Comparative effects of 18 antipsychotics on metabolic function in schizophrenia

*a network meta-analysis*

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Disclosures

I have contributed to speaker meetings organised by Sunovion, Lundbeck, Otsuka, Schwabe Pharma and Recordati
Background you already know

• People with schizophrenia die 15 years earlier than the general population

• 60% of this premature mortality is due to physical conditions, mainly cardiovascular disease

• Prevalence of obesity, diabetes, and hypercholesterolaemia is up to 5x higher in schizophrenia


Lifestyle

Antipsychotics

Less likely to seek help

Illness

Intrinsic risk?

Less likely to get help
Antipsychotics: the good, the bad and the ugly
The good

Antipsychotics are some of the most effective treatments available in medicine, let alone psychiatry.

The good

Patients with schizophrenia live longer if prescribed antipsychotics

Taipale H, Tanskanen A, Mehtala J et al. 20-year follow-up study of physical morbidity and mortality in relationship to antipsychotic treatment in a nationwide cohort of 62,250 patients with schizophrenia (FIN20). World Psychiatry 2020
The bad

Prevalence of obesity, diabetes (see below), and hypercholesterolaemia is up to 5x higher in schizophrenia


Correll CU, Solmi M, Veronese M et al. Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. World Psychiatry 2013
The ugly

Schizophrenia is associated with an excessive mortality of 15-20 years. The majority of that excess mortality is secondary to cardiovascular disease.

Antipsychotics and life-expectancy

- General population
- Schizophrenia

Years lived
Antipsychotics and life-expectancy

General population

Schizophrenia

GAIN

Reductions in suicide and death by misadventure, better self-care
Antipsychotics and life-expectancy

- Increased cardiometabolic risk
  - General population
  - Schizophrenia (+AP)

Years lived
Antipsychotics and life-expectancy

General population

Schizophrenia

Increased cardiometabolic risk
Antipsychotics and life-expectancy

General population

Schizophrenia

+AP

Years lived

GAIN

LOSS

NET GAIN
Guiding ‘metabolically minded’ prescribing

Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis

A crash course in network meta-analysis

Pillinger T, McCutcheon RA, Vano L et al. Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. The Lancet Psychiatry 2020
Methods

• Searched for double-blind RCTs comparing acute treatment of schizophrenia with antipsychotics or placebo

• Extracted change in metabolic data: weight, BMI, glucose, cholesterol, triglycerides
Objectives

• Rank antipsychotics based on metabolic side effects

• Define baseline predictors of antipsychotic-induced metabolic dysregulation

• Define the relationship between metabolic dysregulation and change in psychotic symptoms

Pillinger T, McCutcheon RA, Vano L et al. Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. The Lancet Psychiatry 2020
Results

- Data gathered from 100 RCTs

- 28,955 patients (23,644 antipsychotic-treated, 5311 placebo-treated)

- Data available for: amisulpride, aripiprazole, asenapine, brexipiprazole, cariprazine, clozapine, flupenthixol, fluphenazine, haloperidol, iloperidone, lurasidone, olanzapine, quetiapine, risperidone, paliperidone, sertindole, ziprasidone, and zotepine

Pillinger T, McCutcheon RA, Vano L et al. Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. The Lancet Psychiatry 2020
Results: ranking antipsychotics

<table>
<thead>
<tr>
<th>Weight change (kg)</th>
<th>Mean difference (95% CI)</th>
<th>95% PI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ziprasidone</td>
<td>-0.28 (-1.11 to 0.55)</td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td>-0.23 (-0.83 to 0.35)</td>
<td></td>
</tr>
<tr>
<td>Paliperidone</td>
<td>0.16 (-0.03 to 0.34)</td>
<td></td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>0.34 (0.14 to 0.54)</td>
<td></td>
</tr>
<tr>
<td>Levomepromazine</td>
<td>0.48 (-0.01 to 0.97)</td>
<td></td>
</tr>
<tr>
<td>Cariprazine</td>
<td>0.66 (0.35 to 1.65)</td>
<td></td>
</tr>
<tr>
<td>Aminopropylide</td>
<td>0.66 (0.23 to 1.56)</td>
<td></td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>0.75 (-0.81 to 3.33)</td>
<td></td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>0.88 (0.66 to 1.69)</td>
<td></td>
</tr>
<tr>
<td>Asenapine</td>
<td>1.17 (0.47 to 1.86)</td>
<td></td>
</tr>
<tr>
<td>Risperidone and paliperidone</td>
<td>1.28 (0.98 to 1.59)</td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>1.56 (1.05 to 2.04)</td>
<td></td>
</tr>
<tr>
<td>Iloperidone</td>
<td>1.77 (1.04 to 3.33)</td>
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</tr>
<tr>
<td>Sertraline</td>
<td>2.37 (1.21 to 3.67)</td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>3.01 (1.76 to 4.24)</td>
<td></td>
</tr>
<tr>
<td>Zolpidemine</td>
<td>-0.25 (-0.68 to 0.17)</td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td>-0.77 (-0.26 to 0.13)</td>
<td></td>
</tr>
</tbody>
</table>

