Pharmacological treatment of Schizophrenia

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Prevention Early Intervention and Recovery Service
schizophrenia - symptoms

- delusions and hallucinations
  - dopaminergic hyperfunction
- disorganisation
- negative symptoms
  - dopaminergic hypofunction
- cognitive
- mood and anxiety
vulnerability - stress model

- multifactorial
- stress is the prime trigger
- vulnerability an expression of genetic and environmental factors
- vulnerability dynamic
# Biopsychosocial Model of the Aetiology of Schizophrenia

<table>
<thead>
<tr>
<th>Category</th>
<th>Predisposing</th>
<th>Precipitating</th>
<th>Perpetuating</th>
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<tbody>
<tr>
<td><strong>Bio</strong></td>
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<td>head injury</td>
<td>compliance</td>
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<td></td>
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<td>EE life events</td>
<td>EE hopelessness</td>
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<td>coping style</td>
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<td>poverty</td>
<td>social network</td>
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</tr>
<tr>
<td></td>
<td>gender</td>
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<td>family</td>
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</table>
illness course

- Prodrome - mixed symptomatology often with marked mood symptoms
- acute episode followed by “critical period” during which level of long term functioning is determined
- stable phase - treatment resistance
- rule of thirds
biological treatments

- Medication
  - oral/depot
  - typical/atypical
  - adherence

- ECT

- Biological effects of psychosocial treatments
biological basis of disorder

• interaction of dopaminergic pathways from basal ganglia to the cortex effects:-
  – sensory load of system (thalamus)
  – mesolimbic

• reduced activity in frontal lobe may cause negative symptoms
  – Decrease in reward dependent behaviour
  – Decrease in experience of pleasure
dopamine hypothesis

• Excess of dopaminergic activity in the mesolimbic pathways leads to hallucinations and delusions
• Deficit of dopaminergic activity in the mesocortical pathways leads to negative symptoms
• Supported by:
  – relationship of D₂ blockade to antipsychotic effect - 60 - 70% receptor blockade required for effect on PET
  – dopamine agonists cause psychotic symptoms
Dopamine pathways

[Diagram of brain regions including striatum, cingulate gyrus, frontal cortex, substantia nigra, nucleus accumbens, pituitary, hypothalamus, hippocampus, and ventral tegmental area]
inadequacies of DA hypothesis

• poor response of negative symptoms
  – does this reflect dopamine dysfunction?
• other pharmacological models of acute symptoms ie PCP/NMDA - glutaminergic
• time of response - limited to receptor activity not 2º/3º messenger systems
• PET studies - DA blockade varies for same clinical effect.
Interaction of serotonin and dopamine

• Serotonin inhibits dopamine release via 5HT$_{2A}$ postsynaptic receptors. *Atypical antipsychotics* as a class act as 5HT$_{2A}$ antagonists and reverse in a selective way dopaminergic blockade

• Differential cumulative effect for each dopaminergic pathway
baseline screen

• no generally accepted screen
• symptoms
• psychosocial functioning
• movement disorder screen
• investigations
  – FBC, EUC, LFT, ANA
  – ECG (varies with medication, age)
  – Neuroimaging (CT, MRI)
pharmacological treatments

- Typical antipsychotics (oral or depot)
  - none of proven greater efficacy
  - 300 - 500 chlorpromazine equivalents required
  - 80% respond but
    - commonly left with residuum
    - significant side effects
      - movement disorder EPSE, akathisia, tardive dyskinesia
      - sedation
      - anticholinergic
pharmacological treatments

• Atypical antipsychotics
  – growing number
  – different receptor profiles
  – fewer EPSE
  – less tardive dyskinesia - clozapine & risperidone
  – positive effects on cognitive symptoms
  – only clozapine better on DBPCT
Time course of action

- "calming" effect depends upon route of administration
  - sedating vs other antipsychotics
  - use of benzodiazepines
- "antipsychotic" effect has onset over 1-6 weeks
- with clozapine continued improvements are demonstrable over 12-18 months
Response

• 10-20% don’t show much benefit
• 25% remit without medication
• 4 - 6.5% not discharged after index admission
• improvement over 20th century in outcome with introduction of biological treatments
  – toxic hypothesis of psychosis
  – EI programs aim to reduce time to treatment
how long to treat?

