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Class Update: Second Generation Antipsychotics

Month/Year of Review: January 2014
PDL Class: Second Generation Antipsychotics

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Current Status of Voluntary PDL Preferred/Non-Preferred Second Generation Antipsychotics

Current Preferred Agents	Current Non-Preferred Agents
Clozapine tablet	Aripiprazole (Abilify®) tablet/solution/Discmelt®/IM
Olanzapine tablet	Iloperidone (Fanapt®) tablet
Quetiapine tablet	Paliperidone (Invega®) tablet
Risperidone tablet/solution	Paliperidone (Invega®) Sustenna®
Ziprasidone capsule	Ziprasidone (Geodon®) for injection
	Lurasidone (Latuda®) tablet
	Risperidone (Risperdal®) Consta®
	Asenapine (Saphris®) SL tablet
	Quetiapine (Seroquel®) XR tablet
	Olanzapine (Zyprexa®) Relprevv®
	Olanzapine (Zyprexa®) Zydis®

Current Status of the Voluntary PDL:
Currently, all antipsychotics are available without prior authorization for non-preferred placement. Oregon law prohibits traditional methods of PDL enforcement on mental health drugs. Second generation antipsychotics have been reviewed for clinical efficacy and safety and specific agents were chosen as clinically preferred; this eliminates a copay. Oregon's Medicaid program currently charges no copayment for preferred PDL drugs. There is current prior authorization criteria for low-dose quetiapine (<150 mg/day) to discourage off-label use for insomnia (see Appendix 2).

Research Questions:

- Is there new comparative evidence of a meaningful difference in efficacy or effectiveness of second generation antipsychotics?
- Is there any new comparative evidence of a meaningful difference in harms of second generation antipsychotics?
- Is there new comparative evidence of a meaningful difference in efficacy or harms of second generation antipsychotics in subgroups?
- Is there evidence that the new formulation of aripiprazole is more efficacious or safer in certain populations?

Conclusions:

- There continues to be no consistent differences in the efficacy between clozapine, olanzapine, quetiapine, risperidone, ziprasidone, aripiprazole or asenapine in shorter-term trials.[1] There is moderate quality evidence for aripiprazole, clozapine, olanzapine, quetiapine and risperidone. The comparative evidence is insufficient or very low for aripiprazole long-acting injection, Iloperidone, olanzapine long-acting injection, olanzapine ODT, extended-release paliperidone and lurasidone.[1]
- There is new moderate quality evidence that the risk of relapse may be lower with olanzapine and risperidone than immediate-release quetiapine and with risperidone long-acting injection than with oral risperidone in patients with first-episode schizophrenia.[1]
- There is new moderate quality evidence of no difference in response or remission rates between extended-release paliperidone and either olanzapine or immediate-release quetiapine for manic and mixed episodes of bipolar disorder.[1]
- There continues to be insufficient comparative evidence of efficacy and effectiveness of second generation antipsychotics in the treatment of Major Depressive Disorder, Bipolar Disorder in children and adolescents, Pervasive Developmental Disorders and Disruptive Behavior Disorders.[1]
- There is moderate quality evidence that the rate of clinically important weight gain (> 7% increase from baseline) in clinical trials was greater with olanzapine than with aripiprazole (RR 2.31), asenapine (RR 2.59), clozapine (RR 1.71), quetiapine (RR 1.82), risperidone (RR 1.81) and particularly ziprasidone (RR 5.76) across 3.7 to 24 months. Single studies of olanzapine and olanzapine long-acting injection, olanzapine ODT, and paliperidone palmitate did not find statistically significant differences in risk of weight gain. Data for other second generation antipsychotics was insufficient to assess the risk of clinically important weight gain compared with olanzapine.[1]
- There is limited comparative effectiveness data available for this class in regards to mortality and serious harms.[1]
- High rates of attrition and small sample sizes in randomized clinical trials make it difficult to draw strong conclusions for this class in systematic review.[2–5]
- There continues to be insufficient comparative evidence of a meaningful difference in efficacy or harms of second generation antipsychotics in any subgroup population.[1]
- There is low quality evidence that aripiprazole long-acting injection improves time to relapse compared to placebo; there are no head-to-head trials comparing aripiprazole long-acting injection to other second generation antipsychotics.[6]
- There is insufficient evidence to determine the long-term safety and comparative efficacy of aripiprazole long-acting injection.[6]

Recommendations:

- Based on the lack of long-term effectiveness and safety data, recommend listing aripiprazole long-acting injection as non-preferred on the voluntary PDL.
- No changes are recommended for the second generation antipsychotic preferred drug class list based on safety and efficacy. Costs should be reviewed in executive session.

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Reason for Review:

The Pacific Northwest Evidence-Based Practice Center Drug Effectiveness Review Project (DERP) published an update to the drug class review on second generation antipsychotics in November 2013. This update will summarize findings from the DERP class review regarding the use of second generation antipsychotics and identify any other new relevant comparative effectiveness evidence, high-quality systematic reviews, or evidence-based guidelines. Aripiprazole long-acting injection (LAI) (Abilify Maintena™) was approved for use in February 2013.[6]

Previous Conclusions and Recommendation:
See Appendix 1

Background:

Antipsychotic medications are approved by the U.S. Food and Drug Administration (FDA) for treatment of schizophrenia and bipolar disorder and are divided into conventional, first generation antipsychotics and the second generation (or atypical) antipsychotics. There are currently ten second generation antipsychotics available in the US. They come in a variety of dosage forms (i.e. orally disintegrating tablets or long-acting injectables), have an assortment of FDA-approved indications (ranging from the irritability associated with autistic disorder in children and adolescents to the maintenance treatment of schizophrenia in adults), and are commonly used off-label for various psychiatric conditions. Side effect profiles between agents vary and are often an important factor in treatment selection. These side effects include extrapyramidal symptoms, autonomic effects, increased prolactin levels, metabolic effects, and cardiac risks including risk of ventricular arrhythmias. Commonly used outcomes in clinical trials include the Positive and Negative Syndrome Scale (PANSS) which is a validated 30-item rating scale used to assess the effects of drug treatment in schizophrenia, and the Clinical Global Impression Severity Scale (CGI-S) which measures the subject's current severity of illness. Data from the CATIE trial, a large, multicenter trial for patients with schizophrenia, suggests a minimal clinically important difference in the PANSS Scale is 15 points, but will vary according to a patient's baseline PANSS score.[7]

Long-acting injection (LAI) antipsychotics are widely use, especially for treating patients who show non-adherence or partial adherence to oral therapy. Drug adherence is essential in improving clinical and social outcomes in schizophrenia. First generation antipsychotics LAIs have been available since the late 1960s, and more recently second generation antipsychotic LAI formulations have become available (olanzapine pamoate, paliperidone palmitate, risperidone LAI, and aripiprazole LAI). Data on the safety and efficacy of second generation antipsychotic LAI formulations is lacking, particularly head-to-head data.[8]

Methods:
A Medline literature search was conducted for new meta-analyses and randomized controlled trials (RCT's) comparing Abilify® (aripiprazole), clozapine, risperidone, olanzapine, quetiapine, ziprasidone, paliperidone (Invega®), iloperidone (Fanapt®), asenapine (Saphris®), and lurasidone (Latuda®) since the date of the literature search included in the DERP report. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched

for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources. After review of the citations from Medline and the manual searches, four high-quality systematic reviews, one new guideline, and one new drug formulation were reviewed along with the DERP updated drug class review.