Compared with placebo:
Best: -0.23kg (haloperidol)
Worst: +3.01kg (clozapine)

<table>
<thead>
<tr>
<th>BMI change (kg/m²)</th>
<th>Mean difference (95% CI)</th>
<th>95% PI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ziprasidone</td>
<td>-0.55 (0.86 to 1.96)</td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td>-0.40 (0.68 to 0.22)</td>
<td></td>
</tr>
<tr>
<td>Paliperidone</td>
<td>0.24 (0.05 to 0.42)</td>
<td></td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>0.55 (0.30 to 0.85)</td>
<td></td>
</tr>
<tr>
<td>Levomepromazine</td>
<td>0.32 (0.09 to 0.55)</td>
<td></td>
</tr>
<tr>
<td>Cariprazine</td>
<td>0.19 (0.05 to 0.33)</td>
<td></td>
</tr>
<tr>
<td>Aminopropylide</td>
<td>0.16 (0.03 to 0.29)</td>
<td></td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>0.14 (0.02 to 0.27)</td>
<td></td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>0.10 (0.01 to 0.19)</td>
<td></td>
</tr>
<tr>
<td>Asenapine</td>
<td>0.97 (0.64 to 1.30)</td>
<td></td>
</tr>
<tr>
<td>Risperidone and paliperidone</td>
<td>0.65 (0.34 to 0.96)</td>
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</tr>
<tr>
<td>Quetiapine</td>
<td>0.38 (0.19 to 0.57)</td>
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<tr>
<td>Iloperidone</td>
<td>0.24 (0.10 to 0.38)</td>
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<tr>
<td>Sertraline</td>
<td>0.19 (0.09 to 0.29)</td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>0.18 (0.08 to 0.28)</td>
<td></td>
</tr>
<tr>
<td>Zolpidemine</td>
<td>0.17 (0.08 to 0.26)</td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td>0.15 (0.07 to 0.23)</td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td>-0.25 (-0.68 to 0.17)</td>
<td></td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>-0.50 (0.31 to 0.67)</td>
<td></td>
</tr>
<tr>
<td>Levomepromazine</td>
<td>0.33 (0.15 to 0.51)</td>
<td></td>
</tr>
<tr>
<td>Cariprazine</td>
<td>0.28 (0.05 to 0.51)</td>
<td></td>
</tr>
<tr>
<td>Aminopropylide</td>
<td>0.07 (0.00 to 0.14)</td>
<td></td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>0.03 (0.00 to 0.06)</td>
<td></td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>-0.02 (-0.05 to 0.02)</td>
<td></td>
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<tr>
<td>Asenapine</td>
<td>0.15 (0.08 to 0.22)</td>
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<tr>
<td>Risperidone and paliperidone</td>
<td>0.34 (0.09 to 0.60)</td>
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</tr>
<tr>
<td>Quetiapine</td>
<td>0.33 (0.04 to 0.62)</td>
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</tr>
<tr>
<td>Iloperidone</td>
<td>0.24 (0.37 to 1.29)</td>
<td></td>
</tr>
<tr>
<td>Sertraline</td>
<td>0.33 (0.15 to 0.51)</td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>0.18 (0.08 to 0.28)</td>
<td></td>
</tr>
<tr>
<td>Zolpidemine</td>
<td>0.17 (0.08 to 0.26)</td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td>0.15 (0.07 to 0.23)</td>
<td></td>
</tr>
</tbody>
</table>

Compared with placebo:
Best: -0.25kg/m² (haloperidol)
Worst: +1.07kg/m² (olanzapine)
Normal range 18.5-24.9kg/m²

Results: ranking antipsychotics

Total Cholesterol
Best: -0.09mmol/L (cariprazine)
Worst: +0.56mmol/L (clozapine)
Healthy level below 3.00mmol/L

LDL Cholesterol
Best: -0.13mmol/L (cariprazine)
Worst: +0.20mmol/L (olanzapine)
Health level below 3.00mmol/L
Results: ranking antipsychotics

HDL Cholesterol
Best: +0.05mmol/L (brexpiprazole)
Worst: -0.10mmol/L (amisulpride)

Triglycerides
Best: -0.01mmol/L (brexpiprazole)
Worst: +0.98mmol/L (clozapine)
Healthy level below 2.3mmol/L

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Glucose
Best: -0.29mmol/L (lurasidone)
Worst: +1.05mmol/L (clozapine)
Normal fasting glucose up to 7.8mmol/L

