Antipsychotics

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August 2017
Scope

- Pharmacological theories of schizophrenia and psychotic disorders
- Pharmacology of antipsychotic treatments
- Treatment strategies for schizophrenia and psychoses
History of antipsychotic drugs

• 1952 - chlorpromazine

• 1950’s-60’s – First Generation Drugs (e.g. haloperidol)
  • all have similar antipsychotic efficacy; differ in terms of potency and side effect profile (movement disorder liability (EPSE), sedation etc)

• Late 1960’s
  • clozapine (atypical antipsychotic)
  • greater antipsychotic efficacy; no EPSE or hyperprolactinemia; agranulocytocysis

• 1970’s - relationship between D2 affinity and average daily dose reported

• 1990’s – Second Generation Drugs
  • newer atypicals - risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, amisulpride
  • antipsychotic efficacy = haloperidol
  • Better tolerated (reduced motor side effects – stiffness, dystonia)
Typical vs Atypical Antipsychotics

• Typical antipsychotic drugs (FGAs)
  • Prolactin elevation and extrapyramidal side effects (EPS) were characteristic side effect (e.g. haloperidol)
  • EPS: parkinsonism, akathisia, dystonia; were thought to be inextricably linked with antipsychotic efficacy

• Atypical antipsychotic drugs (SGAs)
  • clozapine: antipsychotic without associated EPS or increases in serum prolactin; active at low levels of D2 occupancy (<60%)
  • “atypical” term later expanded to include its unique activity in treating treatment-resistant patients
  • newer atypicals (quetiapine, olanzapine, risperidone, ziprasidone, amisulpride) have lower liability to cause EPSE, tardive dyskinesia) – SGAs better terminology
  • they may increase prolactin although less than haloperidol
Partial agonist: Aripiprazole

• Novel MoA
• Complex pharmacology - antagonist/partial agonist effects at D2Rs (effects may be greater with ↑ DA tone)
  • also antagonist at 5HT2a and partial agonist at 5HT1a receptors
  • metabolite (DM-1451) antagonist is a pure D2 antagonist

<table>
<thead>
<tr>
<th>Site</th>
<th>Activity</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presynaptic (autoreceptor)</td>
<td>agonist</td>
<td>↓DA release</td>
</tr>
<tr>
<td>Postsynaptic</td>
<td>antagonist</td>
<td>↓DA signalling</td>
</tr>
</tbody>
</table>

• Common adverse events: nausea and vomiting; akathisia, anxiety, restlessness
• Low liability for EPSE and no prolactin elevation

• Case reports of psychotic relapse after switching from atypicals to aripiprazole
• May be more effective as an AD/augmenting agent than as AP
Key Neurotransmitters in Psychosis

• Dopamine

• Glutamate/glycine
Dopamine Pathways in the Brain

5 DA receptors (D1-D5)

- Substantia nigra (A9) (nigrostriatal pathway)
- Ventral tegmentum (A10) (mesolimbic pathway)
- Tubero-infundibular (PRL release)
Relationship between D2 antagonist potency and dose/concentration

No relationship between D1, D3, D4, D5 binding and dose/concentration
D2 occupancy, antipsychotic efficacy and side effects

- All antipsychotics have some degree of D2 antagonism
  - D2 antagonist potency predicts efficacy, daily dose, and liability for EPSE and hyperprolactinemia
  - D2 occupancy for efficacy: ~65%; >80% for EPSE for first gen drugs
5HT-DA Antagonism Theory (Meltzer)

*Psychopharm Bull 1989, 25:390*

- Typical antipsychotics (○) have lower affinity for 5HT2a receptors than D2 receptors (5HT2a/D2 ratio <1)
- Atypical antipsychotics (●) have higher affinity for 5HT2a receptors than D2 receptors (5HT2a/D2 ratio >1)