DERP[1]

Schizophrenia and Related Psychoses

- Effectiveness
  - Strength of evidence for all effectiveness outcomes[1]:
    - Aripiprazole, clozapine, olanzapine, quetiapine and risperidone: Moderate
    - Asenapine, Paliperidone palmitate, and ziprasidone: Low to moderate
    - Extended-release paliperidone and lurasidone: Very low
    - Aripiprazole long-acting injection, Iloperidone, Olanzapine long-acting injection, and olanzapine ODT : Insufficient
  - Suicide: Clozapine was superior to olanzapine in preventing suicide or suicidality in patients at high risk of suicide (number needed to treat=12). This study also reported significantly greater rates of weight gain with olanzapine compared with clozapine (number needed to harm=4). Evidence on other drugs is insufficient for drawing comparative conclusions. [1]
  - Quality of Life: Good-quality trial evidence did not differentiate asenapine, olanzapine, quetiapine, risperidone or ziprasidone. [1]
  - Relapse: Risk of relapse may be lower with olanzapine and risperidone than immediate-release quetiapine and with risperidone long-acting injection versus oral risperidone (first-episode patients).[1] Results were mixed with risperidone versus olanzapine, and not different between long-acting injection risperidone and aripiprazole, lurasidone and oral risperidone or lurasidone and extended-release quetiapine.[1]
  - Hospitalization. Evidence suggested a lower risk of hospitalization with olanzapine than immediate-release quetiapine, risperidone, and ziprasidone, but was not consistent. Very limited evidence suggested that lurasidone results in lower hospitalization rates than immediate-release quetiapine over 12 months.
  - Functioning: Olanzapine, risperidone, immediate-release quetiapine, or ziprasidone were not different on employment or general function outcomes. Social function was not different between long-acting risperidone and paliperidone palmitate injections. [1] Global functioning was superior with olanzapine vs. ziprasidone in patients with depressive symptoms and with immediate-release quetiapine in patients with prominent negative symptoms, but similar between immediate-release quetiapine and risperidone in patients with a first-episode of schizophrenia.[1]
  - Rate and time to discontinuation of drug: Olanzapine was superior to aripiprazole, asenapine, lurasidone, olanzapine long-acting injection, paliperidone palmitate, quetiapine, risperidone, and ziprasidone, but not different to clozapine. [1] Clozapine was found to have lower discontinuation rates than asenapine, lurasidone, paliperidone palmitate, immediate-release quetiapine, risperidone, and ziprasidone. [1] Risperidone was found superior to asenapine, immediate-release quetiapine and ziprasidone, but inferior to lurasidone. This analysis also finds asenapine inferior to aripiprazole. Olanzapine ODT or extended release paliperidone were not found statistically significantly different to any of the other drugs, possibly due to small numbers of comparisons. In studies > six months, olanzapine was also superior to olanzapine ODT, and extended-release paliperidone, clozapine was superior to olanzapine long-acting injection (OR 0.46 (95% CI 0.25 to .88), and aripiprazole was superior to ziprasidone (OR 0.71 (95% CI 0.49 to 0.99) and lurasidone (OR 0.58, 95% CI 0.36 to 0.98). [1] In contrast, shorter studies found no

statically significant differences between the drugs. Olanzapine had longer time to discontinuation than immediate-release quetiapine, risperidone, and ziprasidone.[1]

- Efficacy: Consistent differences in efficacy were not found between clozapine, olanzapine, quetiapine, risperidone, ziprasidone, aripiprazole or asenapine in shorter-term trials.[1]
    - Strength of evidence[1]:
        - Aripiprazole, clozapine, olanzapine, quetiapine and risperidone: Moderate
        - Asenapine, Paliperidone palmitate, Ziprasidone: Low to moderate
        - Extended-release paliperidone and lurasidone: Very low
        - Aripiprazole long-acting injection, Iloperidone, Olanzapine long-acting injection, and olanzapine ODT : Insufficient
- Tolerability and adverse events
    - Strength of evidence for all tolerability and adverse event outcomes[1]:
        - Aripiprazole, clozapine, olanzapine, quetiapine, risperidone and ziprasidone: Moderate
        - Asenapine and Paliperidone palmitate,: Low to moderate
        - Extended-release paliperidone and lurasidone: Very low
        - Aripiprazole long-acting injection, Iloperidone, Olanzapine long-acting injection, and olanzapine ODT : Insufficient[1]
    - Rate of discontinuation due to adverse events: Mixed-treatment comparisons analysis controlling for within-study dose comparisons and study duration indicated clozapine resulted in discontinuation due to adverse events statistically significantly more often than olanzapine, immediate-release quetiapine, or risperidone. [1] Sensitivity analyses of studies of > and < than 6 months found no statistically significant differences, although the point estimates were in the same direction as the overall analysis. [1] Fewer data were available for the lurasidone, new formulation of olanzapine, asenapine and paliperidone palmitate long-acting injection, and no data for iloperidone. [1]
    - Extrapyramidal symptoms: Rates of patients experiencing extrapyramidal symptoms or increases in measures of severity of symptoms were not found to be different among the drugs in most trials.[1]
    - Weight gain: The rate of clinically important weight gain (> 7% increase from baseline) in clinical trials was greater with olanzapine than with aripiprazole (RR 2.31), asenapine (RR 2.59), clozapine (RR 1.71), quetiapine (RR 1.82), risperidone (RR 1.81) and particularly ziprasidone (RR 5.76) across 3.7 to 24 months.[1] Single studies of olanzapine and olanzapine long-acting injection, olanzapine ODT, and paliperidone palmitate did not find statistically significant differences in risk of weight gain.[1] Data for other second generation antipsychotics was insufficient to assess the risk of clinically important weight gain compared with olanzapine.[1]
    - Sexual dysfunction: Evidence on sexual dysfunction is inconsistent for risperidone vs. immediate-release quetiapine. Individual trials found no differences among olanzapine and long-acting paliperidone, risperidone, or ziprasidone or between long-acting formulations of paliperidone and risperidone. [1] This evidence suffers from inadequate sample sizes or lack of explicit methodology to measure symptoms. [1]
    - Metabolic Syndrome: The risk of metabolic syndrome may be greater with olanzapine compared with paliperidone extended release. [1] Fair-quality randomized trials found no significant differences between other second generation antipsychotics. [1]
- Benefits and harms in subgroups
    - Strength of evidence for all benefit and harm in subgroup outcomes[1]:
        - First episode: Low

        - Others: Insufficient
    - First-episode of schizophrenia: Evidence does not support a difference between the drugs in response and remission between olanzapine, immediate-release quetiapine, risperidone, ziprasidone, aripiprazole, or extended-release paliperidone. [1] Evidence for rate or time to discontinuation is inconsistent, with few studies finding better results with olanzapine. [1]
    - Age: Differences in response, persistence, or quality of life based on age were not found between olanzapine and risperidone. Patients < 40 years old were found to be at a higher risk of new-onset diabetes with olanzapine and risperidone relative to risks in older age groups.[1]
    - Race: Limited evidence suggests that Mexican Americans and African American patients discontinued their prescribed second generation antipsychotic 18-19 days earlier than white patients, but an effect of the specific drug (olanzapine or risperidone) was not found.[1]
    - Illicit drug dose: No difference in discontinuation found among users and non-users. Response rates were similar for olanzapine and risperidone in patients with first episode schizophrenia and a history of cannabis use disorder. [1]
    - Obesity: Paliperidone palmitate injection was non-inferior to long-acting risperidone injection in PANSS total score mean change in normal to overweight patients, but was inferior in obese patients.[1]

