

Drug Class Review

Atypical Antipsychotics

Final Report Update 2

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Methods

- Populations
 - Adults:
 - Schizophrenia
 - First episode schizophrenia symptoms
 - Bipolar I disorder
 - Behavioral and psychological symptoms of dementia
 - Youth (under age 18):
 - Pervasive developmental disorders
 - Autistic disorder
 - Disruptive behavior disorders
 - Conduct disorder
 - Oppositional defiant disorder

Methods(continued)



- Interventions
 - Aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone (all formulations)
- Literature Search
 - Electronic searches through November 2007
 - Pharmaceutical company submissions, reference lists Fall 2007
 - Peer review and public comment in April 2008

Schizophrenia and Related Psychoses

Schizophrenia evidence base



- 70 head-to-head trials (35 new in Update 2)
 - 17 (24%) rated poor quality
 - Industry funding of trials : 46%
 - 43% explicitly outpatient settings, 25% inpatient
 - Generalizability is limited primarily to patients with ‘moderate’ to ‘marked’ symptoms
 - Dose comparisons:
 - 22% compared doses within the same range (high/medium/low)
 - 25% compared doses in the high range for one drug to doses in the low range for another drug
- 47 observational trials with effectiveness outcomes
 - 14 new in Update 2; 21 (45%) rated poor quality

Clinical Antipsychotic Trials in Intervention Effectiveness - Schizophrenia (CATIE)



- **CATIE Phase I**
 - Patients randomized to olanzapine, quetiapine, risperidone, ziprasidone, or perphenazine; those who had tardive dyskinesia at baseline were not randomized to perphenazine (Phase Ia)
- **CATIE Phase Ib**
 - Patients who were randomized to perphenazine in Phase I but discontinued the drug prior to 18 months were then randomized to 1 of the 4 atypical antipsychotics
- **CATIE Phase IIT**
 - Patients who discontinued the originally assigned drug in Phase I due to poor tolerability were randomized to ziprasidone or one of olanzapine, risperidone, or quetiapine with no one receiving the same drug assigned in Phase I
- **CATIE Phase IIE**
 - Patients who discontinued the originally assigned drug in Phase I due to inadequate efficacy were randomized to open-label clozapine or to a blinded trial of olanzapine, risperidone, or quetiapine
- **Primary outcome measure: Rate and time to discontinuation of drug**

Effectiveness

- Clozapine was superior to olanzapine in preventing suicidality, including suicide attempts (successful or not) and worsening suicidal behavior, in patients at high risk of suicide in a good quality trial (InterSept)
 - Number needed to treat = 12; for every 12 patients with schizophrenia at high risk for suicide treated with clozapine rather than olanzapine for 2 years, 1 additional suicide or suicide attempt will be prevented

Effectiveness (continued)

- Relapse occurred less often with olanzapine than quetiapine
 - Comparisons of olanzapine with risperidone had mixed findings
 - Trials were 28 weeks to 12 months long
- Hospitalization
 - Risk of hospitalization due to exacerbation of schizophrenia symptoms was lower with olanzapine than quetiapine, risperidone, or ziprasidone
 - CATIE Phase I: 0.29 hospitalizations per person-year of treatment for olanzapine compared with 0.66 for quetiapine, 0.45 for risperidone, and 0.57 for ziprasidone ($P < 0.001$)

Effectiveness (continued)



- Quality of life
 - Quality of life improved with and did not differ among olanzapine, quetiapine, risperidone, or ziprasidone in good-quality trial evidence.
 - Observational evidence was mixed with some favoring olanzapine depending on the outcomes scale selected to measure improvement
- Social function
 - Social function improvement was greater with olanzapine than risperidone in one trial but did not differ in observational studies
 - -Evidence is still limited and conflicting

Effectiveness (continued)



- Rate of Discontinuation of Drug
 - Olanzapine has a lower rate of drug discontinuation than aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone; numbers needed to treat range from 10 to 21.
 - Clozapine has a lower rate of drug discontinuation than aripiprazole, quetiapine, risperidone, and ziprasidone; numbers needed to treat range from 10 to 34.
 - No difference between clozapine and olanzapine was found
- Time to Discontinuation of Drug
 - Olanzapine has a longer time to discontinuation than quetiapine, risperidone and ziprasidone
 - Trials: Difference of 4 months; Observational studies: Difference of ~40 days
 - Clozapine might have a longer time to discontinuation (10.5 months) than olanzapine (2.7 months, $P=0.12$), quetiapine (3.3 months, $P=0.01$), and risperidone (2.8 months, $P<0.02$) in patients with inadequate response to previous treatment (CATIE Phase IIE)
- Paliperidone: Evidence too limited for conclusions

