defiant disorder (ODD) requires the establishment of therapeutic alliances with the child and family (Minimal Standards [MS]). • Cultural issues need to be actively considered in diagnosis and treatment (MS). • The assessment of ODD includes information obtained directly from the child as well as from the parents regarding the core symptoms of ODD, age at onset, duration of symptoms, and degree of functional impairment (MS). • Clinicians should carefully consider significant comorbid psychiatric conditions when diagnosing and treating ODD (MS). • Clinicians may find it helpful to include information obtained independently from multiple outside informants (Clinical Guidelines [CG]). • The use of specific questionnaires and rating scales may be useful in evaluating children for ODD and in tracking progress (Options [OP]). • The clinician should develop an individualized treatment plan based on the specific clinical situation [MS]. Multimodal treatment is often indicated. • The clinician should consider parent intervention based on one of the empirically tested interventions (MS). • Medications may be helpful as adjuncts to treatment packages, for symptomatic treatment and to treat comorbid conditions (CG). o Medication should not be the sole intervention in ODD. o Nonresponsiveness to a specific compound should lead to a trial of another class of medication rather than the rapid addition of other medications. o Treatment options include mood stabilizers, such as divalproex sodium, lithium, antipsychotics, and stimulants. Atypical antipsychotics are the most commonly prescribed medication class for the treatment of acute and chronic maladaptive aggression, regardless of diagnosis. • Intensive and prolonged treatment may be required if ODD is unusually severe and persistent (CG).
Post-Traumatic Stress Disorder (PTSD)	
American Academy of	• The psychiatric assessment should consider differential diagnoses of

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Guideline	Recommendations
Child and Adolescent Psychiatry (AACAP): **Practice Parameter for the Assessment and Treatment of Children and Adolescents with Posttraumatic Stress Disorder (2010)**[307]	other psychiatric disorders and Physical conditions that may mimic posttraumatic stress disorder (PTSD) (MS). • Treatment planning should consider a comprehensive treatment approach which includes consideration of the severity and degree of impairment of the child's PTSD symptoms (MS). • Treatment planning should incorporate appropriate interventions for comorbid psychiatric disorders (MS). • Trauma-focused psychotherapies should be considered first-line treatment for children and adolescents with PTSD (MS). • SSRIs can be considered for the treatment of children and adolescents with PTSD (OP). o There is insufficient data to support the use of SSRIs in the absence of psychotherapy for the treatment of childhood PTSD. • Medications other than SSRIs may be considered for children and adolescents with PTSD (OP) o These include alpha- and beta-adrenergic blockers, atypical antipsychotics, non-SSRI antidepressants, mood-stabilizing agents, and opiates.
Schizophrenia	
American Academy of Child and Adolescent Psychiatry (AACAP): **Practice Parameter for the Assessment and Treatment of Children and Adolescents with Schizophrenia (2001)**[308]	• Adequate treatment requires the combination of psychopharmacological agents and psychosocial interventions [MS]. <u>Pharmacotherapy:</u> • Antipsychotic agents are recommended for the treatment of the psychotic symptoms associated with schizophrenia [MS]. • First-line agents include traditional neuroleptic medications (block dopamine receptors) and the atypical antipsychotic agents (that have a variety of effects, including antagonism of serotonergic receptors). Compared with traditional agents, the atypical antipsychotics are at least as effective for positive symptoms and they may be more helpful for negative symptoms. • The use of antipsychotic drugs requires the following: adequate informed consent, documentation of target symptoms, baseline and follow-up laboratory monitoring, documentation of treatment response, monitoring for known side effects adequate therapeutic trials (appropriate dose for 4-6 weeks), • In general, first-episode patients should receive some maintenance psychopharmacological treatment for 1 to 2 years after the initial episode, given the risk for relapse. • Some patients may benefit from the use of adjunctive agents, including antiparkinsonian agents, mood stabilizers, antidepressants, or benzodiazepines [CG]. <u>Psychosocial Interventions:</u> • Psychoeducational therapy for the patient, including ongoing education about the illness, treatment options, social skills training, relapse prevention, basic life skills training, problem-solving skills and strategies, is recommended [MS]. • Psychoeducational therapy for the family, to increase their understanding of the illness, treatment options, prognosis and for developing strategies to cope with the patient's symptoms, is

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Guideline	Recommendations
	recommended [MS].
Tourette's Syndrome	
European Society for the Study of Tourette Syndrome (ESSTS): **European Clinical Guidelines for Tourette Syndrome and other Tic Disorders. Part II: Pharmacological Treatment (2011)**[309]	• Based on the available evidence, experience with the drug, and experts' preference, risperidone is recommended as a first line agent for the treatment of tics. Weight gain and sedation are common side effects of risperidone therapy. • Aripiprazole has a role in treatment refractory cases and is associated with a smaller risk of severe weight gain. • Clonidine may be used, especially in the presence of comorbid ADHD.
General Guidance	
American Academy of Child and Adolescent Psychiatry (AACAP): **Practice Parameter for the Use of Atypical Antipsychotic Medications in Children and Adolescents (2011)**[310]	• Clozapine-in children and adolescents, the strongest empirical evidence is in patients with refractory schizophrenia or those who require antipsychotic treatment but who have a history of severe EPS with other agents. • Risperidone-of the atypical antipsychotics, it has the most substantial amount of methodologically stringent evidence for use in children and adolescents. • Olanzapine-of the atypical antipsychotics, its receptor binding profile most closely matches that of clozapine. Limited long-term data exists. Olanzapine is associated with substantial weight gain. • Quetiapine, ziprasidone and aripiprazole have clinical trial evidence for use in children and adolescents. • Prior to the initiation of and during treatment with an atypical antipsychotic, the general guidelines that pertain to the prescription of psychotropic medications should be followed (CS). o These include diagnostic assessment, attention to comorbid medical conditions, review of concomitant drugs, multi-disciplinary plan, including education and psychotherapy, and a thorough discussion of the risks and benefits of psychotropic treatment. • When selecting any atypical antipsychotic for use in a child or adolescent, the clinician should follow the most current available evidence in the scientific literature (CS). • Table 16 provides a summary of the literature supporting the use of atypical antipsychotics in specific clinical populations. • There is almost no data to support the use of atypical antipsychotics in pre-school aged children. A marked amount of caution is advised before using these agents in preschoolers. • Due to the specific risks associated with the use of atypical antipsychotics, additional factors to address, prior to the initiation of treatment with the atypical antipsychotics, include obtaining a personal and family history of diabetes and hyperlipidemia, seizures and cardiac abnormalities, as well as any family history of previous response or adverse events associated with atypical antipsychotics (CS). • Dosing of atypical antipsychotics should follow the "start low and go slow" approach and seek to find the lowest effective dose, recognizing that dosing may differ based on the targeted symptoms and patient diagnosis (CG). • If side-effects do occur, a trial at a lower dose should be considered;

