Critical Appraisal

A worked example.
**Clinical Scenario**

20 year old woman on ward. Has had two years of psychosis. Non adherent medications. Has responded to Olanzapine oral but refuses to take IM. Is worried will gain more weight. Is the newer antipsychotic Paliperidone suitable in this situation?

**Step 1: Ask a clinical question using PECOT framework**

<table>
<thead>
<tr>
<th><strong>Population or patient</strong></th>
<th>People with schizophrenia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exposure (intervention)</strong></td>
<td>Paliperidone by long acting injection</td>
</tr>
<tr>
<td><strong>Comparison (control)</strong></td>
<td>Oral olanzapine</td>
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<tr>
<td><strong>Outcomes</strong></td>
<td>1. Control of psychosis and 2. No metabolic symptoms</td>
</tr>
<tr>
<td><strong>Time</strong></td>
<td>months to years</td>
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</table>
Metabolic Effects of Paliperidone Extended Release Versus Oral Olanzapine in Patients With Schizophrenia: A Prospective, Randomized, Controlled Trial.


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Abstract

ABSTRACT: Metabolic effects are generally more pronounced with second-generation than first-generation antipsychotics. This study was designed to compare long-term metabolic effects and efficacy of paliperidone extended release (ER) with those of oral olanzapine in patients with schizophrenia. In this 6-month, multicenter, prospective, randomized, controlled, open-label, parallel-group study, adults with schizophrenia were treated with paliperidone ER (6-9 mg/d; n = 239) or oral olanzapine (10-15 mg/d; n = 220). The primary outcome was mean change in the ratio of serum triglyceride level to high-density lipoprotein level (TG/HDL), a marker of insulin resistance. Other outcome measures included the Positive and Negative Syndrome Scale scores, measures of lipid and glucose metabolism, and body weight. Significant improvements in psychotic symptoms were observed with both treatments (P < 0.0001). The TG/HDL ratio was significantly higher at end point versus baseline with olanzapine compared with that of paliperidone ER. Mean end point change in TG/HDL ratio was 0.097 ± 2.72 for olanzapine (P < 0.0001, reflecting worsening), with no significant change for paliperidone ER (-0.17 ± 2.51). Newly diagnosed impairment in TG and metabolic syndrome was more common with olanzapine (P < 0.05). Insulin resistance, as measured by the homeostasis model assessment of insulin resistance, worsened significantly with olanzapine (P = 0.0003), but not with paliperidone ER. Glucose sensitivity for insulin worsened significantly with olanzapine (P < 0.03), with no significant changes for paliperidone ER. End point increase in body weight was significantly higher with olanzapine than paliperidone ER (3.8 vs 1.2 kg; P = 0.0013). In summary, both paliperidone ER and olanzapine effectively treated schizophrenia; however, undesirable metabolic effects were significantly greater with olanzapine.
Problems

• Not LAI. Instead, oral, sustained release.
  – Thus wrong population.
• Perusal of paper finds outcomes almost exclusively metabolic.
• Open label trial.
• Paper is copyright, and thus not really available for teaching/publication.
Looking again...

- Same search in pubmed – olanzapine + paliperione + trial but filtered for pubmed central.
  - Means that all content is open source.
- NOTE: this is NOT what you would do in clinical work. You would go for a good meta analysis then the best paper you can find.
  - But for teaching purposes... These slides are public.
Efficacy and safety of atypical antipsychotic drugs (quetiapine, risperidone, aripiprazole and paliperidone) compared with placebo or typical antipsychotic drugs for treating refractory schizophrenia: overview of systematic reviews.

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Abstract

CONTEXT AND OBJECTIVE: According to some cohort studies, the prevalence of refractory schizophrenia (RS) is 20-40%. Our aim was to evaluate the effectiveness and safety of aripiprazole, paliperidone, quetiapine and risperidone for treating RS.

METHODS: This was a critical appraisal of Cochrane reviews published in the Cochrane Library, supplemented with reference to more recent randomized controlled trials (RCTs) on RS. The following databases were searched: Medical Literature Analysis and Retrieval System Online (Medline) (1966-2009), Controlled Trials of the Cochrane Collaboration (2009, Issue 2), Embase (Excerpta Medica) (1980-2009), Literatura Latino-Americana e do Caribe em Ciências da Saúde (Lilacs) (1982-2009). There was no language restriction. Randomized controlled trials, systematic reviews and meta-analyses evaluating atypical antipsychotics for treating RS were included.

RESULTS: Seven Cochrane systematic reviews and 10 additional RCTs were included in this review. The data generally showed minor differences between the atypical antipsychotics evaluated and typical antipsychotics, regarding improvement in disease symptoms, despite better adherence to treatment with atypical antipsychotics. Risperidone was specifically evaluated in patients with RS in one of the systematic reviews included, with favorable outcomes, but without definitive superiority compared with other drugs of proven efficacy, like amisulpride, clozapine and olanzapine.

CONCLUSIONS: The findings underscore the difficulty in treating these patients, with high dropout rates and treatment patterns of modest improvement in assessments of effectiveness. Atypical antipsychotics have advantages over typical antipsychotics mainly through their better safety profile, which leads to better adherence to treatment. A combination of antipsychotics may also be an option for some refractory patients.
Criteria for study inclusion

Types of studies

Randomized controlled trials (RCTs) and systematic reviews (SRs) of randomized controlled trials were included. Quasi-randomized studies, defined as studies using inadequate allocation, such as date of birth, day of week, or assignment of subjects to alternative treatments were included in the sensitivity analysis in order to assess effectiveness.

