New Medications in Early Psychosis

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Acknowledgements

   Cambridge Press 2005
   Fivepin Press 2005
3. Dr Anthony Harris (notes and slides)
Summary of talk

- Best evidence treatment of early psychosis
- Possible barriers to treatment
- The newer atypicals
  1. Amisulpride (Solian)
  2. Aripiprazole (Abilify)
Best evidence treatment of early psychosis

- Atypical antipsychotics recommended as first line treatment [rehospitalisation rates over 2 years low for olanzapine (31%) and risperidone (33%) compared with conventional antipsychotics (48%)] Rabinowitz 2001
- Atypicals have less side effects, but still several potentially severe ones (weight gain the most disliked by patients)
Are atypical antipsychotics worth the cost?

Risperidone 4.9 ± 1.9 mg
Haloperidol 11.7 ± 5.0 mg

Csernasky et al, NEJM 364, 16-22.
Barriers to treatment: Becky

- 15 year old girl with learning difficulties
- Six month history of worsening school and social performance
- Three month history of auditory hallucinations
- Chubby with poor motivation to exercise prior to developing psychosis
- Successful treatment of psychotic symptoms with risperidone but increasing trouble with weight
- Develops galactorrhoea
- What are the treatment options?
Barriers to treatment: Nathan

- Seventeen year old young man
- Previously very successful at a selective high school
- Used sport (running, cricket) for mood control and relaxation even when unwell
- Didn’t respond to risperidone
- Olanzapine good for anxiety and psychotic symptoms, found the weight gain impossible to control
1. Amisulpride (Solian)

- Atypical antipsychotic drug recently introduced onto the Australian market
- Available in Europe for > 15 years
- Substitued benzamide class (possibly a dopamine stabiliser and dopamine partial agonist)
- Used for acute and chronic schizophrenia (appears effective for negative symptoms)
How amisulpiride works

• Blocks presynaptic dopamine 2 receptors at low doses
• Blocks post synaptic D2 receptors at higher doses
• Partial agonist at D2 receptors (reduce D output when D concentrations high, increase D output when D concentrations low)
• Blocks D3 receptors (question of clinical effect)
• No apparent action on serotonin receptors (unique amongst the atypicals)
Amisulpride blocks D2/3 receptors
Amisulpride trials
Change in BPRS score of amisulpride/other atypical compared with typical antipsychotics

Change in negative symptom score in acute schizophrenia.

Amisulpride / atypical vs typical antipsychotics

Change in negative symptom scores for amisulpride compared to typical antipsychotics

Difference in negative symptom scores when compared to placebo

Amisulpride / atypicals

Side effects
Overview of side effects

• Overall well tolerated
• CNS – EPS, insomnia, restlessness, anxiety
• Endocrine – increased prolactin causing menstrual problems (amenorrhoea), breast changes (galactorrhoea)
• Theoretical risks for diabetes
• Weight gain (?minimal) and constipation
• Tardive dyskinesia rare
Use of antiparkinsonian medication in comparison to placebo
How to use

• Schizophrenia 400-800mg per day in divided doses
• Negative symptoms only 50-300mg per day
• 50, 100, 200 and 400mg tablet plus 100mg/ml
• Half life approx 12 hours
• Excreted largely unchanged
Costs

- 100mg/ml 60ml bottle ($61 approx)
- 100mg available in boxes of 30 ($26)
- 200mg available in boxes of 60 ($110)
- 400mg available in boxes of 60 ($210)
- Available on the PBS for schizophrenia as authority scripts (script costs $4.60 for concession holders and up to $28.60 for other patients)
Drawbacks

• Dose dependent QT prolongation, worsened with pre-existing conditions
• Accumulates in renal failure (don’t use)
• Dose adjustment not usually necessary with liver failure
• Needs twice daily dosage
• Highly toxic drug in overdose
2. Aripiprazole (Abilify)