Effectiveness (continued)

Mixed treatment comparisons analysis of discontinuations from trials

	Aripiprazole	Clozapine	Olanzapine	Quetiapine	Paliperidone	Risperidone
Clozapine	1.92 (1.32,2.77)	NA				
Olanzapine	1.69 (1.25,2.29)	0.90 (0.72,1.11)	NA			
Quetiapine	1.21 (0.84,1.66)	0.64 (0.49,0.8)	0.72 (0.61,0.83)	NA		
Paliperidone	1.22 (0.77,1.87)	0.65 (0.4,1.02)	0.72 (0.49,1.05)	1.02 (0.66,1.52)	NA	
Risperidone	1.21 (0.9,1.59)	0.64 (0.49,0.81)	0.71 (0.63,0.8)	1.00 (0.85,1.17)	1.02 (0.68,1.48)	NA
Ziprasidone	0.94 (0.66,1.34)	0.5 (0.37,0.65)	0.56 (0.46,0.67)	0.78 (0.62,0.97)	0.8 (0.53,1.2)	0.78 (0.63,0.95)

Adjusted odds ratios (OR) and 95% confidence intervals (CI); Fixed Effects Model; Adjusted for dose level (low, medium, high) within allocated group. OR is column versus row.

Efficacy

- Consistent differences in *efficacy* were not found between clozapine, olanzapine, quetiapine, risperidone, ziprasidone, or aripiprazole
 - Pooled analysis of response rates (45% to 80%) did not indicate statistically significant differences between the drugs
 - Limited evidence did not identify statistically significant differences between risperidone long-acting injection and oral risperidone or olanzapine
 - Only indirect evidence from placebo- controlled trials is available for paliperidone extended release and quetiapine extended release
- Acute agitation
- For reduction of acute agitation aripiprazole IM and olanzapine IM were noninferior to haloperidol IM at 2 hours
- -Post hoc analyses suggest that aripiprazole and olanzapine may reduce agitation more than haloperidol at time points before 2 hours
- Intramuscular to oral transition
 - Olanzapine or haloperidol resulted in similar reductions in agitation with no statistically significant differences found at any time point over 4 days
 - Ziprasidone was superior to haloperidol in the reduction of the agitation during the IM treatment phase; differences were not statistically significant during 7 days of oral dosing

First episode schizophrenia



- Olanzapine and risperidone did not differ significantly in patients with a first episode of symptoms suggestive of schizophrenia
 - Comparative evidence limited to 3 small studies of only these two atypical antipsychotics
 - Both resulted in improvements in positive and negative symptoms
- A larger study, The European First Episode Schizophrenia Trial (EUFEST), is underway
 - Comparing: quetiapine, olanzapine and ziprasidone

Discontinuation due to adverse events

- Mixed treatment comparisons analysis, controlling for within study dose comparisons, indicated higher odds of discontinuing drug due to adverse events with clozapine compared to olanzapine, risperidone, and risperidone
- Higher rates were also seen with olanzapine than with quetiapine and risperidone
- Differences were not found between clozapine or olanzapine and paliperidone or ziprasidone, although smaller sample sizes and indirect comparisons may have limited the ability to find a difference

Discontinuation due to adverse events (continued)

Mixed treatment effects model: Rates of discontinuation due to adverse events

	Aripiprazole	Clozapine	Olanzapine	Quetiapine	Paliperidone	Risperidone
Clozapine	0.69 (0.36,1.15)	NA				
Olanzapine	1.04 (0.66,1.57)	1.56 (1.05,2.25)	NA			
Quetiapine	1.64 (0.96,2.54)	2.46 (1.62,3.48)	1.58 (1.26,1.96)	NA		
Paliperidone	1.68 (0.6,3.87)	2.54 (0.89,5.61)	1.61 (0.67,3.26)	1.04 (0.39,2.33)	NA	
Risperidone	1.48 (0.9,2.2)	2.23 (1.47,3.24)	1.43 (1.15,1.75)	0.91 (0.7,1.14)	1.05 (0.41,2.19)	NA
Ziprasidone	1.06 (0.59,1.71)	1.59 (0.96,2.46)	1.02 (0.77,1.36)	0.65 (0.46,0.91)	0.75 (0.29,1.6)	0.72 (0.52,1)

Fixed effects model odds ratios (OR) and 95% confidence intervals (CI) adjusted for dose (low, medium, high).