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<table>
<tr><th>Guideline</th><th>Recommendations</th></tr>
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however, certain side effects may preclude further treatment with the specific atypical antipsychotic (CG).
• The use of multiple psychotropic medications in refractory patients may, at times, be necessary but has not been studied rigorously and clinicians should proceed with caution (OP).
• The simultaneous use of multiple atypical antipsychotics has not been studied rigorously and generally should be avoided (NE).
  o Consideration of medication combinations should only begin after patients are refractory to medication trials of each atypical antipsychotic and, perhaps, older antipsychotic agents or other evidence-supported agents (such as mood stabilizers) at the appropriate target dose(s) and length of treatment.
• After the failure of one atypical antipsychotic (after 4-6 week therapy), the selection of an alternative agent may include consideration of another atypical antipsychotic and/or a medication from a different class of drugs (OP).
• The acute and long-term safety in children and adolescents has not been fully evaluated and therefore careful and frequent monitoring of side effects is indicated (CG). See table below.
<table>
<tr><th>Monitoring parameters</th><th>Baseline</th><th>4 weeks</th><th>8 weeks</th><th>12 weeks</th><th>Annually</th></tr>
<tr><td>Personal/family history</td><td>X</td><td></td><td></td><td></td><td>X</td></tr>
<tr><td>Weight (BMI)</td><td>X</td><td>X</td><td>X</td><td>X</td><td></td></tr>
<tr><td>Waist circumference</td><td>X</td><td></td><td></td><td></td><td>X</td></tr>
<tr><td>Blood pressure</td><td>X</td><td></td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>Fasting plasma glucose</td><td>X</td><td></td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>Fasting lipid profile (LDL, HDL, TG, total chol.)</td><td>X</td><td></td><td>X</td><td>X</td><td></td></tr>
</table>
• BMI should be obtained at baseline and monitored at regular intervals throughout treatment with an atypical antipsychotic. Careful attention should be given to the increased risk of developing diabetes with the use of atypical antipsychotics, and blood glucose levels and other parameters should be obtained at baseline and monitored at regular intervals (CS).
• In those patients with significant weight changes and/or a family history indicating high risk, lipid profiles should be obtained at baseline and monitored at regular intervals (CG).
• Measurements of movement disorders utilizing structured measures, such as the abnormal involuntary movement scale, should be done at baseline and at regular intervals during treatment and during tapering of the atypical antipsychotic (CS).
• Due to limited data surrounding the impact of atypical antipsychotics on the cardiovascular system, regular monitoring of heart rate, blood pressure and EKG changes should be performed (CG). Due to the increased risk of QTc changes with ziprasidone, obtaining an ECG at baseline and once a stable dose is achieved is recommended.
• Although there is a relationship between atypical antipsychotics and elevation in prolactin, the current state of evidence does not support the need for routine monitoring of prolactin levels in asymptomatic youths (OP).
• The limited long-term safety and efficacy data warrants careful consideration, before the initiation of medication, of the planned duration of the medication trial (CG).
• Abrupt discontinuation of a medication is not recommended (CS).
</td></tr>
</table>

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CS=Clinical Standard (recommendations that are based on rigorous empirical evidence and/or overwhelming clinical consensus); CG=Clinical Guideline (recommendations that are based on strong empirical evidence and/or strong clinical consensus); OP=Option (recommendations that are based on emerging empirical evidence or clinical opinion but lack strong empirical evidence and/or strong clinical consensus); MS= Minimal standard (recommendations that are based on rigorous empirical evidence and/or overwhelming clinical consensus); NE=Not Endorsed (practices that are known to be ineffective or contraindicated)

Table 16. Evidence for the Use of Atypical Antipsychotics (adopted from the AACAP guideline)[310]

	Clozapine	Risperidone	Olanzapine	Quetiapine	Ziprasidone	Aripiprazole
Schizophrenia/ Psychosis	+++	+++*	++++*	++++*	+	++++*
Bipolar Disorder	++	+++*	+++*	++++*	+++	+++*
Disruptive behavior disorders/ Aggression	++	+++	+++	++	+	+
Autism/ PDD irritability	+	++++*	+++	+	+	++++*
Tourettes/ tics		++++	+		+++	
PTSD	+					
Eating Disorder			+			
Long-term safety studies		+		+		

PDD=pervasive developmental disorder; PTSD=post-traumatic stress disorder
++++ Multiple randomized controlled studies
+++ One randomized controlled study
++ Uncontrolled study
+ Case studies
* FDA approved in children and/or adolescents

Conclusions

The antipsychotics are divided into two distinct classes: typical antipsychotics, also called first-generation antipsychotics (FGAs), and the atypical antipsychotics, which collectively are also referred to as second-generation antipsychotics (SGAs).[1] These agents are available in various dosage forms including capsules, tablets, injections, oral solutions, sublingual tablets, and orally disintegrating tablets.