<u>Bipolar Disorder in Adults</u>

- Effectiveness
    - Strength of evidence for all effectiveness outcomes[1]:
        - QOL: Moderate
        - Others: Low
    - Quality of life: no significant difference between risperidone and olanzapine or between asenapine and olanzapine was found. [1]
    - Functional capacity: No significant difference between paliperidone extended release and quetiapine on 12-week GAF scores. [1]
    - Hospitalizations: Observational evidence indicated lower risk of hospitalization with quetiapine monotherapy than with risperidone and olanzapine monotherapies and lower risk with adjunctive aripiprazole than with adjunctive ziprasidone, olanzapine, quetiapine, and risperidone.[1]
- Efficacy: No significant differences in response or remission rates between risperidone and olanzapine or asenapine and olanzapine, or between extended-release paliperidone and either olanzapine or immediate-release quetiapine for manic and mixed episodes. [1] Olanzapine may be superior to paliperidone extended release in preventing recurrence. [1]
    - Strength of evidence for all efficacy outcomes[1]**:**
        - Response or remission in manic/mixed episodes: Moderate
        - Recurrence: Low
- Harms
    - Strength of evidence for all harms outcomes[1]:
        - Diabetes: Insufficient
        - Pneumonia: Low
        - Weight, EPS, Discontinuation: Moderate
    - Diabetes: No direct comparative evidence[1]

- Pneumonia: Similar increases in risk for clozapine, olanzapine, immediate-release quetiapine, risperidone[1]
- Weight gain ≥7%: Higher risk for olanzapine compared with asenapine and for quetiapine compared with paliperidone extended release. [1]
- Extrapyramidal symptoms: Occurred more frequently with paliperidone extended release than olanzapine, but similar among other drugs. [1]
- Discontinuations due to adverse events: Higher rates for asenapine compared with olanzapine, but similar among risperidone, olanzapine, quetiapine, and paliperidone extended release. [1]

<u>Bipolar Disorder in Children and Adolescents</u>

- Effectiveness: Evidence of effectiveness in this population was not found. [1]
  - Strength of evidence: Insufficient[1]
- Efficacy
  - Strength of evidence for all efficacy outcomes[1]:
    - Response in preschool children: Low
    - Manic/mixed episodes: Insufficient
    - Depressed episodes: Insufficient
  - Direct evidence: Rate of response was similar for olanzapine compared with risperidone in preschool-aged children[1]
  - Indirect evidence: Time to discontinuation for any reason was significantly longer for aripiprazole compared to placebo over 72 weeks. [1]
  - Manic and mixed episodes - Response: Significantly greater than placebo for aripiprazole, olanzapine, immediate-release quetiapine, and risperidone as monotherapy and for immediate-release quetiapine in combination with divalproex. [1]
    - Remission: Significantly greater than placebo for aripiprazole, olanzapine, immediate-release quetiapine, and risperidone as monotherapy. [1]
    - Depressed episodes: No significant difference between immediate-release quetiapine and placebo groups in proportion of adolescents who met criteria for response or remission. [1] Also no significant difference was found between extended-release quetiapine and placebo in the proportion of children and adolescents who met criteria for response or remission. [1]
- Harms
  - Strength of evidence for all harms outcomes[1]:
    - Weight: Moderate
    - EPS: insufficient
  - Weight gain: No significant difference in weight gain for olanzapine compared with risperidone in preschool-age children. [1] For acute treatment, compared to placebo, mean weight gain was greatest for olanzapine and was successively lower for quetiapine IR, risperidone, and lowest for aripiprazole. [1] For maintenance treatment, evidence on aripiprazole's effects on weight gain compared with placebo was mixed.[1]
  - Extrapyramidal symptoms: Compared with placebo, rates were significantly greater for both aripiprazole and risperidone.

<u>Major Depressive Disorder</u>

- Effectiveness, Efficacy: No direct comparative evidence available. [1]
  - Strength of evidence: Insufficient[1]

- Harms: Observational evidence suggests that the use of SSRIs plus olanzapine is associated with significantly greater weight gain than SSRIs plus either quetiapine or risperidone. [1]
    - Strength of evidence: Moderate[1]

<u>Pervasive Developmental Disorders and Disruptive Behavior Disorders</u>

- Effectiveness and Efficacy
    - Indirect evidence from placebo-controlled trials of individual drugs was insufficient to draw conclusions about comparative effectiveness due to heterogeneity among trials in populations and outcome measures. No effectiveness evidence was found for either population.[1]
    - Pervasive developmental disorders: No head to head trials were found. Risperidone (five trials), aripiprazole (two trials), and olanzapine (one trial) were superior to placebo for improving behavioral symptoms in children with pervasive developmental disorders. Olanzapine was similar in efficacy to haloperidol in one small study.[1] Conclusions about comparative efficacy could not be drawn from this body of evidence because trials varied in their populations, duration of treatment and outcome measures used.[1]
    - Disruptive behavior disorder: Five fair-quality, short-term placebo-controlled trials found risperidone superior to placebo; one of these was conducted in hospitalized adolescents and the rest in outpatients. Quetiapine showed better efficacy than placebo in one study of adolescents with conduct disorder and moderate-to-severe aggressive behaviors.[1] No evidence was found for other second generation antipsychotics.[1]
    - Strength of evidence: Insufficient[1]
- Safety
    - Indirect evidence from placebo-controlled trials of individual drugs was insufficient to draw conclusions about comparative safety of the different drugs in this class. [1]
    - Weight change: increases reported in short-term trials ranged from 2.7 to 5.7 kg. Weight increase was significantly greater than placebo in trials of aripiprazole, olanzapine, and risperidone, and greater with olanzapine than haloperidol in one trial. In a Cochrane meta-analysis of 2 trials of risperidone in children with autism, the mean difference from placebo in weight gain with risperidone was 1.78 kg (95% CI, 1.15 to 2.41).[1] Longer-term evidence included three 6-month placebo-controlled trials and 4 open-label extension studies of short-term efficacy trials of risperidone. Weight gain ranged from 2.1 to 5.6 kg in studies up to 1 year. In a 2-year open-label extension study of 14 children, mean weight gain was 8.09 kg.[1] Other adverse events were infrequent. [1]
    - Extrapyramidal symptoms: The incidence of extrapyramidal symptoms and other adverse events was low in short-term trials. [1]
    - Longer term safety: No comparative evidence was found. Studies were conducted on risperidone only in longer-term evidence, none were conducted for olanzapine. [1]
- Effectiveness and safety in subgroups
    - No conclusions about comparative effectiveness or harms of second generation antipsychotics based on age, gender, or comorbidities could be made from this body of evidence. [1] Risperidone remained superior to placebo in mean decrease from baseline in ABC Irritability Subscale Score in subgroups of children with autism based on age, gender, ethnicity and income. [1] Risperidone was also superior to placebo in improving symptoms of children with disruptive behavior disorders and below-average IQ. [1]
    - Strength of evidence: Insufficient[1]