Issues:
- Some atypicals (remoxipride) and typicals (loxapine) misclassified by this approach
- Pure 5HT2a blockade is not antipsychotic
Fast-Off D2 Theory (Seeman)

*Am J Psych 2001, 158:360*

-Typical antipsychotics (○) bind more tightly to, and dissociate more slowly from, D2 receptors in their high affinity state (dissociation constants (Kd) < natural ligand, DA)

-Atypical antipsychotics (○) bind more loosely to, and dissociate more rapidly from D2 receptors (Kd > DA)
  - *may allow greater responsiveness to changes in endogenous phasic DA signalling*
Speed of dissociation of antipsychotic drugs from cloned human D2 receptors

Clozapine is a fast-off-D2 antipsychotic

Traditional antipsychotics slowly dissociate from D2

- Quetiapine
- Clozapine
- Remoxipride
- Amisulpride

Olanzapine

- Haloperidol
- Raclopride
- Chlorpromazine

Minutes for 50% release from cloned D2

Influence of speed of D2 dissociation with time course of D2 occupancy for various antipsychotic drugs

One potential impact of faster dissociation - lower risk of tardive dyskinesia with 2nd Gen APs

TD rates ~2 fold higher with FGAs compared with SGAs
Lowest with clozapine
Schizophrenia and Dopamine – what is the connection?

- Pathophysiology:
  - Cocaine/amphetamine can produce psychotic symptoms
  - Patients have increased DA release relative to controls (no differences in brain DA concs, DA receptor density, etc.)

Laruelle M, Biol Psych 1999
Glutamate dysfunction and SCZ

• N-methyl-D-aspartate (NMDA) glutamate receptors
  – Observation: anti-NMDA antibodies and antagonists (PCP; ketamine) produce schizophrenia-like psychotic symptoms in healthy volunteers; precipitate acute relapse in schizophrenic patients
  – Theory: glutamate hypofunction in schizophrenia leads to dysregulation of other systems (DA, others) associated with generation of psychotic symptoms
So then, why do effective antipsychotics block dopamine D2 receptors?

- NMDA hypofunction may contribute to increased midbrain (mesolimbic) DA activity
  - May reduce thalamic “filtering” of input to cortex
- D2 blockade helps normalize this process

- Note: Primary abnormality is NOT in DA system
A. NMDA Receptor Regulation of Mesolimbic Dopamine Pathway: Tonic Inhibition

B. NMDA Receptor Hypofunction in Cortico Brainstream Projections: Hyperactivity of Mesolimbic Dopamine Pathway

Stahl CNS Spectrums 2007
Pharmacological Profiles and Side Effects (2)

• Other pharmacology
  • antagonism of multiple non-DA receptors
  • accounts for side effect profiles
    • $\alpha_1$ antagonism - postural hypotension, dizziness
    • M1 antagonism - dry mouth, constipation, blurred vision
    • H1 antagonism - sedation, weight gain
Table 2. Binding Affinity of Selected Antipsychotics for Specific Neuroreceptors\textsuperscript{a,b}

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>$D_2$</th>
<th>$5-HT_{1A}$</th>
<th>$5-HT_{2A}$</th>
<th>$5-HT_{2C}$</th>
<th>$\alpha_1$</th>
<th>$H_1$</th>
<th>$M_1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>0.34\textsuperscript{c}</td>
<td>1.7\textsuperscript{c}</td>
<td>3.4\textsuperscript{c}</td>
<td>15</td>
<td>57</td>
<td>61\textsuperscript{c}</td>
<td>&gt; 1000</td>
</tr>
<tr>
<td>Clozapine</td>
<td>126</td>
<td>875</td>
<td>16</td>
<td>16</td>
<td>7</td>
<td>6</td>
<td>1.9</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>0.7</td>
<td>1100</td>
<td>45</td>
<td>&gt; 10,000</td>
<td>6</td>
<td>440</td>
<td>&gt; 1500</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>11</td>
<td>&gt; 10,000</td>
<td>4</td>
<td>23</td>
<td>19</td>
<td>7</td>
<td>1.9</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>160</td>
<td>2800</td>
<td>295</td>
<td>1500</td>
<td>7</td>
<td>11</td>
<td>120</td>
</tr>
<tr>
<td>Risperidone</td>
<td>4</td>
<td>210</td>
<td>0.5</td>
<td>25</td>
<td>0.7</td>
<td>20</td>
<td>&gt; 10,000</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>5</td>
<td>3</td>
<td>0.4</td>
<td>1</td>
<td>11</td>
<td>50</td>
<td>&gt; 1000</td>
</tr>
</tbody>
</table>