There are multiple FGAs and, with the exception of haloperidol and pimozide, all are indicated for the treatment of schizophrenia. The FGAs are effective in the treatment of positive symptoms of schizophrenia (agitation, aggression, delusions and hallucinations), but are thought to be less effective against the negative symptoms (avolition, anhedonia, alogia, affective flattening and social withdrawal).[4] FGAs are also approved for the management of various manifestations of other psychotic disorders and the suppression of motor and phonic tics in patients with Tourette's disorder. Adverse events are common with the FGAs, potentially resulting in these agents being used in a more limited capacity.[1,4]

Each of the SGAs has a distinctive neuropharmacologic and adverse event profile, mechanism of action and chemical structure. It should be noted that paliperidone is an active metabolite of risperidone and therefore carries some similarity in chemical structure and pharmacologic effects with the parent drug. When compared to the FGAs, the SGAs are associated with a lower risk of extrapyramidal symptoms (EPS) and tardive dyskinesia, making them a generally better-tolerated treatment option. The SGAs are approved for the treatment of bipolar disorder and/or schizophrenia and are often a preferred treatment over the FGAs since they are thought to have a more favorable outcome in the treatment of the negative symptoms of schizophrenia.[1] Moreover, several agents have recently been approved for the treatment of schizoaffective disorder, irritability associated with autistic disorder and for the adjunctive treatment of major depressive disorder.[6,13,16-17] While the use of atypical antipsychotics in pediatric patients is in many instances off-label, aripiprazole, olanzapine, paliperidone, quetiapine, and risperidone have been recently FDA approved for children and/or adolescents with bipolar disorder and/or schizophrenia. Aripiprazole and risperidone are also FDA approved for use in children and adolescents suffering from irritability secondary to autistic disorder.[6,13]

However, the SGAs are not without their own safety concerns. Clozapine, the first SGA approved by the Food and Drug Administration, has had its use limited due to a risk of agranulocytosis, which has resulted in a black boxed warning.[8,9] This agent also carries a boxed warning for cardiac toxicity, seizures,

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orthostatic hypotension, and respiratory and cardiac arrest. In addition, all SGAs are associated with a risk of metabolic adverse events, including the risk of potentially fatal hyperglycemia and diabetes. Moreover, while the information in the individual product package inserts may vary, all SGAs increase the QTc interval to some degree. Another concern is the use of these agents in patients with dementia. Although atypical antipsychotics have demonstrated efficacy in this patient population, the risks versus benefits must be weighed. A black boxed warning notes an association between the use of atypical antipsychotics and an increased risk of death when used in the treatment of psychosis and behavioral problems in elderly patients with dementia. Specific causes of death are most likely due to cardiac related events (eg, heart failure or sudden death) or infection.[6-11, 13-19, 21-23] Of note, this black box warning is directed at a non-FDA approved, or off-label, use of atypical antipsychotics.[6-11, 13-19, 21-23]

Meta-analyses evaluating the roles of available atypical antipsychotics in the treatment of schizophrenia suggest that all agents are significantly more effective than placebo.[59-71, 81-85] The trends for respective efficacy suggest that clozapine is the most effective agent in the class, followed by olanzapine and risperidone. In clinical trials, aripiprazole tended to exhibit lower efficacy than the other agents.[59-71, 81-85] A meta-analysis in adult patients with bipolar disorder found risperidone to be the most effective treatment option (taking into account both efficacy and tolerability).[81] The next best treatment options, in order of decreased efficacy were olanzapine, haloperidol, quetiapine, carbamazepine, aripiprazole, valproate, lithium, and ziprasidone. Lamotrigine, topiramate and gabapentin were found to be less effective than placebo. In the management of major depressive disorder, aripiprazole, quetiapine, and risperidone augmentation therapies were associated with improved outcomes.[90]

Off-label use of atypical antipsychotics in both adult and pediatric populations is widespread. This review undertook the task of evaluating available literature on the use of atypical antipsychotics for the following off-label indications: anorexia, autism, anxiety disorders, ADHD, dementia, eating disorders, disruptive behavior disorder, insomnia, obsessive compulsive disorder, post-traumatic stress disorder, personality disorder, pervasive developmental disorder, and Tourette's syndrome. Augmentation with atypical antipsychotics for the treatment of patients with anxiety disorders was associated with mixed results.[92,93] Atypical antipsychotics were associated with a moderate effect on anger associated with borderline personality disorder, with no effect on depressive symptoms.[94,95] Mood stabilizers were found to offer greater benefit in these patients.[95] All evaluated atypical antipsychotics were found to improve symptoms of agitation/aggression secondary to dementia.[96-104] When used as a part of multimodal therapy, SGAs have some limited evidence for use in patients with anorexia.[110-112] However, the AHRQ review does not recommend the use of these agents for eating disorders.[202] Available evidence in pediatric patients with clinically significant aggression suggests a potential benefit in the short-term use of SGAs (majority of evidence is with risperidone).[125-143] Aripiprazole and risperidone are supported by evidence-based medicine for use in patients with irritability/agitation or aggression secondary to an autistic spectrum disorder.[147-167] Atypical antipsychotics (aripiprazole, quetiapine, risperidone, olanzapine and ziprasidone) were also shown to reduce tic severity in patients with Tourette's syndrome.[188-196,202]

Available evidence suggests that, except for clozapine, olanzapine is associated with greater weight gain compared to all other atypical antipsychotic agents. In contrast, ziprasidone is associated with a low incidence of weight gain.[227] A systematic review by Safer et al suggests that weight gain is greater in children and adolescents than in adults.[270] In addition, olanzapine is associated with a greater risk of other metabolic side-effects, such as hyperglycemia and hypercholesterolemia, versus other atypical antipsychotics. Likewise, data from the FDA Adverse Reporting System (AERS) indicates that the risk of experiencing a diabetes-related adverse event is greatest with olanzapine, followed by risperidone, and least with ziprasidone and aripiprazole, across all age groups.[256] Of note, despite the increased metabolic risk with olanzapine, the Zodiac study failed to find a significant difference in non-suicide mortality between patients exposed to olanzapine and ziprasidone.[203] Risperidone is associated with the greatest risk of prolactin elevation-related adverse events.[59-71,81-85,273] In addition, risperidone, aripiprazole and ziprasidone are associated with a high incidence of extrapyramidal adverse events.[235] Quetiapine is associated with the least risk of extrapyramidal adverse events.[235] The incidence of sexual dysfunction