Serious Harms

- Strength of evidence for all serious harms outcome[1]:
  - Mortality, cardiovascular disease, tardive dyskinesia: Low
  - Diabetes: Moderate
  - Seizures, agranulocytosis, neuroleptic malignant syndrome: Insufficient
- Mixed Populations, primarily adults with schizophrenia
  - Mortality: Limited comparative evidence was available[1]
    - Quetiapine was found to have statistically significantly lower risk of mortality after 6 months of treatment in older patients with bipolar disorders compared with risperidone, hazard ratio 0.45 (95% CI 0.27 to 0.77). [1] Olanzapine and risperidone were not found to have statistically significant difference in risk, hazard ratio of 0.99 (95% CI 0.61 to 1.60. Cardiovascular mortality was found to be similar between clozapine and risperidone after 6 to 10 years of follow-up, 34.8% with clozapine, and 25% with risperidone (relative risk 1.39, 95% CI 0.61 to 2.5).[1] Stratification by age (< 55 or > 55 years at drug initiation) did not alter these findings, although the absolute rates are more divergent in the older group (e.g. 2.7% and 2.8% at 10 years in the younger group and 16.0% and 5.7% in the older group with clozapine and risperidone, respectively). [1]
  - Cardiac and cardiovascular risk: The risk of cardiovascular mortality was not different between clozapine and risperidone after 6-10 years of follow-up. [1] Clozapine was found to be associated with myocarditis or cardiomyopathy, while olanzapine, immediate-release quetiapine and risperidone were not. [1]
  - Diabetes: Olanzapine resulted in an increased risk of new-onset diabetes (OR, 1.16; 95% CI, 1.0 to 1.31 compared with risperidone). [1] Differences were not found with clozapine, immediate-release quetiapine, or risperidone. [1]
  - Tardive dyskinesia: Risperidone resulted in a small increased risk of new-onset tardive dyskinesia (1% to 2% difference). [1]

Systematic Reviews:

AHRQ Treatment of Adults with Post-Traumatic Stress Disorder (PTSD):
There is a low strength of evidence that risperidone may have some benefit for reducing PTSD symptoms, but insufficient evidence of its effects on depression symptoms. [9]

Cochrane Reviews:

One systematic review was identified from the Cochrane Library evaluating aripiprazole versus other atypical antipsychotics for schizophrenia.[2] This review shows that it remains difficult to draw strong conclusions due to the high attrition rates in these groups. Differences in efficacy between aripiprazole and other second generation antipsychotics (olanzapine, risperidone, ziprasidone) showed no advantage in terms of overall global state (defined as MD average change in CGI-S score) or mental state (defined as MD total change in PANNS score) in head-to-head RCTs.[2] When compared with any one of several new generation antipsychotic drugs in one RCT (n=523), the aripiprazole group showed improvement in energy, mood, negative symptom, somnolence, and weight gain.[2] More nausea was seen in patients given aripiprazole (n=2881, 3 RCTs, RR 3.13; 95% CI 2.12 to 4.61). [2] Weight gain in patients on aripiprazole was less common (n=330,

1 RCT, RR 0.35; 95% CI 0.19 to 0.64). Attrition in studies was 30% to 40% (no differences between groups), limiting validity.[2] There is limited data on the safety and efficacy of aripiprazole compared to other second generation antipsychotics and more large, long-term studies are needed before the clinical application of aripiprazole is fully understood.[2]

In a systematic review evaluating atypical antipsychotics for disruptive behavior disorders in children and youths, the use of risperidone and quetiapine were assessed.[3] There is limited evidence of efficacy of risperidone in reducing aggression and conduct problems in children aged 5 to 18 in short term trials. [3] Findings from one study assessing impact in the longer term suggest that the effects are maintained to some extent for up to six months. [3] Evidence was restricted by heterogeneity of the population and methodological issues in some studies, such as use of enriched designs and risk of selection bias. [3] There is currently no evidence to support the use of quetiapine for disruptive behaviors in these populations. [3] There still exists gaps in research with clinically representative youths and long-term follow-up, which will need to be closed before the effects of this class on disruptive behavior disorders is fully understood. [3]

A Cochrane Review evaluated antipsychotics for acute and chronic pain in adults.[4] Data from five included RCT showed beneficial effects of antipsychotics in the treatment of acute and chronic pain, but sample sizes in RCTs were small and results for antipsychotics in the treatment of different painful conditions are mixed. [4] There is a low level of evidence that antipsychotics may be used as add-on therapy in the treatment of painful conditions, but more data is needed to fully understand the benefit. [4] The most commonly reported adverse effects were extrapyramidal and sedating effects.[4] Further, larger studies are needed to determine the true effects of antipsychotics on patient with acute and chronic pain.[4]

A systematic review of atypical antipsychotics for psychosis in adolescents evaluated atypical antipsychotic medication with placebo or another pharmacological intervention or with psychosocial interventions, standard psychiatric treatment or no intervention in this population.[5] There was no convincing evidence that suggest that atypical antipsychotic medications are superior to typical medications for the treatment of adolescents with psychosis. [5] Atypical medications may be more acceptable to young people because fewer symptomatic adverse effects are seen in the short term. [5] Little evidence is available to support the superiority of one atypical antipsychotic medication over another, but side effect profiles are different for different medications. [5] Treatment with olanzapine, risperidone and clozapine is often associated with weight gain.[5] Aripiprazole is not associated with increase prolactin or with dyslipidemia.[5] Adolescents may respond better to standard-dose as opposed to lower-dose risperidone, but for aripiprazole and ziprasidone, lower doses may be equally effective.[5]

New Guidelines:

Scottish Intercollegiate Guidelines Network: Management of Schizophrenia (March 2013)[10]

- Grades of Recommendation[10]
    - Level A evidence: At least one meta-analysis, systematic review or RCT rated as high quality with very low risk of bias and directly applicable to the target population; or a body of evidence consisting principally of well conducted meta-analyses, systematic reviews or RCTs with low risk of bias directly applicable to the target population and demonstrating overall consistency of results
    - Level B evidence: A body of evidence including high quality systematic reviews of case control or cohort studies directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from high quality meta-analyses, systematic reviews or RCTs with low risk of bias