- Target hallucinations/delusions and disorganisation.
- Recovery is multimodal.
- For first episode - minimum 1 year after resolution of symptoms. May need 2 years.
- For > 1 episode. 5 years after resolution of symptoms with tapering dose.
General principles

• Use one antipsychotic at a time.
• Increase dose slowly, minimise side effects
• Reasonable trial ie 4 weeks at maximal dose
• If treatment fails consider other factors
  – compliance
  – Substance abuse
  – depression
• Trial of clozapine
# oral antipsychotics

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand Names</th>
<th>Sedation</th>
<th>EPSE</th>
<th>Chol</th>
<th>CPZ</th>
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<tr>
<td>Chlorpromazine</td>
<td>LARGACTIL</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
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<td>Thioridazine</td>
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<tr>
<td>Trifluoperazine</td>
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<td>+++</td>
<td>+</td>
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<td>Haloperidol</td>
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<td>+++</td>
<td>+</td>
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<tr>
<td>Pimozide</td>
<td>ORAP</td>
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<tr>
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<td>NAVANE</td>
<td>++</td>
<td>++</td>
<td>++</td>
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<tr>
<td>Risperidone</td>
<td>RISPERDAL</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>1.5</td>
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<tr>
<td>Olanzapine</td>
<td>ZYPREXA</td>
<td>+++?</td>
<td>-</td>
<td>++</td>
<td>3-5</td>
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<tr>
<td>Quetiapine</td>
<td>SEROQUEL</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>?</td>
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<tr>
<td>Clozapine</td>
<td>CLOZARIL</td>
<td>+++</td>
<td>-</td>
<td>XXX</td>
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risperidone

- high affinity 5HT$_{2A}$, 5HT$_7$ and D$_2$
  - antipsychotic effect
  - lower EPSE
  - increased prolactin - breast enlargement/ galactorrhoea and menstrual problems

- alpha$_{1-2}$
  - wt gain (less of a problem than with other atypical antipsychotics)
  - lowered blood pressure and impotence
risperidone

• dose 1-6 mg.
• $t_{1/2} = 3-17$ hrs
• Metabolised P450 2D6 with an active metabolite. Possible interactions with TCAs, SSRIs, phenothiazines, beta-blockers, quinidine
• start 0.5mg and increase
• care with orthostatic effects
• Long acting injection not released in Australia
• Recently shown to be more effective than typical antipsychotic over 1 yr treatment course
olanzapine

- thiobenzodiazepine
- Structurally similar to clozapine. Binding to $D_{2,3,4,1}$; $5HT_{2A,2C,3,6}$; $M$; $H_1$; $\alpha_1$
- alpha - wt gain and sedation
- possible beneficial effect on negative symptoms and depression
olanzapine

- dose range 2.5 - 30 mg
- tendency towards higher range of dose
- $t_{1/2} = 32$ hrs, may be affected by smoking
- Metabolised P450 CYP1A2 & CYP2D6. No active metabolites
- little effect for renal/hepatic impairment
- No clinically significant interactions
quetiapine

- Binding to $D_2$; $5HT_{2A, 6, 7}$; $H_1$; $\alpha_1&2$
- fewer problems with weight gain or prolactin side effects
- efficacy issues unclear
quetiapine

• dose range 200 -12000 mg
• bd dosage recommended
• metabolised CYP3A4 > 2D6, 2C9.
• Decreased levels with hepatic inducing drugs, increased levels with ketoconazole and erythromycin (CYP3A4 inhibitors)
ziprasidone