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was noted to be higher with the use of olanzapine, risperidone, and clozapine than with quetiapine, ziprasidone or aripiprazole.[239]

As mentioned previously, available clinical consensus guidelines do not differentiate among the different SGAs; however, they provide guidance on the place in therapy of antipsychotics as a class in various disease states, both FDA-approved and off-label. The use of these agents for the treatment of schizophrenia is recognized by national and international guidelines as a mainstay in therapy.[297-299,308] Lithium, valproate and/or antipsychotics are recommended as initial therapy of bipolar disorder.[284-287,302-303] Furthermore, the APA guideline recommends the use of antipsychotics for the management of psychosis or agitation in patients with dementia.[288] For the treatment of anxiety disorders, sertraline is recommended as a first-line pharmacotherapeutic agent.[283] Second-line treatment options include SNRIs or switching to alternative SSRIs. Augmentation therapy with antipsychotics is an option in treatment-refractory patients but the guidelines recommend that initiation of combination therapy be limited to specialists. In MDD, first-line treatment options include SSRIs, SNRIs, bupropion or mirtazapine.[291-293] Antipsychotic augmentation therapy is an option for patients who have failed antidepressant monotherapy. In OCD, SSRIs and cognitive behavioral therapy are recommended as first-line treatment options.[294] Patients who have failed an SSRI trial may be offered augmentation therapy with an antipsychotic or cognitive behavioral therapy. Similarly, SSRIs and SNRIs are considered to be first-line treatment options for the treatment of PTSD.[295] Atypical antipsychotics may be used as adjunctive therapy for the management of treatment-refractory PTSD. Furthermore, the ESSTS guideline recommends risperidone as a first-line agent for the treatment of tics.[309] Aripiprazole has a role in treatment-refractory patients. Moreover, the AACAP guideline acknowledges that atypical antipsychotics are the most commonly prescribed class of drugs for the treatment of maladaptive aggression, regardless of diagnosis; yet emphasize that pharmacotherapy should not be used as the only intervention in children with oppositional defiant disorder.[306] Although the antipsychotics are not addressed in national and international insomnia treatment guidelines, the National Institute of Health (NIH) Consensus and State-of-the-Science Statement on Manifestations and Management of Chronic Insomnia in Adults state that due to the lack of evidence supporting the short and long term efficacy of antipsychotics, in addition to their significant risks, their use in the treatment of chronic insomnia cannot be recommended.[311]

In a practice guideline on the use of atypical antipsychotics in children and adolescents, issued by the AACAP in 2011, the panel recommends that prior to initiation of antipsychotic therapy patients should undergo a thorough diagnostic assessment, evaluation for comorbid medical conditions and concomitant medications.[310] Furthermore, a multidisciplinary plan that includes education and psychotherapy should be established. The prescriber should also have a thorough discussion of the risks and benefits of psychotropic medication. Of the atypical antipsychotics, risperidone is recognized as an agent with the most substantial amount of methodologically stringent evidence for use in pediatric patients. Of note, combination antipsychotic therapy has not been well studied and should be avoided, unless the patient has failed trials of all antipsychotic agents, used as monotherapy. In addition, there is almost no data to support the use of atypical antipsychotics in pre-school aged children. The guideline recommends a marked amount of caution before using these agents in pre-schoolers. Given the risk of metabolic side-effects, pediatric patients receiving atypical antipsychotic therapy should be closely monitored for changes in weight, blood pressure, fasting plasma glucose and lipid profile.

Therapeutic duplication with the atypical antipsychotics is also of concern in adults due to the inherent risks of polypharmacy (eg, adverse events, drug interactions, decreased adherence) and lack of sufficient evidence and guidelines supporting clinical value with such practice. This risk is exemplified by results of clinical trials demonstrating that combination antipsychotic therapy results in a greater risk of metabolic adverse events.[245-253]

Therefore, to ensure their appropriate use, all brand and generic products within the antipsychotics class should be managed, taking into consideration factors that would optimize a balance of inducing and maintaining symptom efficacy, minimization of non-therapeutic effects, and enhancing cost-effectiveness.

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Appendix Ia: Summary of the Strength of Evidence for Off-Label Efficacy Outcomes (adopted from 2011 AHRQ systematic review)[202]

Indication	Strength of Evidence	Findings	Conclusions
Dementia	**High**	The 2011 meta-analysis of PCTs, aripiprazole, olanzapine, and risperidone were superior to placebo as treatment of behavioral symptoms as measured by total scores on BEHAVE-AD, BPRS, and NPI. Effect sizes were generally considered to be "small" in magnitude. Psychosis –risperidone was superior to placebo, as measured by thepsychosis subscales of the BEHAVE-AD, BPRS, and NPI. Results for aripiprazole did not meet conventional levels of statistical significance. Agitation – Aripiprazole, olanzapine and risperidone were superior to placebo, as measured by the agitation subscales of the BEHAVE-AD, BPRS, NPI, and CMAI. Three head to head trials compared atypicals; none was found superior.	Aripiprazole, olanzapine, and risperidone **have efficacy** as treatment for behavioral symptoms of dementia.
Depression			
Augmentation of SSRI/SNRI	**Moderate** (risperidone, aripiprazole, quetiapine) **Low** (olanzapine, ziprasidone)	The meta-analysis used "response" to treatment and remission as outcome. Pooling trials that reported the HAM-D as outcome, the relative risk of responding for participants taking quetiapine or risperidone was significantly higher than for placebo. Other trials reported MADRS scores; the relative risk of responding for participants taking aripiprazole was significantly higher than those taking placebo. Risperidone was included in two trials. These reported the drug superior to placebo. The relative risk of responding for participants taking aripiprazole was significantly higher than those taking placebo. Olanzapine had only two trials, so pooling was not performed; the trials reported olanzapine superior to placebo. In one available ziprasidone trial, the drug was superior to placebo in terms of MADRS scores. One trial compared ziprasidone at differing levels augmenting sertraline to sertraline alone. This trial found a greater improvement in CGI-S and MADRS scores augmenting with ziprasidone at 160mg than either augmentation with ziprasidone at 80mg or sertraline alone. However, there was no significant difference in HAMD-17, CGI-I or HAM-A scores.	Aripiprazole, quetiapine, and risperidone **have efficacy** as augmentation to SSRIs/SNRIs for major depressive disorder. Olanzapine and ziprasidone **may also have efficacy.**
Monotherapy	**Moderate**	Olanzapine alone was no better than placebo in improving symptoms at 6 or 12 weeks in three trials. Outcomes were too heterogeneous to allow pooling. In five PCTs, quetiapine was superior according to relative risk of both	Olanzapine **does not have efficacy** as monotherapy for major depressive disorder. Quetiapine **has efficacy** as monotherapy for major depressive disorder