Tolerability

- Extrapyramidal symptoms
 - Many trials and studies found no differences among various atypical antipsychotics
 - among olanzapine, quetiapine, risperidone, and ziprasidone in CATIE Phases I, Ib, II E, and II T
 - among these and aripiprazole in an additional trial
 - between olanzapine and aripiprazole (2 studies) or quetiapine (3 studies)
 - between olanzapine and risperidone in 8 of 10 trials (N=2223 total)
 - between olanzapine and clozapine in 3 of 4 trials
 - between clozapine and risperidone in 3 of 5 studies
 - Several trials found differences in severity between drugs
 - worse with risperidone than quetiapine in 3 of 4 trials
 - Worse with ziprasidone than olanzapine in 3 of 4 trials
 - Evidence was inadequate to make conclusions about aripiprazole and paliperidone

Tolerability (continued)

- Serum lipids
 - Olanzapine and clozapine associated with greater increases in triglycerides than quetiapine or risperidone, differences in LDLc or total cholesterol were not seen
 - Olanzapine associated with greater change in triglycerides, LDLc, and total cholesterol compared with ziprasidone
 - Olanzapine associated with greater increases in triglycerides and HDLc (but not total cholesterol or LDLc) compared with aripiprazole
 - Increases in triglycerides ranged from 26 – 79 mg/dL with olanzapine

Tolerability (continued)

- Sexual dysfunction
 - Limited evidence from 2 small studies indicated fewer reports or less severe symptoms with quetiapine compared with risperidone
 - Risperidone and ziprasidone were similar in a small inpatient study
- Somnolence, dizziness, and salivation
 - Clozapine
 - Higher rates of somnolence compared with risperidone
 - Higher rates of somnolence, dizziness and hypersalivation compared with olanzapine
 - Quetiapine
 - Higher rates of somnolence, dizziness and dry mouth than risperidone
 - Differences were not found between olanzapine and risperidone

Subgroups



- There is very limited comparative evidence in subgroup populations
 - Patients age >60 years (2 trials) or age 50-65 years (subgroup of 1 large trial) did not differ from younger patients in efficacy or quality-of-life measures
 - Patients age < 45 years (1 study) had higher risk of new-onset diabetes with olanzapine and risperidone (compared with conventional antipsychotics) than older patients
 - Mexican-American and African American patients discontinued their prescribed atypical antipsychotic 18-19 days earlier than White Americans
 - Interaction between this finding and the specific drug (olanzapine or risperidone) was not found

Bipolar Disorder

Bipolar disorder evidence base



- Effectiveness/major harms
 - Four observational studies (3 new in Update 2)
- Efficacy/tolerability
 - Head-to-head trials: 2 (both new in Update 2)
 - Comparisons to placebo and other mood stabilizers: 39 (9 new in Update 2)
- Gaps in Evidence
 - No trials of paliperidone
 - Evidence on rapid cycling limited to post hoc subgroup analyses
 - No evidence in population subgroups

Effectiveness in retrospective database studies



- Mental health-related hospitalizations occurred less frequently with quetiapine than with olanzapine or risperidone
 - Hazard ratio for risperidone or olanzapine compared with quetiapine 1.19 (95% CI 1.01 to 1.40) after at least 2 months (N=10 037)
- Findings were mixed for 12-month persistence outcomes
 - Medication possession ratio did not differ among olanzapine (0.68), quetiapine (0.71), and risperidone (0.68; N=825)
 - Among olanzapine, quetiapine, risperidone, and ziprasidone, the number of treatment days was greater for olanzapine monotherapy (73 days) and ziprasidone adjunctive therapy (118 days; N=1516)

Improvement in efficacy outcomes in patients with *acute* manic or mixed symptoms was found with olanzapine, quetiapine and risperidone compared to placebo



	Response rate ^a Relative risk (95% CI)		Remission Rates	Improved QOL
	Monotherapy	Adjunctive		
Aripiprazole	1.82 (1.43-2.32)			
Olanzapine	1.76 (1.31-2.36)	1.47 (1.17-1.84)	68%	X
Quetiapine	1.46 (0.81-2.64)	1.46 (1.21-1.76)	46% to 69%	
Risperidone	1.75 (1.41-2.18)	1.38 (0.97-1.97)	38%	
Ziprasidone	1.49 (1.13-1.98)			