\textsuperscript{a}From Preskorn,\textsuperscript{14} with permission, based on Richelson,\textsuperscript{17} Abilify package insert,\textsuperscript{18} Arnt and Skarsfeldt,\textsuperscript{19} Bymaster et al.,\textsuperscript{20} and Seeger et al.\textsuperscript{21}

\textsuperscript{b}Data represented as $K_i$ (nM).

\textsuperscript{c}Data with cloned human receptors.

Abbreviations: $5-HT =$ serotonin, $\alpha_1 =$ alpha-1 norepinephrine, $D =$ dopamine, $H_1 =$ histamine 1, $M_1 =$ muscarinic acetylcholine-1.

Smaller numbers = higher affinity
Treatment of schizophrenia

- Emergency management
- The first few weeks/choice of antipsychotic
- Side effects
- Longer term use and switching
- Early lack of response
- Maintenance
- Managing relapse
Emergency Management

• Aggressive, agitated patients
  • Reassurance; reduce stimulation; provide structure
  • Try to diagnose initially
    • Note: you may need to medicate acutely psychotic and aggressive patients before diagnostic workup.

• If IM drug treatment needed:
  • Haloperidol 2-5mg plus lorazepam 2mg
  • Olanzapine (10mg IM; can repeat hourly)
  • Droperidol 5-10mg IM
  • Lorazepam alone IM (1-3mg/hr)

• Diagnostic and medical workup ASAP afterwards
The first few weeks of treatment

• Initial Choice of Drug:
  • Use atypical compounds over (e.g.) haloperidol
    • (+)fewer EPSE; (+)improved patient acceptance due to better tolerability;
  • No proven differences in speed of response with any compounds
  • Titrate dose based on response/side effects
  • Most patients will respond to initial treatment
    • Olanzapine 10-30mg/day
    • Amisulpride 800-1200mg/day
    • Risperidone 3-6mg/day
      • (higher doses not more effective)
SGAs are not created the same - relative efficacy of SGAs vs selected FGAs (Leucht; Lancet 2013)

Figure 3: Forest plot for efficacy of antipsychotics drugs compared with placebo
Treatments are ranked according to their surface under the cumulative ranking (SUCRA) values (appendix p 98).
SMD=standardised mean difference. Crl=credible interval.

Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis
Stefan Leucht, Andrea Cipriani, Loukia Spinell, Dimitris Mourids, Demis Ogy, Franziska Richter, Myto Samara, Corrado Barbui, Rolf R. Engel, John R. Geddes, Werner Risling, Marko Paul Hopf, Bettine Lassig, Georgios Solant, John M. Davis
In the meta-analysis by Leucht et al. (Lancet 2013), the effect of discontinuation and weight gain for various antipsychotic drugs was compared. The results indicate a higher risk of discontinuation and weight gain with active drug treatment compared to placebo. The drugs are ranked based on their effectiveness and tolerability, with some showing a higher risk of discontinuation and others a higher risk of weight gain.