- Atypical antipsychotic drug recently introduced onto the Australian market
- Dopamine partial agonist and dopamine stabiliser
- Used for acute and chronic schizophrenia (can be effective for negative symptoms)
- Some evidence for effectiveness as a mood stabiliser and for behavioural disorders in childhood and adolescence
How aripiprazole works

- Partial agonism at D2 receptors (reducing D when levels high, reducing psychotic symptoms)
- Increases D output when levels low (reducing negative symptoms)
- Some action at D3 receptors
- Partial agonism at 5HT1A receptors (probably clinically significant)
- Blockade of Serotonin 2A receptors (decreased motor side effects, improved cognitive and affective symptoms)
- Little or no effect on acetyl choline, histamine or noradrenaline receptors
Abilify acts as a functional antagonist in the presence of dopamine

* Pharmacological activity was measured in CHO cells expressing human D₂ receptors

McQuade
2002
Partial agonism

Abilify acts as a functional agonist in the absence of dopamine

*Pharmacological activity was measured in CHO cells expressing human D2 receptors

Adapted from McQuade 2002
Aripiprazole trials
Long term efficacy: Positive symptoms

Abilify had comparable efficacy to haloperidol in treating positive symptoms in a 52-week trial.

Kujawa 2002
Data from Australian registration package
Abilify resulted in a significant reduction from baseline in the PANSS negative score in a 52-week trial.

Data from a prospective 52-week, double-blind, haloperidol-controlled trial.

Kujawa 2002
Data from Australian registration package

Long term efficacy: Negative symptoms
Side effects
Side effects

- Dizziness
- Insomnia
- Akathisia, activation but not EPSE
- Nausea + vomiting
- Headache / extremity pain
- Sedation
- Not weight gain, prolactin
- Theoretical risk of tardive dyskinesia
How to use

• Usual dosage range 15-30 mg/day
• Lower doses suggested if not acutely psychotic (5-10mg/day)
• Tablets 5, 10, 15, 20 and 10mg
• Can use once daily dose
• Very long half life (longer to reach steady state, longer to wash out)
• Metabolised by CYP450 3A4 and 2D6 (potential for interactions including with fluoxetine, fluvoxamine, paroxetine and carbamazepine)
Costs

- 5mg tab has been approved by TGA but is not in all suppliers yet.
- 10mg available in boxes of 30 ($135)
- 15mg available in boxes of 30 ($200)
- 30mg available in boxes of 30 ($285)
- Both available on the PBS for schizophrenia as authority scripts ($4.60 for concession holders and up to $28.60 for other patients)
Drawbacks

- Potential for akathisia/activation especially in adolescents and the elderly
- Increased death rate in the elderly
- Problems if sedation is required
- Risk of drug interactions

Note:
- No problem with renal or hepatic impairment (probably OK in cardiac impairment)
- Does not appear dangerous in overdose
Comparison of atypical antipsychotics
Comparative effects of second generation antipsychotics

Arch.Gen.Psych
553-564
## Comparison of side effects

<table>
<thead>
<tr>
<th></th>
<th>Risperidone</th>
<th>Olanzapine</th>
<th>Clozapine</th>
<th>Quetiapine</th>
<th>Amisulpiride</th>
<th>Aripiprazole</th>
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<tbody>
<tr>
<td><strong>Wt Gain</strong></td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td><strong>Sedation</strong></td>
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<td>++</td>
<td>+++</td>
<td>+</td>
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<td>0</td>
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<tr>
<td><strong>EPS</strong></td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0 (akathisia)</td>
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<tr>
<td><strong>Antichol.</strong></td>
<td>0</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>↑<strong>Prolactin</strong></td>
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<td>+</td>
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<td>0</td>
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<tr>
<td><strong>Hypotension</strong></td>
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Summary

• Both amisulpride and aripiprazole are effective antipsychotics
• Both can be effective against negative symptoms (possibly due to their actions as partial dopamine agonists)
• The side effects profiles are different but both are generally well tolerated
• Both can be useful second line treatments in early psychosis and other psychotic disorders