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		responding and remitted as measured by MADRS.	
Obsessive Compulsive Disorder (OCD)			
Augmentation of SSRIs	**Moderate** (risperidone) **Low** (olanzapine)	The 2006 meta-analysis pooled results of 9 trials of risperidone, olanzapine, or quetiapine as augmentation therapy in patients who were resistant to treatment with SSRI. Atypical antipsychotics had a clinically important benefit, (measured by the Yale-Brown Obsessive-Compulsive Scale (YBOCS), when used as augmentation therapy. Relative risk of "responding" significant for augmentation with quetiapine and risperidone. The updated 2011 meta-analysis found risperidone superior to placebo, as measured by changes in the Y-BOCS. There were too few studies (2) of olanzapine augmentation to permit separate pooling of this drug. Both trials reported olanzapine superior to placebo. One new head to head trial found no difference in effect between olanzapine and risperidone as SSRI augmentation. One new head to head trial found quetiapine more effective than ziprasidone as SSRI augmentation. In one new trial, quetiapine produced a significant reduction in Y-BOCS score, while clomipramine did not.	Risperidone **has efficacy** in improving OCD symptoms when used as an adjunct to SSRI in treatment refractory patients. Olanzapine **may have efficacy.** Quetiapine is more **efficacious** than ziprasidone and clomipramine.
Augmentation of citalopram	**Low** (quetiapine) **Very low** (risperidone)	One trial of risperidone reported no differences between groups in achieving a response to therapy, but patients maintained on risperidone had a significantly longer period of time to relapse compared with placebo (102 days vs. 85 days). Two trials found quetiapine superior to placebo as augmentation for citalopram, according to Y-BOCS and CGI-I scores.	Quetiapine and risperidone **may be efficacious** as augmentation to citalopram in OCD patients.
Post-Traumatic Stress Disorder	**Moderate** (risperidone) **Low** (Olanzapine) **Very Low** (Quetiapine)	Three trials enrolled men with combat-related PTSD; these showed a benefit in sleep quality, depression, anxiety, and overall symptoms when risperidone or olanzapine was used to augment therapy with antidepressants or other psychotropic medication. Three trials of olanzapine or risperidone as monotherapy for abused women with PTSD were inconclusive regarding efficacy. One trial found a 3-fold decline in PTSD Scale (CAPS) scores in patients treated with quetiapine monotherapy compared with placebo. There were too few olanzapine studies (two) to pool; one reported olanzapine superior to placebo, while one did not. A meta-analysis of risperidone, using	Risperidone is **efficacious** in reducing combat-related PTSD symptoms when used as an adjunct to primary medication.

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		CAPS scores as outcome, found risperidone to be superior to placebo. In a meta-analysis by condition, atypical antipsychotics were efficacious for combat-related PTSD but not PTSD in abused women.	
Personality Disorders			
Borderline	**Low** (aripiprazole) **Very low** (quetiapine, olanzapine)	Four trials provide evidence that olanzapine is superior to placebo and may be superior to fluoxetine. The benefit of adding olanzapine to dialectical therapy in one trial was small. Two trials of olanzapine found no difference from placebo in any outcomes compared with placebo. Aripiprazole was superior to placebo in one small trial. Another trial found aripiprazole superior to placebo in improving SCL-90, HAM-D, and HAM-A scores at 8 months and less self-injury at 18 months. A trial of ziprasidone found no significant difference in CGI-BPD, depressive, anxiety, psychotic or impulsive symptoms compared with placebo at 12 weeks. One trial found quetiapine to be superior to placebo on BPRS and PANSS scales. Due to heterogeneity of outcomes, a meta-analysis could not be performed.	Olanzapine had **mixed results** in 7 trials, aripiprazole was found **efficacious** in two trials, quetiapine was found **efficacious** in one trial, and ziprasidone was found **not efficacious** in one trial.
Schizotypal	**Low**	Risperidone was superior to placebo in one small trial. In another trial risperidone was found to be no different from placebo on a cognitive assessment battery.	Risperidone had **mixed results** when used to treat schizotypal personality disorder in two small trials.
Tourette's Syndrome	**Low**	Risperidone was superior to placebo in one small trial, and it was at least as effective as pimozide or clonidine for 8 to 12 weeks of therapy in the three other trials. One trial of ziprasidone showed variable efficacy compared with placebo.	Risperidone **is at least as efficacious as pimozide or clonidine** for Tourette's syndrome
Anxiety	**Moderate**	Three placebo-controlled trials of quetiapine as monotherapy for Generalized Anxiety Disorder (GAD) could be pooled; relative risk of responding on HAM-A favored the quetiapine group. One head to head trial showed no difference between risperidone and paroxetine on HAM-A score improvement. One trial each found quetiapine equally effective as paroxetine and escitalopram.	Quetiapine **has efficacy** as treatment for Generalized Anxiety Disorder
Attention Deficit/Hyperactivity Disorder			
No comorbidity	**Low**	One trial showed risperidone superior to placebo in reducing scores on the Children's Aggression Scale –Parent version (CAS-P).	Risperidone **may be efficacious** in treating children with ADHD with no serious co-occurring disorders.
Mental retardation	**Low**	One trial showed risperidone led to greater reduction in SNAP-IV (Swanson, Nolan, and Pelham teacher & parent rating scale) scores than methylphenidate.	Risperidone **may be superior to methylphenidate** in treating ADHD symptoms in mentally retarded children.