Results: ranking antipsychotics

Summary: ranking antipsychotics based on metabolic side effects

- Olanzapine and clozapine show comparatively worse side-effect profiles
- Aripiprazole, brexipiprazole, cariprazine, lurasidone, and ziprasidone are associated with most favourable metabolic outcomes. These drugs can be considered safer options in those at an increased risk of developing metabolic complications

Applying ‘metabolically minded’ prescribing


<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Weight</th>
<th>Body-mass index</th>
<th>Glucose</th>
<th>LDL cholesterol</th>
<th>Total cholesterol</th>
<th>HDL cholesterol</th>
<th>Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>0.10</td>
<td>0.08</td>
<td>0.59</td>
<td>0.59</td>
<td>0.59</td>
<td>0.63</td>
<td></td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>0.10</td>
<td></td>
<td>0.42</td>
<td>0.12</td>
<td>0.25</td>
<td>0.24</td>
<td>0.33</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>0.26</td>
<td>0.11</td>
<td>0.55</td>
<td>0.48</td>
<td>0.50</td>
<td>0.26</td>
<td>0.33</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>0.32</td>
<td>0.37</td>
<td>0.09</td>
<td>0.27</td>
<td>0.27</td>
<td>0.45</td>
<td>0.26</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>0.37</td>
<td></td>
<td>0.70</td>
<td>0.07</td>
<td>0.16</td>
<td>0.47</td>
<td>0.28</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>0.38</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amisulpride</td>
<td>0.41</td>
<td></td>
<td>0.14</td>
<td>0.64</td>
<td>0.83</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>0.45</td>
<td></td>
<td>0.40</td>
<td>0.66</td>
<td>0.52</td>
<td>0.18</td>
<td>0.23</td>
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<tr>
<td>Flupenthixol</td>
<td>0.44</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Asenapine</td>
<td>0.56</td>
<td></td>
<td>0.22</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risperidone and Paliperidone</td>
<td>0.58</td>
<td>0.56</td>
<td>0.46</td>
<td>0.54</td>
<td>0.55</td>
<td>0.51</td>
<td>0.39</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>0.65</td>
<td>0.68</td>
<td>0.47</td>
<td>0.91</td>
<td>0.82</td>
<td>0.59</td>
<td>0.71</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>0.70</td>
<td></td>
<td>0.73</td>
<td></td>
<td>0.19</td>
<td></td>
<td></td>
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<tr>
<td>Sertindole</td>
<td>0.81</td>
<td>0.72</td>
<td>0.36</td>
<td></td>
<td>0.26</td>
<td></td>
<td>0.29</td>
</tr>
<tr>
<td>Zotepine</td>
<td>0.88</td>
<td></td>
<td>0.94</td>
<td></td>
<td></td>
<td>0.94</td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td>0.90</td>
<td>0.85</td>
<td>0.97</td>
<td></td>
<td></td>
<td>0.97</td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>0.92</td>
<td>0.93</td>
<td>0.67</td>
<td>0.96</td>
<td>0.91</td>
<td>0.76</td>
<td>0.83</td>
</tr>
</tbody>
</table>

P-score

0 0.50 1.0
Baseline predictors of metabolic change

- Greater increases in glucose were predicted by higher baseline weight (p=0.0015) and male sex (p=0.0082)
- Non-white ethnicity was associated with greater increases in total cholesterol (p=0.040) compared with white ethnicity

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Improvements in symptom severity are associated with:

- Increases in weight ($r=0.36$, $p=0.0021$)
- Increases in BMI ($r=0.84$, $p<0.0001$)
- Increases in total-cholesterol ($r=0.31$, $p=0.047$)
- Increases in LDL cholesterol ($r=0.42$, $p=0.013$)
- Decreases in HDL cholesterol ($r=-0.35$, $p=0.035$)
Improvements in symptom severity are associated with:

- Increases in weight ($r = 0.36$, $p=0.0021$)
- Increases in BMI ($r = 0.84$, $p<0.0001$)
- Increases in total-cholesterol ($r = 0.31$, $p=0.047$)
- Increases in LDL cholesterol ($r = 0.42$, $p=0.013$)
- Decreases in HDL cholesterol ($r = -0.35$, $p=0.035$)
Summary

• Marked variations exist in the metabolic side-effects of antipsychotics
• Aripiprazole, brexipiprazole, cariprazine, lurasidone, and ziprasidone are associated with better metabolic outcomes
• Increased baseline weight, being male, and non-Caucasian are potential risk factors for antipsychotic-induced metabolic disturbance
• Clinical decisions to use antipsychotics with fewer metabolic side-effects should consider that clinical improvement is associated with development of these side-effects

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Thank you

- Oliver Howes
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