**A. All-cause discontinuation OR (95% Crl)**
- Amisulpride 0.43 (0.32 to 0.57)
- Olanzapine 0.46 (0.41 to 0.52)
- Clozapine 0.46 (0.32 to 0.65)
- Paliperidone 0.48 (0.39 to 0.58)
- Risperidone 0.53 (0.46 to 0.60)
- Aripiprazole 0.61 (0.51 to 0.72)
- Quetiapine 0.61 (0.52 to 0.71)
- Chlorpromazine 0.65 (0.5 to 0.84)
- Zotepine 0.69 (0.41 to 1.07)
- Asenapine 0.69 (0.54 to 0.86)
- Iloperidone 0.69 (0.56 to 0.84)
- Ziprasidone 0.72 (0.59 to 0.86)
- Lurasidone 0.77 (0.61 to 0.96)
- Sertindole 0.78 (0.61 to 0.98)
- Haloperidol 0.8 (0.71 to 0.90)

**B. Weight gain SMD (95% Crl)**
- Haloperidol 0.09 (-0.00 to 0.17)
- Ziprasidone 0.10 (-0.02 to 0.22)
- Lurasidone 0.10 (-0.02 to 0.21)
- Aripiprazole 0.17 (0.05 to 0.28)
- Asenapine 0.20 (0.05 to 0.35)
- Quetiapine 0.23 (0.07 to 0.39)
- Paliperidone 0.38 (0.27 to 0.48)
- Risperidone 0.42 (0.33 to 0.50)
- Sertindole 0.43 (0.34 to 0.53)
- Chlorpromazine 0.55 (0.34 to 0.76)
- Iloperidone 0.62 (0.49 to 0.74)
- Clozapine 0.65 (0.31 to 0.99)
- Zotepine 0.71 (0.47 to 0.96)
- Olanzapine 0.74 (0.67 to 0.81)

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Leucht; Lancet 2013

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Drug Treatment

• Antipsychotics should be given for 1-2 year after first psychotic episode
• 1y ~70% relapse if untreated
• >50% of patients may require long term Rx
• Issues – poor compliance/insight
• Mental Health Act
to support compliance
APs vs placebo for relapse in schizophrenia

Leucht; Lancet 2012
Longer term use and switching...CATIE study
Clinical Antipsychotic Trials of Intervention Effectiveness; NEJM 2005, 353:1209

• Prospective randomized **blinded** comparison of up to 18 months Rx with olanzapine, risperidone, quetiapine, ziprasidone and perphenazine in schizophrenia. NIMH funded.

• Outcome measures:
  - % discontinuing treatment
  - Time to discontinuation
  - Reasons for discontinuation (inefficacy, tolerability issues)
  - Psychopathology measures (PANSS and CGI)

• Population:
  - Well matched for demographics, illness characteristics across groups

<table>
<thead>
<tr>
<th></th>
<th>Olanzapine</th>
<th>Quetiapine</th>
<th>Risperidone</th>
<th>Perphenazine</th>
<th>Ziprasidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>336</td>
<td>337</td>
<td>341</td>
<td>261</td>
<td>185</td>
</tr>
<tr>
<td>Mean modal dose (mg)</td>
<td>20.1</td>
<td>543.4</td>
<td>3.9</td>
<td>20.8</td>
<td>112.8</td>
</tr>
</tbody>
</table>
**CATIE study (2)**

- No differences in SAEs, suicides/attempts, EPSE, akathisia across groups
- Significant advantage for olanzapine in rate of response on PANSS, CGI

