Psychopharmacology of schizophrenia and other psychotic disorders

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Scope

• Pharmacological theories of schizophrenia and psychotic disorders
• Pharmacology of antipsychotic treatments
• Treatment strategies for schizophrenia and psychoses
Psychosis

- Syndrome (mixture of symptoms) that may occur in many different disorders
  - delusions, hallucinations, distorted reality testing, abnormal speech and behavior, motor disturbances
  - paranoid, excited/disorganised or depressive
- Defining feature of schizophrenia, schizoaffective disorder, drug-induced psychotic disorder, etc
- May occur in mania, depression, dementias (Alzheimer’s; Parkinson’s)

- All treatments based on efficacy in schizophrenic patients, but also effective in psychotic symptoms in other disorders
  - may not be approved by Medsafe for these indications
Key Neurotransmitters in Psychosis

- Dopamine
- Glutamate/glycine
Dopamine Pathways in the Brain

- Substantia nigra (A9) (nigrostriatal pathway)
- Caudate/Putamen (Striatum)
- Cingulate cortex
- Frontal cortex
- Nucleus Accumbens
- Olfactory Tubercle
- Amygdala
- Hypothalamus (tuberoinfundibular pathway)
- Ventral tegmentum (A10) (mesolimbic pathway)
Schizophrenia and Dopamine

- **Symptoms:** delusions; hallucinations; disturbances of thought; bizarre behavior; personality change; apathy; withdrawal; etc; episodic or progressive patterns

- **Rates:** peak onset in late teens-early 30’s; ~ 1% lifetime prevalence

- **Pathophysiology:**
  - mesolimbic dopaminergic dysfunction/overactivity (hypothesized)
  - cocaine/amphetamine produce psychotic symptoms
  - Psychotogenic effects at lower doses than controls
  - increased DA release relative to controls (no differences in brain DA concs, DA receptor density, etc.)

- **Treatment:**
  - All effective drugs are dopamine D2 antagonists (+ other pharmacological effects); potency correlates with daily dose

- **Side effects:**
  - Tremor, stiffness; restlessness; akathisia

Laruelle M, Biol Psych 1999
Parkinson’s Disease and Dopamine

- **Symptoms:**
  - tremor; rigidity/stiffness; slowing of movements; hypokinesia; postural changes;

- **Rates**
  - onset in 50’s; highest in elderly; protracted course with high disability/morbidity

- **Pathophysiology:**
  - loss of nigrostriatal dopaminergic neurons
    - MPTP (DA neurotoxin) produces PD

- **Treatment:**
  - Increase synaptic dopamine concentrations
    - (L-DOPA; DA agonists; inhibitors of MAO-B and COMT)
    - gradual loss of efficacy over time

- **Side effects of treatment:**
  - Dyskinesia; psychosis; hyperprolactinemia/galactorrhea
Dopaminergic Effects/Side Effects

- **Drugs that increase DA neurotransmission** (↑ synaptic DA)
  - **most are effective symptomatic treatments for PD**
  - **may precipitate/worsen psychosis/dyskinesia**
  - **potentially addictive**
  - **other s/e: nausea, GI symptoms**
    - Postsynaptic agonists (*DA from L-DOPA; bromocriptine, pramipexole*)
    - Inhibitors of enzymes which degrade DA (MAOIs (selective MAO-B-I: *deprenyl*); COMT inhibitors (*entocapone*)
    - Inhibitors of DA reuptake or inducers of DA release (*cocaine, d-amphetamine* - not yet shown to help PD)

- **Block DA neurotransmission** (postsynaptic antagonism)
  - **worsen PD; may induce reversible Parkinsonian sx**
  - **improve psychotic symptoms**
  - **antiemetic, prokinetic**
    - Typical neuroleptics - D2 antagonists (*haloperidol* etc plus newer agents)
    - Atypical neuroleptics (D2 antagonism + ?: *clozapine*)
Several genes associated with schizophrenia may affect glutamate receptors