^a pooled results from Sherk 2007 systematic review

Aripiprazole and olanzapine showed better efficacy than placebo in maintenance of response in patients with mania or mixed symptoms



- 72% taking aripiprazole had no relapse compared with 49% taking placebo ($P < 0.05$)
 - 26-week study of 161 patients
- 47% taking olanzapine relapsed compared with 80% taking placebo ($P < 0.001$)
 - 52-week study of 361 patients

Olanzapine and quetiapine showed better efficacy than placebo in bipolar depression



Trial			
Treatments	Response ^a		Remission ^b
Tohen, 2003			
Olanzapine	39%; <i>P</i> =0.02		33%; <i>P</i> =0.02
Placebo	30%		25%
BOLDER I			
Quetiapine	58%; <i>P</i> <0.001		53%; <i>P</i> <0.001
Placebo	36%		28%
BOLDER II			
Quetiapine	60%; <i>P</i> <0.01		52%; <i>P</i> <0.05
Quetiapine	58%; <i>P</i> <0.05		52%; <i>P</i> <0.01
Placebo	45%		37%

Tolerability



- Acute sedative effect
 - quetiapine was found to have higher rates of somnolence than risperidone in a small (N = 30) 2-day trial
 - quetiapine (83%) compared with risperidone (31%, $P < 0.05$).
- Sexual function
 - Greater worsening of sexual function with risperidone than olanzapine in 3 week trial (N=256)
- Serum prolactin
 - Increase in serum prolactin was greater with risperidone (52 mg/mL) than olanzapine (8 mg/mL, $P < 0.001$) in a 3-week trial (N=256)
- Weight gain
 - weight gain was greater with olanzapine (2.60 kg) compared with risperidone (1.60 kg; $P < 0.001$) in a 3 week trial (N=256)

Tolerability (continued)

Atypical antipsychotic compared with placebo: Pooled estimates from Scherk 2007

Atypical antipsychotic	Regimen	Weight gain (kg), SMD (95% CI)	Rate of EPS-related AEs RR (95% CI)
Aripiprazole	Monotherapy	0.16 (-0.02 to 0.33)	4.95 (2.38-10.28)
Olanzapine	Monotherapy	0.75 (0.49-1.01)	NR
	Adjunctive	0.99 (0.75-1.23)	NR
Quetiapine	Monotherapy	0.44 (0.17-0.72)	1.25 (0.66-2.73)
	Adjunctive	0.53 (0.36-0.69)	NR
Risperidone	Monotherapy	0.29 (-0.19 to 0.78)	3.32 (1.17-9.36)
	Adjunctive	0.51 (0.23-0.79)	1.88 (0.56-6.32)
Ziprasidone	Monotherapy	0.0 (-0.29 to 0.29)	7.07 (0.95-52.41)
	Adjunctive	NR	5.55 (1.98-15.55)

Behavioral and Psychological Symptoms of Dementia

Behavioral and psychological symptoms of dementia evidence base



- 7 head-to-head trials (2 new this update)
 - Olanzapine compared with risperidone (5 trials) and/or quetiapine (2 trials)
 - 3 fair, 4 poor-quality
 - Most short-term (2-10 weeks); CATIE-AD: 36 weeks
 - 5 of 7 trials very small (N=19 to 86); 2 larger (N=421 and 494)
 - Mainly frail, elderly residents of nursing homes; the majority were white and female
 - Doses in the low range for each drug: olanzapine < 7 mg, Quetiapine \leq 80 mg, Risperidone \leq 1.0 mg
- 10 Placebo-controlled trials and 7 trials compared with conventional antipsychotics
- Gaps in Evidence
 - No evidence for paliperidone or ziprasidone
 - No evidence in population subgroups

Low dose olanzapine, quetiapine, and risperidone similar in effectiveness to each other and to placebo

- CATIE-AD
 - Rate of response at 12 weeks (CGI-C) was similar
 - Olanzapine 32%, risperidone 26%, quetiapine 29%, placebo 21% ($P=0.22$)
 - Time to discontinuation for any reason was similar across the groups
 - Overall withdrawals were similar across the groups
 - Olanzapine 80%, risperidone 82%, quetiapine 77%, placebo 85% ($P=0.052$)
 - Withdrawals due to lack of efficacy
 - Olanzapine and risperidone similar: Hazard ratio 0.84 (0.53-1.32)
 - Risperidone and quetiapine similar: Hazard ratio 0.75 (0.49-1.16)
 - Olanzapine superior to quetiapine: Hazard ratio 0.63 (0.41-0.96)
- Two additional fair-quality head-to-head trials found no differences between risperidone and either olanzapine or quetiapine on any measure