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Bipolar	**Low**	Two trials of aripiprazole showed no effect on SNAP-IV (Swanson, Nolan, and Pelham teacher & parent rating scale) scores than placebo.	Aripiprazole is **inefficacious** in reducing ADHD symptoms in children with bipolar disorder.
Eating Disorders	**Moderate** (olanzapine) **Low** (quetiapine)	In a pooled analysis of 3 trials, there was no difference in change in BMI at either one or three months with olanzapine compared with placebo. One trial of quetiapine reported no statistical difference from placebo in BMI increase at three months.	Olanzapine and quetiapine **have no efficacy** in increasing body mass in eating disorder patients.
Insomnia	**Very Low**	In one small trial (N=13) of quetiapine, sleep outcomes were not statistically different from placebo.	Quetiapine may be **inefficacious** in treating insomnia.
Substance Abuse			
Alcohol	**Moderate** (aripiprazole) **Low** (quetiapine)	Two trials of aripiprazole and one of quetiapine reported percentage of patients completely abstinent during follow-up. In a pooled analysis, the effect versus placebo was insignificant.	Aripiprazole is **inefficacious** in treating alcohol abuse/ dependence. Quetiapine may also be **inefficacious.**
Cocaine	**Low**	Two trials of olanzapine and one of risperidone reported there was no difference in efficacy versus placebo as measured by the Addiction Severity Index (ASI).	Olanzapine is **inefficacious** in treating cocaine abuse /dependence. Risperidone may also be **inefficacious.**
Methamphetamine	**Low**	One trial found aripiprazole inefficacious in reducing use of intravenous amphetamine, as measured by urinalysis. Another trial found aripiprazole inefficacious in reducing craving for methamphetamine.	Aripiprazole is **inefficacious** in treating methamphetamine abuse/ dependence.
Methadone	**Low**	One trial of methadone-treated patients found no difference between risperidone and placebo in reduction of cocaine or heroin use.	Risperidone is an **inefficacious** adjunct to methadone maintenance

ADHD=attention-deficit hyperactivity disorder; BEHAVE-AD=Behavioral Pathology in Alzheimer's Disease Scale; BPRS=Brief Psychiatric Rating Scale; CGI-BPD=Clinical Global Impression Scale for Borderline Personality Disorder; CGI-I=Clinical Global Impression Improvement; CGI-S=Clinical Global Impression-Severity; CMAI =Cohen-Mansfield Agitation Inventory; HAM-A = Hamilton Anxiety Scale; HAM-D=Hamilton Depression Rating Scale; MADRS=Montgomery-Asberg Depression Rating Scale; MDD=major depressive disorder; NPI=Neuropsychiatric Inventory; OCD=obsessive-compulsive disorder; PANSS=Positive and Negative Syndrome Scale; PCT=placebo-controlled trial; PTSD=post-traumatic stress disorder; SSRI=selective serotonin reuptake inhibitor; SNRI=serotonin-norepinephrine reuptake inhibitors; ZAN-BPD=Zanarini Rating Scale for Borderline Personality Disorder

Appendix Ib: Summary of Adverse Events of Atypical Antipsychotics for Off-Label Use (adopted from 2011 AHRQ systematic review)[202]

Adverse Event	Head-to-Head Studies	Active Comparator Studies	Placebo-Controlled Studies
Weight Gain			
Elderly	In one large trial (CATIE-AD) patients who were treated with olanzapine, quetiapine, or risperidone averaged a monthly gain of 1.0, 0.7, and 0.4 lbs respectively, compared with a monthly weight loss of 0.9 lbs for placebo patients.	More common in patients taking olanzapine than risperidone or conventional antipsychotics, particularly if their BMI was less than 25 at baseline, according to a large cohort study.	According to the meta-analysis, more common in patients taking olanzapine and risperidone than placebo.
Adults	More common in olanzapine patients than ziprasidone patients in one trial.	More common among patients taking olanzapine than patients taking conventional antipsychotics	According to the meta-analysis, more common in patients taking aripiprazole, olanzapine, quetiapine, and risperidone than placebo.

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		in three trials. More common in patients taking aripiprazole than patients taking conventional antipsychotics in one trial. More common among patients taking olanzapine than patients taking mood stabilizers in two trials.	
Children/Adolescents	No head to head studies	No difference between clonidine and risperidone in one trial.	More common in patients taking risperidone in two PCTs. No difference in one small PCT of ziprasidone.
Mortality-in the elderly	No difference between olanzapine and risperidone according to a meta-analysis of six trials of olanzapine published in 2006.	Six large cohort studies compared mortality in elderly patients taking atypical and conventional antipsychotics. Four of these studies found a significantly higher rate of death with conventional antipsychotics, while two found no statistical difference in mortality between the drug classes.	The difference in risk for death was small but statistically significant for atypicals, according to a 2006 meta-analysis which remains the best available estimate. Sensitivity analyses found no difference between drugs in the class. Patients taking atypicals had higher odds of mortality than those taking no antipsychotics in the two cohort studies that made that comparison. There are no trials or large observational studies of ziprasidone in this population.
Endocrine			
Elderly	No evidence reported	No evidence reported	No difference in endocrine events in risperidone patients in one PCT. Regarding diabetes, risk was elevated but not statistically significant in one industry-sponsored cohort study of olanzapine patients.
Adults	Diabetes more common in patients taking olanzapine than patients taking risperidone in one trial.	No evidence reported	Endocrine events more common in patients taking quetiapine, risperidone, and ziprasidone in one PCT each. More common in olanzapine in two pooled PCTs. Diabetes more common in patients taking quetiapine in six pooled PCTs; however, the pooled odds ratio was elevated at 1.47 but not statistically significant. More common in olanzapine patients in one PCT; the odds ratio of 5.14 was not statistically significant, with very wide confidence intervals (0.6 to 244). Lower odds of diabetes in risperidone patients in one large observational study.
Cerebrovascular Accident (CVA)	No evidence reported	Hospitalization for CVA was increased in the first week after initiation of typical antipsychotics, but not for initiation of atypicals in a large cohort study.	More common in risperidone patients than placebo according to four PCTs pooled by the manufacturer. In a meta-analysis of PCTs, risperidone was the only drug associated with an increase. More common in olanzapine than placebo according to five PCTs pooled by the manufacturer.
Extrapyramidal Symptoms (EPS)			
Elderly	More common in patients taking aripiprazole and risperidone patients than patients taking quetiapine in one large trial (CATIE-AD).	No evidence reported	More common in patients taking risperidone, according to the meta-analysis. Quetiapine and aripiprazole were not associated with an increase. More common in olanzapine in one PCT.
Adults	No evidence reported	Less likely in patients taking quetiapine than mood stabilizers in one small trial. Less likely in patients taking	More common in patients taking aripiprazole, quetiapine, and ziprasidone than placebo according to the meta-analysis.