    - Level C evidence: A body of well conducted case control or cohort studies with low risk of confounding or bias and a moderate probability that the relationship is not causal, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from high quality systematic reviews of case control or cohort studies
    - Level D evidence: Non-analytic studies (case reports, case series) or expert opinion; or extrapolated evidence from well conducted case control or cohort studies with a low risk or confounding or bias and a moderate probability that the relationship is causal
- Antipsychotic tolerability
    - Healthcare professionals and patients should work together to find the most appropriate medication and the lowest effective dose. There should be detailed discussion with service users outlining the potential benefits and harms of individual medications. Service user preference should be elicited and taken into account (expert consensus). [10]
    - Local arrangements for physical heath monitoring should be put in place at the time of antipsychotic prescribing (expert consensus).[10]
- Initial treatment in first episode psychosis
    - Following initiation of antipsychotics in the first episode of psychosis, the medicine should be continued for at least two weeks unless there are significant tolerability issues, and an assessment of dose and response should be monitored during this early phase (level D evidence).[10]
    - If there is no response to medication after four weeks, despite dose optimization, a change in antipsychotic should be considered (level D evidence).[10]
    - Where there is a partial response, patients should be reassessed after eight weeks unless there are significant adverse effects (level D evidence).
    - Minimum effective dose of either first- or second-generation antipsychotics should be used in individuals in the first episode of schizophrenia (level D evidence). [10]
    - Following remission of the first episode of schizophrenia, the duration of maintenance treatment with an antipsychotic should be at least 18 months (level D evidence).[10]
- Treating acute exacerbation or recurrence
    - Consider amisulpride, olanzapine or risperidone as the preferred medications with chlorpromazine and other low-potency first-generation antipsychotics providing suitable alternatives.[10] Consideration should be given to previous response to individual antipsychotic medications and adverse effect profiles (level A evidence). [10]
    - The medication should be continued for at least four weeks unless there are significant tolerability issues (level D evidence).[10]
    - Where a partial response is seen after review at four weeks, the medication should be reassessed after eight weeks unless there are significant adverse effects (level D evidence).[10]
- Treatment to prevent relapse during remission
    - Antipsychotics should be used for maintenance treatment in remission (level A evidence).[10]
    - Preferred medications are amisulpride, olanzapine or risperidone; suitable alternatives are chlorpromazine and other low-potency first-generation antipsychotics (level B evidence).[10]
    - Remission should be treated for a minimum of 2 years (level A evidence).[10]
    - Patients who request depot and those with medication adherence difficulties should be offered maintenance treatment with depot antipsychotic medication (level B evidence).[10]
- Treatment-resistant schizophrenia

- Clozapine should be offered to service users who have treatment-resistant schizophrenia (level A evidence).[10]
- Clozapine should be considered for patients whose schizophrenia has not responded to two antipsychotics including a second-generation antipsychotic medication (level B evidence).[10]
- A trial of clozapine augmentation with a second SGA should be considered for patients whose symptoms have not responded adequately to clozapine alone, despite dose optimization.[10] Treatment should be continued for a minimum of 10 weeks (level C evidence).[10]
- A trial of clozapine augmentation with lamotrigine may be considered for patients whose symptoms have had an insufficient response to clozapine alone (level B evidence).[10]
- Prescribing high dose antipsychotics should only be considered after adequate trials of antipsychotic monotherapy and augmentation, including a trial of clozapine, has failed (level D evidence).[10]

- Management of adverse effects[10]

Concern and/or risk	Strength of evidence	Consider
Extrapyramidal Side Effects	B	SGAs or low-potency FGAs
Tardive Dyskinesia	B	SGA
Sedation	B	Haloperidol or aripiprazole
Weight Gain	A	Haloperidol, aripiprazole, or amisulpride (not available in the US)
Weight gain on antipsychotic medications	A	Lifestyle interventions
	B	Metformin

- Comorbidities
  - Second-generation antipsychotics should be considered for individuals with schizophrenia which is in remission who have comorbid depressive symptoms (level B evidence).[10]

Horizon Scan

A recent AHRQ Horizon Scan report identified two antipsychotics in Phase III trials for the treatment of schizophrenia.[11] These agents target different receptors than currently approved agents, including a glycine transporter and a nicotine receptor, and will be used to treat negative symptoms and cognitive symptoms of schizophrenia.

New Formulations:

Aripiprazole long-acting injection (LAI) (Abilify Maintena™) was approved for use in February 2013. [6] The initial and usual maintenance dose of aripiprazole LAI is 400 mg once a month.[6] The dose can be reduced to 300 mg or 200 mg monthly based on drug interactions or tolerability. Patients should have established tolerability to aripiprazole before receipt of the LAI formulation.[6] Oral aripiprazole, 10-30 mg/day, or another oral antipsychotic must be continued for 2-weeks after the initial dose, and then discontinued. [6]

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Aripiprazole LAI's efficacy and safety are based on experience with the oral formulation as well as pharmacokinetic trials and one 52-week randomized, double-blind, placebo-controlled trial.[12] The primary outcome was time to impending relapse in subjects who were stabilized on treatment with aripiprazole-IM depot for at least 12 weeks and then randomly assigned to either aripiprazole-IM-depot or placebo. [12] The randomized trial was terminated early because the difference in time to relapse met a predetermined statistically significant threshold (p=0.001) favoring aripiprazole LAI. [12] The rate of impending relapse was 10% with aripiprazole LAI and nearly 40% in the placebo group in the final analysis (HR 5.03; 95% CI 3.15-8.02. [12] The duration of exposure was limited due to the study's premature termination.[12]

Insomnia, headache and tremor were the most common adverse events reported with aripiprazole LAI relative to placebo. [6] Extra pyramidal symptoms were more common in the aripiprazole LAI group with the difference accounted for by Parkinson's symptoms.[6] Aripiprazole LAI shares the same contraindications, warnings and precautions as the oral form. Concurrent use of CYP 2D6 and 3A4 inhibitors requires a reduction in the monthly dose of aripiprazole. [6] Aripiprazole LAI should be avoided in patients taking a CYP3A4 inducer.[6]

Possible disadvantages of this new formulation include the requirement that patient continue oral aripiprazole for the 2 weeks following their first LAI dose as this could mistakenly lead to continuation of oral antipsychotics.[6] Unlike risperidone long-acting injection, aripiprazole LAI does not have a label indication for bipolar disorder and no trials have been published to support such off-label use.[6]

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Appendix 1:

Previous Conclusions by DERP[13,14]:

Schizophrenia:

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

Bipolar Disorder

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

Major Depressive Disorder

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

Dementia

1. There was no consistent evidence that any atypical antipsychotic was superior to haloperidol for treating behavioral and psychological symptoms of dementia.
2. There were no significant differences between drugs or between drug and placebo on a variety of evaluation scales.

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3. The incidence of Parkinsonism is higher with olanzapine and risperidone compared to immediate release quetiapine and placebo in patients with dementia.

Children with Pervasive Developmental Disorder or Disruptive Behavior Disorder

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

Serious Harms

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

Off-Label Uses

- There is moderate to high level of evidence available to support the following off-label use of the listed atypical antipsychotics.
    - Generalized anxiety disorder: quetiapine
    - Dementia (overall): aripiprazole, risperidone
    - Dementia (psychosis): risperidone
    - Dementia (agitation): olanzapine, risperidone
    - Depression (selective serotonin reuptake inhibitor (SSRI)/ selective serotonin-norepinephrine reuptake inhibitor (SNRI) augmentation): aripiprazole, quetiapine, risperidone
    - Depression (monotherapy): quetiapine
    - Obsessive Compulsive Disorder (SSRI augmentation): risperidone
    - Post-Traumatic Stress Disorder (PTSD): risperidone
- Based upon findings from the AHRQ report on off-label antipsychotics, it is recommended to maintain the current dose limit for quetiapine (limits doses <150mg for >3 months) to prevent off-label use.
- Due to the need for voluntary compliance with the PDL for this drug class, it is recommended that educational outreach interventions be considered in the management strategy.
    - As one example, academic detailing can be used to promote appropriate utilization and minimize inappropriate off-label use.