- Under consideration by TGA
- Structurally dissimilar to other antipsychotics. Binding to $D_{2,3}; 5HT_{1D, 2A, 2C, 7}; \alpha_1; SRI, NRI$. $5HT_{1A}$ agonist.
- Effective antipsychotic, ? antidepressant
- No weight gain (↑ nausea)
- QTc interval increase, sedation
- Dose 80-160 mg daily
amisulperide

- Substituted benzamide, with affinities to sulperide
- Binds to $D_{2,3}$ receptors at low doses presynaptic dopamine autoreceptors and at higher doses post synaptically
- Biphasic absorption, renal excretion
amisulperide

- Negative symptoms < 400 mg daily, positive symptoms 400 – 1200 mg. Antidepressant action.
- ↑ prolactin, insomnia, somnolence, EPSE (low)
- Increases QTc interval. Beware of interactions:
  - Class Ia (quinidine), III (sotalol, amiodarone) antiarhythmics
  - Cisapride, IV erythromycin, pentamide
clozapine

Indications

• treatment resistant Schizophrenia
  – failure to respond to at least two other antipsychotics
  – reasonable trials
  – depot trial
• severe side effects to other antipsychotics
• severe tardive dyskinesia
• aggression
clozapine

- wide range of effective dose 75 - 900mg
  - plasma range 200 - 400 ng/ml a limited guide
- $t_{1/2} = 12$ hrs, however biphasic
- wide range of receptor sensitivity
  - $D_{2,3,4,1}$
  - $5HT_{1A,2A,2C,3,6,7}; \alpha_{1&2}; H_1, M$
clozapine

- Metabolised CYC 1A2, 3A4
- Contraindicated with any other medication that may suppress bone marrow
clozapine screen

- CPMS - compulsory monitoring requires
  - FBC (WBC>3.5), Blood Gp
- usual additional
  - temp., HR, weight
- myocarditis
  - cardiac enzymes
  - Echocardiogram after 6 months
# depot antipsychotics

<table>
<thead>
<tr>
<th>generic</th>
<th>brand names</th>
<th>sedation</th>
<th>EPSE</th>
<th>Chol</th>
<th>300 CPZ/day</th>
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<td>haloperidol dec.</td>
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<tr>
<td>flupenthixol dec.</td>
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<td>++</td>
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<tr>
<td>zuclopenthixol dec.</td>
<td>CLOPIXOL</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>200</td>
</tr>
</tbody>
</table>
depot medications

- only typical antipsychotics
  - fluphenazine decanoate 25mg 2 weeks
  - flupenthixol dec. 40mg 2 weeks
  - haloperidol dec. 50 mg 4 weeks
  - zuclopenthixol dec 200 mg 2 weeks
- prolonged use associated with
  - large dose of medication
  - movement disorders
Side effects

- Extrapyramidal
- Akathisia
- Tardive Dyskinesia
- Cholinergic
- Sedation
- Cardiovascular
- Endocrine

- Cognitive
- Neuroleptic Malignant Syndrome
- Mood
- Blood dyscrasias
- Hepatic
- Dermatological
movement disorders

- higher rate of movement disorders at baseline

- extrapyramidal up to 60%
  - dystonia - oculogyric, torticollis, laryngeal
  - choreoathetosis
  - parkinsonism/akinesia

- Tx - anticholinergics eg benztropine 2mg
tardive dyskinesia

• hyperkinetic neuromuscular disorder

• receptor up-regulation or hypersensitivity secondary to exposure to antipsychotic medication
  – orobuccal

• 4% per year. Risks - age, female, physical illness, total dose, mood disorder

• Tx - decrease dose. ?Na.valporate, Vit.E,
akathisia

- distressing subjective sense of physical and mental restlessness accompanied by physical manifestations of restlessness
- related to depression, suicide and later poor treatment adherence
- treatment - antipsychotic reduction, anticholinergics, beta blockers, benzodiazepines
cardiovascular system

- increased incidence of sudden death with typical antipsychotics and clozapine (RR = 2.4)

- prolongation of QTc interval - caution with all antipsychotics, recent warning with thioridazine.