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		olanzapine or aripiprazole than patients taking conventional antipsychotics in one trial each.	
Sedation			
Elderly	More common in elderly patients taking olanzapine or quetiapine than risperidone according to the meta-analysis, but not statistically significant.	No difference in one trial of olanzapine versus benzodiazepines. No difference in three trials of olanzapine and three of risperidone versus conventional antipsychotics.	More common in patients taking aripiprazole, olanzapine, quetiapine, and risperidone than placebo according to the meta-analysis.
Adults	More common in patients taking quetiapine than risperidone in two trials. No difference in one trial of risperidone versus olanzapine.	Olanzapine patients had higher odds than mood stabilizer patients in two trials. More common in olanzapine and quetiapine patients than SSRIs patients in three and two trials respectively. Olanzapine patients had lower odds than patients taking conventional antipsychotics in the pooled analysis of three trials.	More common in patients taking aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone than placebo in the meta-analysis.
Children/Adolescents	No head-to-head trials	No difference in one small trial of clonidine versus risperidone. More patients on haloperidol than risperidone reported sleep problems in one trial.	Less common in aripiprazole patients than placebo patients in one PCT. No difference from placebo in one small PCT of ziprasidone.

BMI=body mass index; CATIE-AD=Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease; CVA=cerebrovascular accident; EPS=extrapyramidal symptoms; PCT=placebo-controlled trial; SSRI=serotonin selective reuptake inhibitor

Appendix IIa: Summary of the Strength of Evidence for Efficacy Outcomes in Children and Adolescents (adopted from the 2012 AHRQ systematic review)[109]

Outcome	Comparison (# of studies)	Strength of Evidence	Summary
Pervasive developmental disorder			
Autistic symptoms	FGA vs. SGA (2 RCTs)	Low	No significant difference
	SGA vs. placebo (7 RCTs)	Low	Significant effect in favor of SGA on ABC (MD = 218.3; 95% CI: 227.1 to 29.5; I2 = 79.6%); CARS (MD = 24.9; 95% CI: 28.5 to 21.4; I2 = 64%).
CGI	SGA vs. placebo (3 RCTs)	Low	No significant difference
OC symptoms	SGA vs. placebo (3 RCTs)	Low	Significant effect in favor of SGA (MD = 21.7; 95%CI: 23.2 to 20.3; I2 = 49%).
Medication adherence	SGA vs. placebo (2 RCTs)	Low	No significant difference
Disruptive behavior disorder			
Aggression	SGA vs. placebo (5 RCTs)	Low	No significant difference
Anxiety	SGA vs. placebo (4 RCTs)	Low	No significant difference
Behavior symptoms	SGA vs. placebo (7 RCTs)	Moderate	Significant effect in favor of SGA for ABC (MD = 221.0; 95% CI: 231.1 to 210.8; I2 = 62%); BPI (MD = 23.8; 95%CI: 26.2 to 21.4; I2 = 0%); NCBRF (MD = 26.9; 95% CI: 210.4 to 23.5; I2 = 62%).
CGI	SGA vs. placebo (7 RCTs)	Moderate	Significant effect in favor of SGA for CGI–I (MD = 21.0; 95% CI: 21.7 to 20.3; I2 = 45%); CGI–S (MD = 21.3; 95%CI: 22.2 to 20.5; I2 = 78%).
Medication adherence	SGA vs. placebo (5 RCTs)	Low	No significant difference

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Bipolar Disorder			
CGI	SGA vs. placebo (7 RCTs)	Moderate	Significant effect in favor of SGA (MD = 20.7; 95% CI: 20.8 to 20.5; I2 = 36%).
Depression	SGA vs. placebo (7 RCTs)	Low	No significant difference
Manic Symptoms	SGA vs. placebo (7 RCTs)	Low	All except one study significantly favored SGA (studies not pooled due to high heterogeneity).
Medication adherence	SGA vs. placebo (7 RCTs)	Low	Significant effect in favor of placebo (RR = 2.0; 95% CI: 1.0 to 4.0; I2 = 0%).
Suicide-related behavior	SGA vs. placebo (7 RCTs)	Moderate	No significant difference for suicide-related deaths, attempts, or ideation.
Schizophrenia			
CGI	FGA vs. SGA (3 RCTs)	Low	Significant effect in favor of SGA (MD = 20.8; 95% CI: 21.3 to 20.3; I2 = 0%).
	Clozapine vs. olanzapine (2 RCTs)	Low	No significant difference
	Olanzapine vs. risperidone (3 RCTs)	Low	No significant difference
	SGA vs. placebo (6 RCTs)	Moderate	Significant effect in favor of SGA (MD = 20.5; 95% CI: 20.7 to 20.3; I2 = 28%).
Positive and negative symptoms	FGA vs. SGA (3 RCTs)	Low	No significant difference
	Clozapine vs. olanzapine (2 RCTs, 1 PCS)	Low	No significant difference
	Olanzapine vs. risperidone (3 RCTs, 1 PCS)	Low	No significant difference
	SGA vs. placebo (6 RCTs)	Moderate	Significant effect in favor of SGA (MD = 28.7; 95% CI: 211.8 to 25.6; I2 = 38%).
Medication adherence	FGA vs. SGA (2 RCTs, 1 PCS)	Low	No significant difference
	Clozapine vs. quetiapine (2 RCTs)	Low	No significant difference
	Olanzapine vs. risperidone (4 RCTs, 1 PCS)	Low	No significant difference
	SGA vs. placebo (2 RCTs)	Low	No significant difference
Suicide-related behaviors	SGA vs. placebo (5 RCTs)	Low	No significant difference
Tourette syndrome			
Tics	SGA vs. placebo (2 RCTs)	Moderate	Significant effect in favor of SGA (MD = 27.0; 95% CI: 210.3 to 23.6; I2 = 0%)
Behavioral symptoms			
Autistic symptoms	Risperidone vs. placebo (2RCTs)	Low	Significant effect in favor of risperidone in one study; NR in second study