<table>
<thead>
<tr>
<th></th>
<th>Olanzapine</th>
<th>Quetiapine</th>
<th>Risperidone</th>
<th>Perphenazine</th>
<th>Ziprasidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>% discontinued</td>
<td>64</td>
<td>82</td>
<td>74</td>
<td>75</td>
<td>79</td>
</tr>
<tr>
<td>Median (95% CI) time to discontinuation (months)</td>
<td>9.2 (6.9-12.1)</td>
<td>4.6 (3.9-5.5)</td>
<td>4.8 (4.0-6.1)</td>
<td>5.6 (4.5-6.3)</td>
<td>3.5 (3.1-5.4)</td>
</tr>
<tr>
<td>D/C – lack of efficacy (%)</td>
<td>15</td>
<td>28</td>
<td>27</td>
<td>25</td>
<td>24</td>
</tr>
<tr>
<td>D/C – intolerability (%)</td>
<td>19</td>
<td>15</td>
<td>10</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>D/C – pt’s decision (%)</td>
<td>24</td>
<td>33</td>
<td>30</td>
<td>30</td>
<td>34</td>
</tr>
<tr>
<td>Risk of rehospitalization</td>
<td>0.29</td>
<td>0.66</td>
<td>0.45</td>
<td>0.51</td>
<td>0.57</td>
</tr>
<tr>
<td>Weight gain (lbs)</td>
<td>9.4</td>
<td>1.1</td>
<td>0.8</td>
<td>-2.0</td>
<td>-1.6</td>
</tr>
<tr>
<td>Weight gain/mo. Rx (lb/mo)</td>
<td>2.0</td>
<td>0.5</td>
<td>0.4</td>
<td>-0.2</td>
<td>-0.3</td>
</tr>
<tr>
<td>Δ Cholesterol (mg/dL)</td>
<td>9.7</td>
<td>5.3</td>
<td>-2.1</td>
<td>0.5</td>
<td>-9.2</td>
</tr>
<tr>
<td>Δ Prolactin (ng/dL)</td>
<td>-6.1</td>
<td>-9.3</td>
<td>15.4</td>
<td>0.4</td>
<td>-4.5</td>
</tr>
</tbody>
</table>
CATIE study (3)

• Most (74%) patients discontinue their antipsychotic medication within 18 months

• Olanzapine was most effective drug overall on multiple measures
  • Discontinuation rate and time to discontinuation
  • Rate of rehospitalization
  • Better initial symptomatic improvement (PANSS, CGI)

• Perphenazine was clinically no different from other atypicals

• Olanzapine had worst tolerability profile, mainly relating to metabolic consequences
Oral vs Depot Medications

- Depots given 2-4 weekly by community nurse
- Lower risk of relapse
  - Regular appointments
  - Verified dosing/improved compliance

Paliperidone oral vs depot PK profile - Medsafe datasheet
Rehospitalization in first episode SCZ – orals vs depots

Tiihonen, AJP 2012
Use of clozapine

• Risk/benefit assessment suggests it should only be used where there is demonstrated treatment resistance

• Register with Novartis. Get baseline WCC; repeat weekly for first 18 weeks, monthly thereafter. Use DHB protocol (MIDAS)

• Titrate dose from 12.5mg/day up to 300mg/day over 2-3 weeks; final dose based on blood levels

• Very low/no EPSE, TD

• Side effects: neutropenia (3%); agranulocytosis (1%); seizures (5% @>600mg/day); weight gain; hypersalivation; tachycardia; orthostatic hypotension; cardiomyopathy; potentially fatal constipation
Special Subgroups

• **Psychosis in Parkinson’s Disease**
  • conventional antipsychotics worsen PD symptoms
  • try to reduce DA agonist dose
  • Low dose clozapine

• **Psychosis in Alzheimer’s disease**
  • patients may be extremely sensitive to anticholinergic/antihistaminic side effects
  • age-associated pharmacokinetic changes - lower doses
  • **Mortality increased by both FGAs and SGAs (Mechanism)**
  • Low dose QUET/OLZ (antihistaminic)

• **Psychosis in HIV+ patients**
  • extremely sensitive to drug effects; v low doses (<100mg CPZ/day)

• **Dementia with Lewy Bodies**
  • extremely sensitive to antipsychotic s/e; ChEI (rivastigmine) may be better choice;
  • very low dose clozapine

• **Pregnancy in schizophrenic patients**
  • slight ↑ risk of foetal abnormalities
  • balance need to treat vs potential for foetal abnormalities