Appendix 2: Low dose quetiapine PA criteria

Low-Dose quetiapine (Seroquel® and Seroquel XR®)

Goal(s):

- To promote and ensure use of quetiapine that is supported by the medical literature.
- To discourage off-label use for insomnia.
- Promote the use of non-pharmacologic alternatives for chronic insomnia

Initiative: Require Prior Authorization for quetiapine doses <150 mg/day for greater than 90 days.
HSN = 14015

Length of Authorization: Up to 12 months (criteria specific)

Covered alternatives for insomnia:

- Covered alternatives listed at www.orpdl.org
- zolpidem
- benzodiazepine sedatives are available for short-term (15 doses/30days) without PA.
- mirtazapine (Off-label use)

Table.1 Adult (>18 years old) FDA-Approved Indications for quetiapine

Bipolar Disorder	296.0, 296.4, 296.6-296.8,296.89	
Major Depressive Disorder	296.2, 296.24, 296.3, 296.23, 296.33, 296.34, 296.5, 296.53, 296.54	For Seroquel XR® only, Adjunctive therapy with antidepressants for Major Depressive Disorder
Schizophrenia	295, 295.4, 295.44, 295.45, 295.6,295.62, 295.64, 295.85, 295.95, 295.80-295.82,295.40-295.42, 295.90-295.92	
Bipolar Mania	296.1, 296.3, 296.4, 296.43, 296.44	
Bipolar Depression	296.5	

Table.2. Pediatric FDA-Approved Indications

Schizophrenia	Adolescents (13-17 years)	
Bipolar Mania	Children and Adolescents (10 to 17 years),	Monotherapy

Approval Criteria		
1. What is the diagnosis?	Record the ICD9 code. Do not proceed and deny if diagnosis is not listed in Table. 1 or Table 2 above. (Medically Appropriate)	
2. Is the prescription for quetiapine less than 150 mg/day? (Verify that day's supply entry is accurate)	**Yes:** Go to #3.	**No:** Trouble-shoot claim processing with the pharmacy.
3. Is planned duration of therapy greater than 90 days?	**Yes:** Go to #4.	**No:** Approve for titration up to maintenance dose (60days).
4. Is reason for dose <150 mg/day due to any of the following: • low dose needed due to debilitation from a medical condition or age; • unable to tolerate higher doses; • stable on current dose; or • impaired drug clearance?	**Yes:** Approve for up to 1 year.	**No:** Deny, (Medically Appropriate). • Provide tapering schedule if needed. See below. • Approve up to 6 months to allow taper.

Suggested tapering strategies for quetiapine:

According to the manufacturer, downward dosage adjustments may be made dependent upon the clinical response and tolerance of the patient. Several other references which include the Journal of Family Practice, the Texas Medication Algorithm Project Procedural Manual on Bipolar Disorder Algorithms, and the State of Connecticut Department of Developmental Services Neuroleptic Taper Protocol recommend reducing the antipsychotic dose by 10 to 25 % of the current regimen every 1 to 2 weeks, with the exception of the State of Connecticut Protocol recommendation of additional decreases every 3 to 6 months as tolerated.

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Appendix 3: Abstracts of potentially relevant systematic reviews

Khanna, P. *et al.* Aripiprazole versus other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev* **2,** CD006569 (2013).

BACKGROUND: In most western industrialised countries, second generation (atypical) antipsychotics are recommended as first line drug treatments for people with schizophrenia. In this review we specifically examine how the efficacy and tolerability of one such agent - aripiprazole - differs from that of other comparable second generation antipsychotics.

OBJECTIVES: To evaluate the effects of aripiprazole compared with other atypical antipsychotics for people with schizophrenia and schizophrenia-like psychoses.

SEARCH METHODS: We searched the Cochrane Schizophrenia Group Trials Register (November 2011), inspected references of all identified studies for further trials, and contacted relevant pharmaceutical companies, drug approval agencies and authors of trials for additional information.

SELECTION CRITERIA: We included all randomised clinical trials (RCTs) comparing aripiprazole (oral) with oral and parenteral forms of amisulpride, clozapine, olanzapine, quetiapine, risperidone, sertindole, ziprasidone or zotepine for people with schizophrenia or schizophrenia-like psychoses. Data collection and analysis.

DATA COLLECTION AND ANALYSIS: We extracted data independently. For dichotomous data we calculated risk ratios (RR) and their 95% confidence intervals (CI) on an intention-to-treat basis based on a random-effects model. Where possible, we calculated illustrative comparative risks for primary outcomes. For continuous data, we calculated mean differences (MD), again based on a random-effects model. We assessed risk of bias for each included study.

MAIN RESULTS: We included 12 trials involving 6389 patients. Aripiprazole was compared to olanzapine, risperidone and ziprasidone. All trials were sponsored by an interested drug manufacturer. The overall number of participants leaving studies early was 30% to 40%, limiting validity (no differences between groups). When compared with olanzapine no differences were apparent for global state (no clinically important change: n = 703, 1 RCT, RR short-term 1.00 95% CI 0.81 to 1.22; n = 317, 1 RCT, RR medium-term 1.08 95% CI 0.95 to 1.22) but mental state tended to favour olanzapine (n = 1360, 3 RCTs, MD total Positive and Negative Syndrome Scale (PANSS) 4.68 95% CI 2.21 to 7.16). There was no significant difference in extrapyramidal symptoms (n = 529, 2 RCTs, RR 0.99 95% CI 0.62 to 1.59) but fewer in the aripiprazole group had increased cholesterol levels (n = 223, 1 RCT, RR 0.32 95% CI 0.19 to 0.54) or weight gain of 7% or more of total body weight (n = 1095, 3 RCTs, RR 0.39 95% CI 0.28 to 0.54). When compared with risperidone, aripiprazole showed no advantage in terms of global state (n = 384, 2 RCTs, RR no important improvement 1.14 95% CI 0.81 to 1.60) or mental state (n = 372, 2 RCTs, MD total PANSS 1.50 95% CI -2.96 to 5.96). One study compared aripiprazole with ziprasidone (n = 247) and both the groups reported similar change in the global state (n = 247, 1 RCT, MD average change in Clinical Global Impression-Severity (CGI-S) score -0.03 95% CI -0.28 to 0.22) and mental state (n = 247, 1 RCT, MD change PANSS -3.00 95% CI -7.29 to 1.29). When compared with any one of several new generation antipsychotic drugs the aripiprazole group showed improvement in global state in energy (n = 523, 1 RCT, RR 0.69 95% CI 0.56 to 0.84), mood (n = 523, 1 RCT, RR 0.77 95% CI 0.65 to 0.92), negative symptoms (n = 523, 1 RCT, RR 0.82 95% CI 0.68 to 0.99), somnolence (n = 523, 1 RCT, RR 0.80 95% CI 0.69 to 0.93) and weight gain (n = 523, 1 RCT, RR 0.84 95% CI 0.76 to 0.94). Significantly more people given aripiprazole reported symptoms of nausea (n = 2881, 3 RCTs, RR 3.13 95% CI 2.12 to 4.61) but weight gain (7% or more of total body weight) was less common in people allocated aripiprazole (n = 330, 1 RCT, RR 0.35 95% CI 0.19 to 0.64). Aripiprazole may have value in aggression but data are limited. This will be the focus of another review.

AUTHORS' CONCLUSIONS: Information on all comparisons are of limited quality, are incomplete and problematic to apply clinically. Aripiprazole is an antipsychotic drug with a variant but not absent adverse effect profile. Long-term data are sparse and there is considerable scope for another update of this review as new data emerges from the many Chinese studies as well as from ongoing larger, independent pragmatic trials.