Dysbindin, DISC-1, neuregulin

- These proteins help to promote long term potentiation and improve efficiency of neurotransmission
- Underactivity of these genes could lead to elimination of “weak” glutamate synapses during brain maturation
- DISC-1 also affects transport of synaptic vesicles into presynaptic terminals
- Dysbindin also affects activity of vesicular transporter for Glu

D-amino acid oxidase activator (DAOA)

- Alters activity of enzyme that metabolizes D-serine (endogenous ligand)

RSG4 (regulator of G-protein signaling 4)

- Affects mGluR signalling via G-proteins

Figure 2. Schizophrenia — disorder at synapses.
Schematic diagram of putative mechanisms of susceptibility gene products (shown in red) at glutamate and dopaminergic synapses in schizophrenia. Terminals of glutamate (Glu) and dopamine (DA) neurons are shown synapsing at a dendritic spine. Neuregulin1 activates the ErbB receptor, leading to internal sequestration of NMDA receptors (not shown). Dysbindin (Dys) is involved in pre-synaptic glutamate release, whilst D-amino acid oxidase activator (DAOA) regulates the metabolism of serine, an essential coagonist of NMDA receptors. Catechoh-O-methyltransferase (COMT) inactivates dopamine in the pre-frontal cortex. (D1/D5: dopamine receptors; Gs: G protein; AC: adenylyl cyclase; PKA: protein kinase A; CREB: cAMP response element binding protein; AMPA: AMPA glutamate receptor; NMDA: NMDA glutamate receptor).
Glutamate theory

• N-methyl-D-aspartate (NMDA) glutamate receptors
  – **Observation:** antagonists (PCP; ketamine) produce schizophrenia-like psychotic symptoms in healthy volunteers (adults but not children); precipitate acute relapse in schizophrenic patients
  – **Theory:** glutamatergic hypofunction in schizophrenia leads to dysregulation of other systems (DA, others)
  – **Treatment trials:**
    • direct agonist: glutamate - neurotoxic; not possible to administer
    • indirect/modulatory agonists: glycine (full agonist); D-cycloserine (partial agonist)
    • D-cycloserine in combination with typical antipsychotics improves negative and cognitive symptoms (no change in positive symptoms)
    • D-cycloserine plus clozapine (atypical) - worsening of negative symptoms
History of antipsychotic drugs

- 1952 - Laborit/Delay and Deniker: chlorpromazine
- 1950’s-60’s
  - haloperidol, thioridazine, fluphenazine, thiothixine, many others
  - all have similar antipsychotic efficacy; differ in terms of potency and side effect profile (EPSE liability, sedation; increased prolactin etc)
- 1960’s
  - clozapine (atypical antipsychotic)
  - greater antipsychotic efficacy; no EPSE or hyperprolactinemia; agranulocytocysis
  - 1988: positive Kane study in treatment-resistant schizophrenia
- 1970’s - relationship between D2 affinity and average daily dose reported
- 1990’s
  - newer atypicals - risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole
  - antipsychotic efficacy = haloperidol
  - EPSE/prolactin increase < haloperidol
  - ? selective targeting of A10 (VTA) vs A9 (SN) DA neurons
Typical vs Atypical Antipsychotics

- **Typical antipsychotic drugs**
  - 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**
  - 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,
  - they do increase prolactin although less than haloperidol
Pharmacological Profiles and Side Effects (1)

- 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: 60-70%; >80% for EPSE
Relationship between D2 antagonist potency and average daily dose
Pharmacological Profiles and Side Effects (2)

- **Other pharmacology**
  - antagonism of multiple non-DA receptors
  - accounts for key side effect profile
    - \(\alpha_1\) antagonism - postural hypotension, dizziness
    - M1 antagonism - dry mouth, constipation, blurred vision
    - H1 antagonism - sedation, weight gain

- **Theories of pharmacology of atypicals**
  - ratio of 5HT2:D2 antagonism (>1) may reduce EPSE liability, reduce prolactin secretion
  - low affinity and fast dissociation of drug from D2 receptor may predict atypicality
Table 2. Binding Affinity of Selected Antipsychotics for Specific Neureceptors<sup>a,b</sup>