- clozapine
  - myocarditis
  - cardiomyopathy
anticholinergic side effects

- common with typical antipsychotics and clozapine
- peripheral
  - dry mouth, blurred vision, constipation, bladder
  - tachycardia, hyperthermia
  - idiosyncratic hypersalivation for clozapine
- central
  - learning difficulties, delirium
neuroleptic malignant syndrome

- exposure to dopaminergic agents
- risk factors of dehydration, physical illness, high doses of neuroleptics, ?lithium
- Sx - confusion, autonomic instability, rigidity, raised CPK
- Tx - drug withdrawal, supportive
Endocrine / obesity

• Obesity
  – All bar ziprasidone
  – Significant problem with clozapine, olanzapine
  – Satiety?

• Endocrine
  – Type II diabetes
  – ↑ Prolactin
    • Risperidone, amisulperide
Epidemiology of obesity in this population mental health

- **Canada:** Coodin et al 2001
  - Canadian population mean 12% BMI>30
  - Patients with schizophrenia: 42.1% BMI>30
    - Av. BMI male = 28.5 (sd=6.3) vs 26.3 population
    - Av BMI female = 30.0 (sd = 6.5) vs 24.3 population

- **Germany – adolescent/young adult MH** (Theisen et al, 2002)
  - Obesity defined as BMI>90th percentile
  - 45% male, 56% female adolescent pts
  - 64% clozapine, 56% atypicals, 30% typical antipsychotics
neurocognitive deficits

• difficult to disentangle from effects of chronic psychosis
  – Attention
  – Memory
  – Executive functions

• reflect sedation and decreased motivation
blood dyscrasias

- phenothiazines (<1%) and clozapine (1-2%)
  - agranulocytosis
  - thrombocytopenia
  - eosinophilia
- risks - age, genetic, myelosuppressive agents
- monitor
serotonin syndrome

• over stimulation of the serotonergic system
• Dx
  – cognitive - delirium, agitation
  – autonomic - hyperthermia, sweating, tachycardia, dilated pupils, tachypnea
  – neuromuscular - tremor, rigidity, myoclonus, hyperreactivity, ataxia, chills
• Tx - withdraw, support, benzo’s/ cyproheptadine
mood disorders

• dysphoria
• depression frequent co-morbid condition
• reactive and secondary to medication
• frequently seen during prodrome and recovery
• suicide rate 10% in schizophrenia
motivation/negative symptoms

• Negative symptoms overlap with side effects of antipsychotic medication
• decreased motivation, conative and cognitive activity
• indifference to surroundings
gender issues

• reproduction and medication
  – low teratotoxicity
  – menstrual changes and galactorrhoea

• sexuality
  – low libido
  – erectile problems/ impotence

• appearance
other reactions

- polydipsia and water intoxication
- seizures
- hepatotoxicity
- cardiac arrhythmias
- dermatological
- temperature regulation abnormalities
compliance or treatment adherence

• significant problem for all medicine
• especially when patient is uncertain or resistant about taking medication

• How to improve
  – educate and negotiate treatment
  – simplify regimen
  – relieve side effects
  – consider depot
personal responses

- reactions to diagnosis
  - Denial
  - Engulfment
  - Acceptance

- Importance of support through illness to battle hopelessness.

- Higher suicide rate in those with higher premorbid hopes and expectations
Biopsychosocial treatment

• Need to use psychological and social intervention
  – CBT
  – Cognitive remediation
  – Social skills, communication

• Medication never enough by itself

• Rehabilitation must be planned from early in the course of the disorder
treatment environment

- Institutional environment
  - too little stimulation = negative symptoms
  - too much stimulation = relapse of symptoms

- PTSD from psychosis
- community treatment preferred