Atypical antipsychotics were similar to placebo and conventional antipsychotics in efficacy measures



- Compared with placebo
 - In 10 placebo-controlled trials (4 new this update), results were mixed, with no drug consistently shown to be superior to placebo in all studies or on all outcomes
 - In dose-ranging studies, lower doses (aripiprazole 2 mg, olanzapine 1-2.5 mg, risperidone 0.5 mg) were less efficacious
- Compared with conventional antipsychotic drugs
 - In 7 trials (4 new this update), efficacy was generally similar between atypical and conventional antipsychotics (haloperidol or promazine) (4 new trials in Update #2)
- No studies of ziprasidone or paliperidone

Tolerability

- Withdrawals due to adverse events
 - In CATIE-AD, withdrawals for intolerability, adverse events, or death higher than placebo, but no differences between drug groups (olanzapine 24%, quetiapine 16%, risperidone 18%, placebo 5%)
 - Other head-to-head trials did not find differences between olanzapine and risperidone in withdrawals due to adverse events
- Parkinsonism or extrapyramidal side effects
 - Higher in olanzapine and risperidone than quetiapine or placebo groups in CATIE-AD, (olanzapine 12%, risperidone 12%, quetiapine 2%, placebo 1%; $P < 0.001$)
 - No difference between quetiapine and risperidone in extrapyramidal side effects in a second head-to-head trial

Children and Adolescents with Autism or Disruptive Behavior Disorders

Children and adolescents with autism or disruptive behavior disorders evidence base



- No head-to-head trials and No effectiveness trials
- Risperidone: most evidence
 - 5 placebo-controlled trials (2 new this update) in autism
 - 5 placebo-controlled trials (1 new this update) in disruptive behavior disorders
- Olanzapine
 - 1 placebo-controlled trial in autism (new this update)
 - 1 trial compared with haloperidol in autism
- Quetiapine
 - Short-term, uncontrolled, observational studies only
- Gaps in Evidence
 - Population subgroups

Systematic reviews found improvement in behavioral symptoms with olanzapine and risperidone



- Jesner 2007 (Cochrane review, risperidone only)
 - Relative risk of improvement on CGI: 4.83 (2.21 to 10.59)
 - Risperidone showed improvement on the Aberrant Behavior Checklist (mean difference compared with placebo, 95% CI):
 - Irritability: -8.09 (-12.99 to -3.19)
 - Social withdrawal/lethargy: -8.09 (-12.99 to -3.19)
 - Hyperactivity: -8.09 (-12.99 to -3.19)
 - Stereotypy: -8.09 (-12.99 to -3.19)
 - Inappropriate speech: -8.09 (-12.99 to -3.19)
- Dinca 2005; Jensen 2007 (qualitative synthesis only)
 - Both drugs effective for behavioral symptoms
 - No evidence that one drug is superior to another
 - Conclusions limited by lack of evidence

Newer evidence supports findings of benefit in Autism



- Risperidone improved behavioral symptoms more than placebo in school-age children with autism in both short term (3 trials, 8 weeks) and longer term (2 trials, 6 months – new this update) studies
 - No difference from placebo in one trial in preschool age children
- Olanzapine improved behavioral symptoms more than placebo in school-age children with autism in short term trials (2 trials, 8 weeks; 1 new this update)
 - Olanzapine showed improvement compared with placebo (50% compared with 20%) on the CGI-I, but not other scales
 - Similar efficacy for olanzapine and haloperidol on the CGI-I ($P=0.494$)

Newer evidence supports findings of benefit of risperidone in disruptive behavior disorders



- 4 short-term trials (6 to 10 weeks) and 1 longer term trial (6 months - new this update) found greater improvement on behavior scales compared with placebo
 - No trials of other atypical antipsychotics in this population have been published

Tolerability

- Rates of overall withdrawals, withdrawals due to adverse events and Incidence of extrapyramidal side effects were low in short-term trials
- Evidence suggests greater weight gain with risperidone compared with placebo or haloperidol
 - Weight gain ranged from 2.7 kg to 5.7 kg, significantly greater than placebo and haloperidol
 - Cochrane meta-analysis (2 trials): Mean difference in weight gain for risperidone compared with placebo was 1.78 kg (95% CI 1.15 to 2.41)
- Three 6-month placebo-controlled trials of risperidone found no difference from placebo in other adverse events