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>D&lt;sub&gt;2&lt;/sub&gt;</th>
<th>5-HT&lt;sub&gt;1A&lt;/sub&gt;</th>
<th>5-HT&lt;sub&gt;2A&lt;/sub&gt;</th>
<th>5-HT&lt;sub&gt;2C&lt;/sub&gt;</th>
<th>α&lt;sub&gt;1&lt;/sub&gt;</th>
<th>H&lt;sub&gt;1&lt;/sub&gt;</th>
<th>M&lt;sub&gt;1&lt;/sub&gt;</th>
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</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>0.34&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.7&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3.4&lt;sup&gt;c&lt;/sup&gt;</td>
<td>15</td>
<td>57</td>
<td>61&lt;sup&gt;c&lt;/sup&gt;</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>
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<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>
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<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>25</td>
<td>1</td>
<td>11</td>
<td>50</td>
</tr>
</tbody>
</table>

<sup>a</sup> From Preskorn,<sup>14</sup> with permission, based on Richelson,<sup>17</sup> Abilify package insert,<sup>18</sup> Arnt and Skarsfeldt,<sup>19</sup> Bymaster et al.,<sup>20</sup> and Seeger et al.<sup>21</sup>

<sup>b</sup>Data represented as K<sub>i</sub> (nM).

<sup>c</sup>Data with cloned human receptors.

Abbreviations: 5-HT = serotonin, α<sub>1</sub> = alpha-1 norepinephrine, D = dopamine, H<sub>1</sub> = histamine 1, M<sub>1</sub> = muscarinic acetylcholine-1.
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*
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

- Recent 4wk trial shows efficacy of 15-30mg/day = haloperidol 10mg/day; main unique adverse events: nausea and vomiting; low liability for EPSE and no prolactin elevation (J Clin Psych 2002, 63:763-771)
- Case reports of psychotic relapse after switching from atypicals to aripiprazole
- Other late stage partial agonist: bifeprunox (D2 and 5HT1a partial agonist)
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 medicate acutely psychotic and aggressive patient before diagnostic workup.
  – If IM drug treatment needed:
    • Haloperidol 2-5mg plus lorazepam 2mg
    • Olanzapine (10mg IM; can repeat hourly)
    • Ziprasidone 10-20mg IM; 40mg/24h
    • Lorazepam alone IM (1-3mg/hr)
  – Diagnostic and medical workup ASAP afterwards
The first few weeks of treatment

• Issues
  – choice of initial drug - typical vs atypical
  – balance speed of response with side-effect liability

• Initial 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 pooled FGAs.
Management of Side Effects - General

- Important: helps maximise chances that patients will comply with treatment
  - poor tolerability is a leading cause for treatment failure due to non-compliance
- Is dose appropriate for patient?
  - lower doses may be needed by elderly, patients with reduced renal/hepatic function, etc.
  - ? Overexposure due to slower metabolism (genetic - CYP2D6 poor metabolizer; patients co-administered inhibitors of CYP2D6 or -3A4)
- Consider:
  - is an intervention needed?
  - temporary/permanent dose reduction
  - slower titration to final dose
  - switch to alternative class
  - use of additional medication to treat side effects
## Management of Specific Side Effects