Loy, J. H., Merry, S. N., Hetrick, S. E. & Stasiak, K. Atypical antipsychotics for disruptive behaviour disorders in children and youths. *Cochrane Database Syst Rev* **9,** CD008559 (2012).

BACKGROUND: Disruptive behaviour disorders include conduct disorder, oppositional defiant disorder and disruptive behaviour not otherwise specified. Attention deficit hyperactivity disorder (ADHD) is frequently associated with disruptive behaviour disorders. The difficulties associated with disruptive behaviour disorders are demonstrated through aggression and severe behavioural problems. These often result in presentation to psychiatric services and may be treated with medications such as atypical antipsychotics. There is increasing evidence of a significant rise in the use of atypical antipsychotics for treating disruptive behaviour disorders in child and adolescent populations.

OBJECTIVES: To evaluate the effect and safety of atypical antipsychotics, compared to placebo, for treating disruptive behaviour disorders in children and youths.

SEARCH METHODS: We searched the following databases in August 2011: CENTRAL (2011, Issue 3), MEDLINE (1948 to August Week 1), EMBASE (1980 to 2011 Week 32), PsycINFO (1806 to August Week 2 2011), CINAHL (1937 to current), ClinicalTrials.gov (searched 15 August 2011), Australian New Zealand Clinical Trials Registry (ANZCTR) (searched 15 August 2011), CenterWatch (searched 15 August 2011) and ICTRP (searched 15 August 2011).

SELECTION CRITERIA: We included randomised controlled trials with children and youths up to and including the age of 18, in any setting, with a diagnosis of a disruptive behaviour disorder. We included trials where participants had a comorbid diagnosis of attention deficit hyperactivity disorder, major depression or an anxiety disorder.

DATA COLLECTION AND ANALYSIS: Two review authors independently selected the studies and disagreements were resolved by discussion. Two review authors extracted data independently. One review author entered data into Review Manager software and another checked it. We contacted trial authors for information about adverse effects and to provide missing data.

MAIN RESULTS: We included eight randomised controlled trials, spanning 2000 to 2008. Seven assessed risperidone and one assessed quetiapine. Three of the studies were multicentre. Seven trials assessed acute efficacy and one assessed time to symptom recurrence over a six-month maintenance period. We performed meta-analyses for the primary outcomes of aggression, conduct problems and weight changes but these were limited by the available data as different trials reported either mean change scores (average difference) or final/post-intervention raw scores and used different outcome measures. We also evaluated each individual trial's treatment effect size where possible, using Hedges' g.For aggression, we conducted two meta-analyses. The first included three trials (combined n = 238) using mean difference (MD) on the Aberrant Behaviour Checklist (ABC) Irritability subscale. Results yielded a final mean score with treatment that was 6.49 points lower than the post-intervention mean score with placebo (95% confidence interval (CI) -8.79 to -4.19). The second meta-analysis on aggression included two trials (combined n = 57) that employed two different outcome measures (Overt Aggression Scale (modified) (OAS-M) and OAS, respectively) and thus we used a standardised mean difference. Results yielded an effect estimate of -0.18 (95% CI -0.70 to 0.34), which was statistically non-significant. We also performed two meta-analyses for conduct problems. The first included two trials (combined n = 225), both of which employed the Nisonger Child Behaviour Rating Form - Conduct Problem subscale (NCBRF-CP). The results yielded a final mean score with treatment that was 8.61 points lower than that with placebo (95% CI -11.49 to -5.74). The second meta-analysis on conduct problems included two trials (combined n = 36), which used the Conners' Parent Rating Scale - Conduct Problem subscale (CPRS-CP). Results yielded a mean score with treatment of 12.67 lower than with placebo (95% CI -37.45 to 12.11), which was a statistically non-significant result. With respect to the side effect of weight gain, a meta-analysis of two studies (combined n = 138) showed that participants on risperidone gained on average 2.37 kilograms more than those in the placebo group over the treatment period (MD 2.37; 95% CI 0.26 to 4.49).For individual trials, there was a range of effect sizes (ranging from small to large) for risperidone reducing aggression and conduct problems. The precision of the estimate of the effect size varied between trials.

AUTHORS' CONCLUSIONS: There is some limited evidence of efficacy of risperidone reducing aggression and conduct problems in children aged 5 to 18 with disruptive behaviour disorders in the short term. For aggression, the difference in scores of 6.49 points on the ABC Irritability subscale (range 0 to 45) may be clinically significant. For conduct problems, the difference in scores of 8.61 points on the NCBRF-CP (range 0 to 48) is likely to be clinically significant. Caution is required due to the limitations of the evidence and the small number of relevant high-quality studies. The findings from the one study assessing impact in the longer term suggest that the effects are maintained to some extent (small effect size) for up to six months. Inadequately powered studies produced non-significant results. The evidence is restricted by heterogeneity of the population (including below average and borderline IQ), and methodological issues in some studies, such as use of enriched designs and risk of selection bias. No study addressed the issue of pre-existing/concurrent psychosocial interventions, and comorbid stimulant medication and its dosage was only partially addressed. There is currently no evidence to support the use of quetiapine for disruptive behaviour disorders in children and adolescents. It is uncertain to what degree the efficacy found in clinical trials will translate into real life clinical practice. Participants in the studies were recruited from clinical services but those who agree to take part in the clinical trials are a subset of the overall population presenting for care. There are no research data for children under five years of age. Further high-quality research is required with large samples of clinically representative youths and long-term follow-up to replicate current findings.

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Seidel, S. *et al.* Antipsychotics for acute and chronic pain in adults. Cochrane Database of Systematic Reviews 2013, Issue 8. Art. No.: CD004844. DOI: 10.1002/14651858.CD004844.pub3.

BACKGROUND: This is an updated version of the original Cochrane review published in Issue 4, 2008. The role of antipsychotics as adjuvant analgesics is a subject of longstanding controversy. Neuroleptanalgesia (that is a state of quiescence, altered awareness, and analgesia produced by a combination of taking an opioid analgesic and an antipsychotic), an established term for the management of acute pain, was shown to negatively influence disease course and total mortality in unstable angina patients. Nevertheless, antipsychotics are used to treat chronic pain (for example chronic headache, fibromyalgia and diabetic neuropathia). With atypical antipsychotics, a new class of antipsychotics, both fewer extrapyramidal side effects and additional benefits may be available.

OBJECTIVES: To assess the analgesic efficacy and adverse effects of antipsychotics in acute or chronic pain in adults.

SEARCH METHODS: The following databases were searched: CENTRAL, on The Cochrane Library, (Issue 12 of 12, 2012); MEDLINE (1966 to 11/1/2013); EMBASE (1980 to 2013 week 03) and PsycINFO 1806 to Jan week 3 2013. Searches were run originally in 2007 and then again in 2011 and 2013.

SELECTION CRITERIA: Randomised controlled trials (RCTs) of adults prescribed any dose of an oral antipsychotic for acute or chronic pain, where subjective pain assessment was described as either the primary or a secondary outcome, were included in this review.

DATA COLLECTION AND ANALYSIS: Data were extracted by two independent review authors, and results were compared for differences. Discrepancies were resolved by discussion. All trials were quality scored according to the methods set out in section six of the Cochrane Handbook for Systematic Reviews of Interventions.