Longer-term safety in children

- Observational study based on New Zealand prescription event monitoring data
 - 420 children aged 2 to 5 years; 43% disruptive behavior, 34% pervasive developmental disorders
 - 93% prescribed risperidone, 8% quetiapine, 2% olanzapine, 1% clozapine
 - Risperidone: Incidence of weight increase 7.4%
 - Two reports of diabetes mellitus
 - Overall, 26.5% discontinued medication
 - 8% discontinued for adverse reaction, 11% because drug was no longer needed

Serious Harms

Mortality

Five observational studies, limited evidence

- Schizophrenia
 - One comparative study found increased all-cause mortality among patients taking risperidone compared with those taking clozapine
- Elderly
 - 3 studies found increased risk of mortality with olanzapine compared with conventional antipsychotics, but no statistically significant difference with clozapine or risperidone
 - Evidence on mortality from remaining studies is non-comparative
 - An FDA analysis of unpublished data from 17 placebo controlled trials found that in older patients with dementia who take atypical antipsychotics are at increased risk [compared to those taking placebo]

Vascular events

- Cerebrovascular disease events occurred more often with risperidone and olanzapine than placebo in 9 trials
 - Rate with risperidone was 4%, with placebo 2%; 4 trials, 2 unpublished
 - Rate with olanzapine was 1.3%, with placebo 0.4%; 5 trials, 3 unpublished)
 - Increased rate of stroke not found in retrospective studies

Cardiac Effects

- Cardiac effects are associated with some atypical antipsychotics
 - Clozapine was associated with myocarditis or cardiomyopathy; olanzapine, quetiapine and risperidone were not
 - Risperidone was associated with a greater risk of cardiac arrest than clozapine
 - Aripiprazole was associated with lower odds of cardiomyopathy than conventional antipsychotics
 - -Ziprasidone was associated with higher odds of hypertension than conventional antipsychotics

Diabetes mellitus

- Olanzapine increased risk more than risperidone in 3 of 5 retrospective cohort studies (1 new this update)
 - In the largest study, risk with olanzapine was greater among women and highest early in exposure to the drug
 - Olanzapine was no different in risk than quetiapine and clozapine in two small retrospective cohort studies
- Clozapine was compared directly and indirectly to olanzapine, with conflicting findings
- Quetiapine did not increase risk relative to olanzapine, risperidone, or clozapine in 1 direct and 1 indirect comparison
- No evidence was found on risk with aripiprazole, paliperidone, or ziprasidone

Weight gain

- Comparative evidence from 6 long-term studies of >63 000 patients is consistent with findings of 20 randomized controlled trials (2 new this update)
- Amount and risk of clinically significant weight gain is greater with olanzapine than risperidone
 - Pooled weighted mean difference from 5 observational studies is 1.61 kg over 3 to 36 months and the pooled estimate from 12 trials is 1.8 kg
 - Trials give a pooled odds ratio of 2.26 for important weight gain (> 7%) with olanzapine compared with risperidone. Number needed to treat = 7.
- Amount of weight gain in descending order (data from trials):
 - Olanzapine > clozapine > quetiapine > risperidone > ziprasidone
- Comparison of weight gain with olanzapine compared with other atypical antipsychotics less clear
- Limited evidence about other atypical antipsychotics
 - Indirect evidence suggests significant weight gain with clozapine
 - Ziprasidone appears to not cause weight gain, on average
 - Data for aripiprazole and paliperidone are too limited for conclusions

Tardive dyskinesia

- Comparative evidence from one study found the rate of tardive dyskinesia greater with risperidone (3%) than olanzapine (1%) after 6 months. Neither risperidone nor olanzapine differed from quetiapine.
- Uncontrolled studies indicate the rates associated with individual drugs are:
 - Clozapine: 1 to 7% over 6 to 26 months
 - Risperidone: 0 to 5% over 6 to 26 months
 - Higher rates were found in studies of older patients, 2.6 to 5%
 - Incidence was associated with dose in one analysis
- Olanzapine: A pooled analysis of 3 trials of olanzapine found a rate of new-onset tardive dyskinesia of 7.1% over a median exposure of 8 months

Other serious harms

- Neuroleptic malignant syndrome was not studied in comparisons of atypical antipsychotics
- Seizures
 - Seizures were associated with clozapine in 2 studies (rates 2.9% and 4.2%) of ≥ 2 years' follow-up
 - association may be related to size of dose and duration of exposure
- Agranulocytosis was reported with clozapine
 - 13 studies reported incidence: 0% to 2.4%

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