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Symptom</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DA blockade</strong></td>
<td>Parkinsonism; akathisia; dystonia</td>
<td>Anticholinergic (biperiden, trihexyphenidyl, procyclidine, benztropine, etc; IV or IM for dystonia); propranolol for akathisia; decrease dose of neuroleptic</td>
</tr>
<tr>
<td></td>
<td>Tardive dyskinesia</td>
<td>Prevention (2\textsuperscript{nd} Gen have lower incidence); dose reduce or discontinue antipsychotic; ?clozapine and ?other atypicals</td>
</tr>
<tr>
<td></td>
<td>Neuroleptic Malignant Syndrome</td>
<td>Emergency; stop neuroleptic; BDZs; supportive Rx; ? dantrolene</td>
</tr>
<tr>
<td><strong>α1-antagonism</strong></td>
<td>Dizziness/ hypotension</td>
<td>Dose reduce; change to amisulpride/quetiapine/ziprasidone</td>
</tr>
<tr>
<td><strong>Histamine antagonism</strong></td>
<td>Weight gain</td>
<td>Diet; change drug to amisulpride/ziprasidone/aripiprazole</td>
</tr>
<tr>
<td></td>
<td>Sedation</td>
<td>Dose reduce; change to amisulpride/risperidone</td>
</tr>
<tr>
<td><strong>Acetylcholine antagonism</strong></td>
<td>Blurred vision</td>
<td>Dose reduce; change to risperidone/ziprasidone/AMI/ARI</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>Stool softener; fibre+</td>
</tr>
<tr>
<td></td>
<td>Dry mouth</td>
<td>Sugarless gum</td>
</tr>
</tbody>
</table>
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</td>
<td>9.2</td>
<td>4.6</td>
<td>4.8</td>
<td>5.6</td>
<td>3.5</td>
</tr>
<tr>
<td>discontinuation (months)</td>
<td>(6.9-12.1)</td>
<td>(3.9-5.5)</td>
<td>(4.0-6.1)</td>
<td>(4.5-6.3)</td>
<td>(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
Early lack of response

- **Poor response early in therapy:**
  - Is diagnosis correct (drug dependence/withdrawal/medical illness/etc)?
  - Is treatment duration too short?
  - Is there toxicity from Rx regimen (side effects; drug interactions etc)?
  - Is antipsychotic dose adequate?
  - Is the patient taking his/her meds?
  - Is the patient taking something else (cannabis/Kronic/P/.....)

- **Possibilities:**
  - p.r.n. benzodiazepine for acute agitation/disturbance
  - Review ward milieu/circumstances
  - Review antipsychotic dose (NB: excessive dosing may increase toxicity and do little for psychotic symptoms)
  - Consider changing antipsychotic
  - Consider adding valproate
  - Consider adding lithium
  - Consider ECT
Maintenance treatment (1)

- First episode Rx for 1-2 years; ≥2 episodes Rx for 5 years (and longer)
- ~75% of patients will relapse within 18 months of stopping antipsychotic therapy

- Low vs regular dose maintenance
  - higher relapse rates with lower depot fluphenazine doses (biweekly IM)
  - some benefit in terms of better tolerability

![Graph showing rate of relapse](chart.png)
• Continuous or Intermittent Rx
  – is intermittent Rx (at first sign of prodromal symptoms) effective?
  – relapse rates over 12 months:

<table>
<thead>
<tr>
<th>Study</th>
<th>Intermittent Rx</th>
<th>Continuous Rx</th>
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<tbody>
<tr>
<td>Schooler 1997</td>
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<td>Pietzcker 1993</td>
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<td>Jolley 1989-90</td>
<td></td>
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<td>Herz 1991</td>
<td></td>
<td></td>
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<tr>
<td>Carpenter 1990</td>
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</table>

Rate of relapse (%)
Managing relapse (1)

• Check compliance and aggravating factors
  – (low motivation/high stress/intolerable side effects/lack of social support to take meds)
  – assess need for psychosocial intervention
• If compliant (i.e. breakthrough symptoms while on Rx), consider changing to alternative antipsychotic
  – higher doses of old drug usually don’t work and have high s/e rates
  – crossover (switch) approach to avoid withdrawal relapse
  – base choice of new drug on prior treatments
  – <2 trials of older/newer drugs - try non-clozapine alternative
  – 2 or more trials - try clozapine
Managing Relapse (2)

• If relapse due to planned dose reduction/discontinuation
  – restart patient on original dose regimen

• If noncompliant/uncooperative/no insight, consider depot antipsychotic
  – once stabilised, determine IM depot dose by (10-15 x oral daily dose)
  – give once monthly IM
Use of clozapine

- Risk/benefit assessment suggests it should only be used where there is demonstrated treatment resistance;
- Register with Caremark. Get baseline WCC; repeat weekly for first 6 months, monthly thereafter;
- Titrate dose from 12.5mg/day up to 300mg/day over 1-2 weeks;
- Caution with concomitant BDZs (risk of respiratory depression);
- 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
  - 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 fetal abnormalities
  - balance need to treat vs potential for fetal abnormalities