MAIN RESULTS: A total of 770 participants were involved in the 11 included studies. Data from five included randomised double-blind studies showed beneficial effects of antipsychotics in the treatment of acute and chronic pain. Quantitative analysis of these studies showed a significant reduction of mean pain intensity after administration of the antipsychotic compared to placebo or another active compound, weighted mean difference (WMD) -1.78 (95% CI -2.71 to -0.85) for the continuous data; and relative risk (RR) 0.43 (95% CI 0.25 to 0.73), number needed to treat to benefit (NNT) 2.6 for the dichotomous data. Nevertheless, the test for heterogeneity was significant for both the continuous data (P = 0.0007) and the dichotomous data (P = 0.04). Obviously this makes the calculated NNT less reliable and caution is warranted when interpreting these results. The most frequently reported adverse effects were extrapyramidal (that is involuntary movements, parkinsonism and akathisia) and sedating effects.

AUTHORS' CONCLUSIONS: The recent search found five new studies which were all excluded, so the review remains the same as previously. Antipsychotics might be used as an add-on therapy in the treatment of painful conditions. Nevertheless, extrapyramidal and sedating side effects have to be considered before using antipsychotics for treating painful conditions. Results for antipsychotics in the treatment of different painful conditions are mixed and most sample sizes in the reviewed RCTs are small. Further studies on atypical antipsychotics in larger double-blind placebo-controlled studies that include standardised pain assessment and documentation are warranted.

Kumar, A., Datta, S. S., Wright, S. D., Furtado, V. A. & Russell, P. S. Atypical antipsychotics for psychosis in adolescents. Cochrane Database of Systematic Reviews 2013, Issue 10. Art. No.: CD009582. DOI: 10.1002/14651858.CD009582.pub2.

BACKGROUND: Schizophrenia often presents in adolescence, but current treatment guidelines are based largely on studies of adults with psychosis. Over the past decade, the number of studies on treatment of adolescent-onset psychosis has increased. The current systematic review collates and critiques evidence obtained on the use of various atypical antipsychotic medications for adolescents with psychosis.

OBJECTIVES: To investigate the effects of atypical antipsychotic medications in adolescents with psychosis. We reviewed in separate analyses various comparisons of atypical antipsychotic medications with placebo or a typical antipsychotic medication or another atypical antipsychotic medication or the same atypical antipsychotic medication but at a lower dose.

SEARCH METHODS: We searched the Cochrane Schizophrenia Group Register (October 2011), which is based on regular searches of BIOSIS, CENTRAL, CINAHL, EMBASE, MEDLINE and PsycINFO. We inspected references of all identified studies and contacted study authors and relevant pharmaceutical companies to ask for more information.

SELECTION CRITERIA: We included all relevant randomised controlled trials (RCTs) that compared atypical antipsychotic medication with placebo or another pharmacological intervention or with psychosocial interventions, standard psychiatric treatment or no intervention in children and young people aged 13 to 18 years with a diagnosis of schizophrenia, schizoaffective disorder, acute and transient psychoses or unspecified psychosis. We included studies published in English and in other languages that were available in standardised databases.

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DATA COLLECTION AND ANALYSIS: Review authors AK and SSD selected the studies, rated the quality of the studies and performed data extraction. For dichotomous data, we estimated risk ratios (RRs) with 95% confidence intervals (CIs) using a fixed-effect model. When possible, for binary data presented in the 'Summary of findings' table, we calculated illustrative comparative risks. We summated continuous data using the mean difference (MD). Risk of bias was assessed for included studies.

MAIN RESULTS: We included 13 RCTs, with a total of 1112 participants. We found no data on service utilisation, economic outcomes, behaviour or cognitive response. Trials were classified into the following groups. 1. Atypical antipsychotics versus placebo. Only two studies compared one atypical antipsychotic medication with placebo. In one study, the number of non-responders treated with olanzapine was not different from the number treated with placebo (1 RCT, n = 107, RR 0.84, 95% CI 0.65 to 1.10); however, significantly more (57% vs 32%) people left the study early (1 RCT, n = 107, RR 0.56, 95% CI 0.36 to 0.87) from the placebo group compared with the olanzapine group. With regard to adverse effects, young people treated with aripiprazole had significantly lower serum cholesterol compared with those given placebo (1 RCT, n = 302, RR 3.77, 95% CI 1.88 to 7.58). 2. Atypical antipsychotics versus typical antipsychotics When the findings of all five trials comparing atypical antipsychotic medications with a typical antipsychotic medication were collated, no difference in the mean end point Brief Psychiatric Rating Scale (BPRS) score was noted between the two arms (5 RCTs, n = 236, MD -1.08, 95% CI -3.08 to 0.93). With regard to adverse effects, the mean end point serum prolactin concentration was much higher than the reference range for treatment with risperidone, olanzapine and molindone in one of the studies. However, fewer adolescents who were receiving atypical antipsychotic medications left the study because of adverse effects (3 RCTs, n = 187, RR 0.65, 95% CI 0.36 to 1.15) or for any reason (3 RCTs, n = 187, RR 0.62, 95% CI 0.39 to 0.97). 3. One atypical antipsychotic versus another atypical antipsychotic. The mean end point BPRS score was not significantly different for people who received risperidone compared with those who received olanzapine; however, the above data were highly skewed. Overall no difference was noted in the number of people leaving the studies early because of any adverse effects between each study arm in the three studies comparing olanzapine and risperidone (3 RCTs, n = 130, RR 1.15, 95% CI 0.44 to 3.04). Specific adverse events were not reported uniformly across the six different studies included in this section of the review; therefore it was difficult to do a head-to-head comparison of adverse events for different atypical antipsychotic medications. 4. Lower-dose atypical antipsychotic versus standard/higher-dose atypical antipsychotic. Three studies reported comparisons of lower doses of the atypical antipsychotic medication with standard/higher doses of the same medication. One study reported better symptom reduction with a standard dose of risperidone as compared with a low dose (1 RCT, n = 257, RR -8.00, 95% CI -13.75 to -2.25). In another study, no difference was reported in the number of participants not achieving remission between the group receiving 10 mg/d and those who received 30 mg/d of aripiprazole (1 RCT, n = 196, RR 0.84, 95% CI 0.48 to 1.48). Similarly in the other study, authors reported no statistically significant difference in clinical response between the two groups receiving lower-dose (80 mg/d) and higher-dose (160 mg/d) ziprasidone, as reflected by the mean end point BPRS score (1 RCT, n = 17, MD -4.40, 95% CI -19.20 to 10.40).

AUTHORS' CONCLUSIONS: No convincing evidence suggests that atypical antipsychotic medications are superior to typical medications for the treatment of adolescents with psychosis. However, atypical antipsychotic medications may be more acceptable to young people because fewer symptomatic adverse effects are seen in the short term. Little evidence is available to support the superiority of one atypical antipsychotic medication over another, but side effect profiles are different for different medications. Treatment with olanzapine, risperidone and clozapine is often associated with weight gain. Aripiprazole is not associated with increased prolactin or with dyslipidaemia. Adolescents may respond better to standard-dose as opposed to lower-dose risperidone, but for aripiprazole and ziprasidone, lower doses may be equally effective. Future trials should ensure uniform ways of reporting.

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