ABC=Aberrant Behavior Checklist, BPI=Behavior Problem Inventory, CARS=Childhood Autism Rating Scale, CGI–I=Clinical Global Impressions–Improvement, CGI–S=Clinical Global Impressions–Severity, NCBRF=Nisonger Child Behavior Rating Scale, NR=not reported, OC=obsessive-compulsive, PCS=prospective cohort study, RR=relative risk

Appendix IIb: Summary of Evidence for Adverse Events in Children and Adolescents (adopted from 2012 AHRQ systematic review)[109]

Outcome	Strength of Evidence	SGA vs. SGA	Placebo-Controlled Studies
Dyslipidemia	Low	Aripiprazole was significantly favored over olanzapine (RR = 0.25; 95% CI: 0.08–0.8)[a] and 95% CI: 271.3 to 27.4).[a] No significant differences were observed for clozapine versus olanzapine, olanzapine versus quetiapine and quetiapine versus risperidone.	Significant effect in favor of placebo over aripiprazole (RR = 2.5; 95% CI: 1.4, 4.4)[a], olanzapine (RR = 2.4; 95% CI: 1.2–4.9; I^2 = 45%), and quetiapine (RR = 2.4; 95% CI: 1.1–5.4; I2 = 0%).

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	Moderate	Significant effect in favor of risperidone compared with olanzapine for cholesterol (MD = 10.2 mg/dL; 95% CI: 3.1–17.2; I^2 = 0%) and triglycerides (MD = 17.3 mg/dL; 95% CI: 3.5–31.1; I2 = 0%).	NA
EPS	Low	No significant difference for clozapine versus olanzapine, clozapine versus risperidone, olanzapine versus quetiapine, olanzapine versus risperidone, quetiapine versus risperidone.	No significant differences for placebo compared with olanzapine or quetiapine.
	Moderate	NA	Significant effect in favor of placebo over aripiprazole (RR = 4.2; 95% CI: 2.4–7.2; I^2 = 0%) and risperidone (RR = 2.7; 95% CI: 1.4–4.9; I^2 = 0%).
Insulin Resistance	Low	No significant difference for olanzapine versus quetiapine, olanzapine versus risperidone or quetiapine versus risperidone.	No significant difference between aripiprazole and placebo or olanzapine and placebo.
Prolactin-related sexual side effects	Low	Significant effect in favor of clozapine over olanzapine (MD = 210.8 ng/dL; 95% CI: 216.7 to 24.8; I^2 = 21%). No significant difference for quetiapine versus risperidone.	Significant effect in favor of placebo over risperidone in 7 or 8 studies (not pooled due to heterogeneity). No significant difference for quetiapine compared with placebo.
	Moderate	Significant effect in favor of olanzapine over risperidone (RR = 0.4; 95% CI: 0.2–0.6; I^2 = 0%).	Significant effect in favor of aripiprazole over placebo (MD = 24.1 ng/mL; 95% CI: 26.3 to 21.8; I2 = 0%). Significant effect in favor of placebo over olanzapine (MD = 11.5 ng/mL; 95% CI: 8.8–14.1; I2 = 0%).
Sedation	Low	No significant differences for clozapine versus olanzapine, olanzapine versus quetiapine, olanzapine vs risperidone, quetiapine vs risperidone.	Significant effect in favor of placebo over aripiprazole (RR = 2.7; 95% CI: 1.1–6.5; I2 = 76%). No significant difference in placebo comparisons with olanzapine and quetiapine.
	Moderate	NA	Significant effect in favor of placebo over risperidone (RR = 2.9; 95% CI: 1.5–5.5; I^2 = 32%) and ziprasidone (RR = 3.0; 95%CI: 1.7–5.2; I^2 = 0%).
Weight gain	Low	Significant effect in favor of aripiprazole over olanzapine (MD = 24.1 kg; 95%CI: 25.5 to 22.7),a quetiapine(MD = 21.6 kg; 95% CI: 23.0 to 20.3)[a] and risperidone (MD = 22.3 kg; 95%CI: 23.9 to 20.7).a No significant difference for clozapine versus olanzapine, clozapine versus risperidone, and quetiapine versus risperidone.	No significant difference for ziprasidone compared with placebo.
	Moderate	Significant effect in favor of quetiapine over olanzapine (RR = 1.5; 95%CI: 1.1–2.0; I^2 = 0%) and risperidone over olanzapine (MD = 2.4 kg; 95%CI: 1.5–3.3; I^2 = 72%).	Significant effect in favor of placebo over aripiprazole (MD=0.8 kg; 95%CI: 0.4–1.2; I^2 = 13%), olanzapine (MD = 4.6 kg; 95% CI: 3.1–6.1; I2 = 70%), quetiapine (MD = 1.8 kg; 95% CI: 1.1–2.5; I^2= 49%), and risperidone (MD = 1.8 kg; 95% CI: 1.5–2.1; I^2 = 0%).

AE=adverse event; EPS=extrapyramidal symptom; RR=relative risk.
a=Only 1 study contributed to this estimate; therefore, an I^2 value could not be calculated.

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