Studies published as abstracts were included when sufficient information on methods and results were provided. For questions or incomplete data, the main authors were contacted and interviewed to obtain additional information or complement the existing data.

Types of participants

Patients with refractory schizophrenia were included. Randomized clinical trials that evaluated patients with refractory and non-refractory schizophrenia and did not distinguish between these groups in the analysis were not included.
Types of outcomes

Primary outcomes:

• Improved overall psychopathology: scales such as PANSS (Positive and Negative Syndrome Scale), BPRS and CGI;

• Adherence to treatment: time until discontinuation of medication, frequency of treatment discontinuation and reasons for discontinuation.

• Improvement of specific symptoms: positive, negative or cognitive.

Secondary outcomes:

• Suicide.

• Specific mortality, i.e. mortality due to schizophrenia.

• Relapse: appearance of positive and negative symptoms.

• Need for hospital admission.

• Incidence of adverse events.

• Quality of life.

• Cost analysis.
Study selection
Two reviewers independently assessed the titles and abstracts of all articles identified in the search, and evaluated the full texts of articles that described studies that might potentially be included in this review.

Assessment of methodological quality
The methodological quality, defined as the degree of confidence that the design and reporting of the study were free from bias, was evaluated by the authors, taking into account the results from the Cochrane systematic reviews included. For additional randomized clinical trials that were analyzed, the randomization process was the main methodological criterion evaluated.

Data analysis
The main meta-analyses in the systematic reviews were discussed and complemented with individual studies that evaluated patients with refractory schizophrenia. All the tests were performed using the intention to treat method, and all randomized patients were included in the analysis, regardless of their adherence or outcome.
Compared with placebo, the patients receiving paliperidone had a lower dropout rate in the study ($n = 1647$; five RCTs; RR 0.68; CI 0.61 to 0.76; NNT 7; CI 6 to 9)
The patients taking paliperidone had higher rates of improvement in general condition and disease symptoms, compared with placebo (n = 1420; four RCTs; RR 0.69; CI 0.63 to 0.75; NNT 5; CI 4 to 6)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Paliperidone</th>
<th>Placebo</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>N-H,Fixed, 95% CI</td>
<td>%</td>
<td>M-H,Fixed, 95% CI</td>
</tr>
<tr>
<td>Davidsson et al.</td>
<td>194/359</td>
<td>98/120</td>
<td>0.66 [0.58, 0.75]</td>
<td>36.0%</td>
<td></td>
</tr>
<tr>
<td>Kane et al.</td>
<td>164/374</td>
<td>88/126</td>
<td>0.63 [0.53, 0.74]</td>
<td>32.2%</td>
<td></td>
</tr>
<tr>
<td>Marder et al.</td>
<td>109/222</td>
<td>69/105</td>
<td>0.75 [0.62, 0.91]</td>
<td>22.9%</td>
<td></td>
</tr>
<tr>
<td>Tsimos et al.</td>
<td>47/76</td>
<td>27/38</td>
<td>0.87 [0.67, 1.14]</td>
<td>8.8%</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1031</td>
<td>389</td>
<td>0.69 [0.63, 0.75]</td>
<td>100.0%</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 514 (Paliperidone), 282 (Placebo)

Heterogeneity: Chi² = 5.22, df = 3 (P = 0.18); I² = 43%

Test for overall effect: Z = 8.52 (P < 0.00001)

**Figure 5.** Efficacy of paliperidone versus placebo, in relation to improvements in general condition and disease symptoms.
The use of paliperidone resulted in lower recurrence of psychosis (n = 1638; five RCTs; RR 0.45; CI 0.31 to 0.66; NNT 16; CI 13 to 26)
With regard to adverse events, in comparison with placebo, paliperidone resulted in:

- higher incidence of tachycardia (n = 1638; five RCTs; RR 1.88; CI 1.3 to 2.86; NNH 21; CI 11 to 90);

- significantly higher elevation of prolactin, for both men (n = 413, 4 RCTs, WMD 27.68; CI 23.66 to 31.69) and women (n = 252, 4 RCTs, WMD 87.39; CI 74.27 to 100.51);

- higher rate of extrapyramidal disorders (n = 1638; five RCTs; RR 2.21; CI 1.3 to 3.9; NNH 28; CI 12 to 129);

- greater weight gain (n = 769, 4 RCTs, WMD 1.07; CI 0.65 to 1.49; I² index 78%) in the meta-analysis of three RCTs comparing paliperidone with olanzapine. The loss rate during the studies was similar in both groups of patients (around 40% over six weeks of study).
In assessing the improvement of symptoms over the six-week period, there was no significant difference favoring olanzapine in the PANSS assessment (n = 715; DMP 2.44; CI -0.52 to 5.35).

The group taking paliperidone had lower weight gain (n = 660; three RCTs; DMP -0.88; CI -1.38 to -0.37).
Patients taking olanzapine had a lower rate of movement disorders

- extrapyramidal disorders (n = 1327; three RCTs; RR 2.99; CI 1.4 to 6.2);
- hyperkinesis (n = 1327; three RCTs; RR 3.14; CI 1.5 to 6.4);
- stiffness (n = 1327; two RCTs; RR 9.28; CI 1.3 to 68.5).
Questions to consider?

- Is the question correct?
- Is the search well described?
- Can you work out what happened to all the papers?
- Has the analysis of the papers been described?
- Are the outcomes consistent with protocol?
- What do you make of the conclusion?
- How applicable is this analysis to my patients?