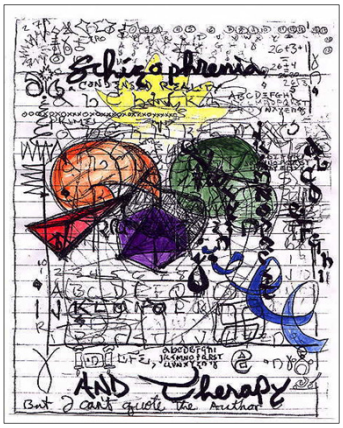
Schizophrenia and antipsychotics

Dr K Outhoff



Some thoughts

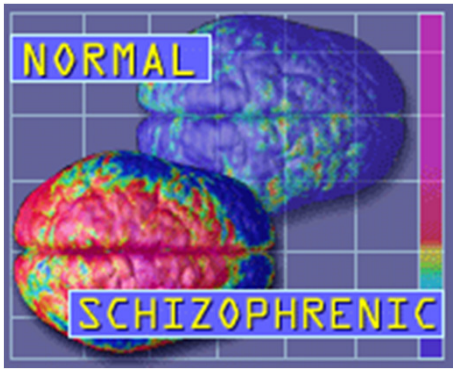
- Lifetime prevalence of schizophrenia = 1%
- Early detection and treatment may result in better prognosis and functional outcome
- Early recognition hindered by insidious onset
- Primary aim of treatment is to accomplish rapid remission of the acute psychotic episode using the most effective and best tolerated drugs
- Literature suggests that patients are more responsive to treatment during their first episode regardless of antipsychotic used
- But are more sensitive to extrapyramidal side effects (acute dystonia, parkinsonism)
- 80% will recover from first episode
- 70% will relapse within 5-7 years
- Drugs need to be withdrawn gradually

More thoughts

- Antipsychotic drugs have a central role in the treatment of schizophrenia
- Newer , atypical antipsychotics are increasingly considered superior to conventional drugs
- Older, conventional antipsychotics are cheaper

3 classes of antipsychotic drugs

Class	(1) Conventional	(2) Atypical	(3) Clozapine
M.O.A	**D2 antagonists**	**SDA**	**SDA**
Other receptors	Ach H1 Alpha-1	H1	Ach H1 Alpha-1 5HT and Dopamine
Oral	Chlorpromazine Haloperidol Trifluoperazine	Risperidone Olanzapine Ziprasidone Quetiepine Aripriprazole Amisulpride	Clozapine
Depot	Flupenthixol (Clopixol) Fluphenazine (Modecate)	Risperidone	



Biological basis of symptoms

Positive symptoms (delusions, hallucinations, distortions, disorganised speech and behaviour, catatonic behaviour, agitation:

- Overactivity dopamine meso-limbic pathway

Negative symptoms (blunted affect, emotional withdrawal, poor rapport, passivity, apathetic social withdrawal, stereotyped thinking, affective flattening, alogia, avolition, anhedonia, attentional impairment, lack of spontaneity):

- Overactivity of inhibitory glutamate systems in Dorsolateral prefrontal cortex

Dopamine hypothesis and the 4 pathways in the brain: impact of antipsychotics

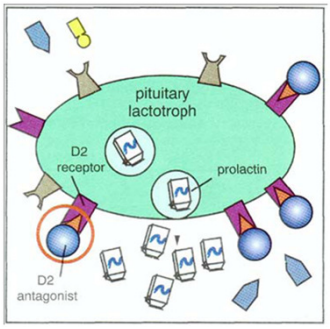
1. Mesolimbic :
- positive symptoms of psychosis (hallucinations and delusions)

2. Nigrostriatal: movement
- if blocked, causes extrapyramidal symptoms: movement disorders:
  acute: akathisia, dystonia, tremor, rigidity, akinesia, bradykinesia,
  late: irreversible tardive dyskinesia

3. Mesocortical: cognition
- Blockade leads to neuroleptic-induced deficit syndrome ie cognitive side effects or worsening negative symptoms

4. Tubero-infundibular: controls prolactin
- When blocked, prolactin rises, galactorrhoea

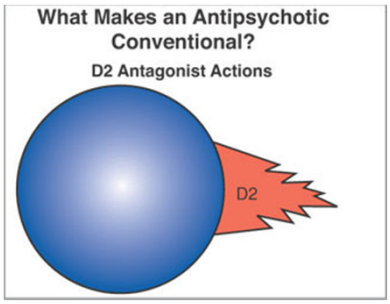
Increase in prolactin from blocking D2 receptors



Conventional antipsychotics (neuroleptics)

Oral
- Chlorpromazine
- Haloperidol (less sedation)
- Trifluoperazine (less hypoT, more EPS)
- Thioridazine(withdrawn – cardiac SEs)

Depot
- Flupenthixol (Clopixol)
- Fluphenazine (Modecate)



Conventional antipsychotics therapeutic effects:

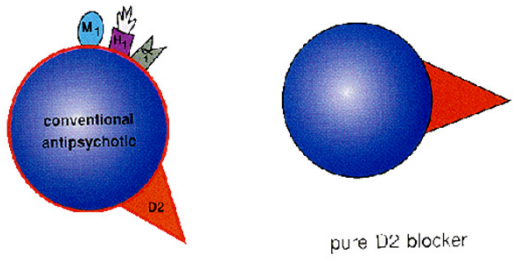
Block postsynaptic D-2 receptors in the 4 dopamine pathways
(70-90% D2 receptors blocked)

- Therapeutic
- EPSE: acute and chronic
- Negative symptoms exacerbated
- Prolactin increase with galactorrhoea

Movement disorders due to blocking D2 receptors in Nigrostriatal pathway

- Akathisia (type of restlessness)
- Abnormal involuntary movements
- Seizures
- Parkinsonism: tremor, rigidity, bradykinesia
- Dystonia (twisting movements esp. Face and neck)
- Tardive dyskinesia hyperkinetic movements esp face, neck, extremities: lip-smacking, chewing, tongue protrusions, facial grimacing

Conventional antipsychotics are multipotent blockers



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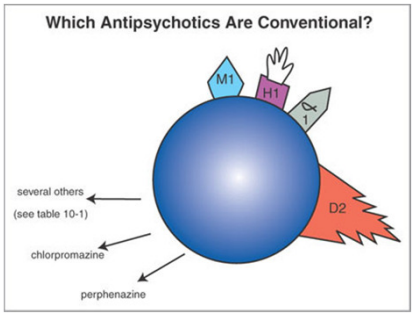
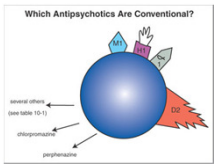


Conventional antipsychotics
Multipotent blockers: other side effects

Antihistamine H1
- Weight gain
- Sedation

Alpha-1
- Postural hypotension,
- Reflex tachycardia

Muscarinic
- Protective against EPSE
- Dry mouth
- Blurred vision
- Constipation
- Urinary retention



Other effects of conventional neuroleptics eg chlorpromazine

Jaundice
Eye:
- Ocular disorders
- Corneal and lens opacities
- Pigmentary retinopathy

Rash:
- Photosensitivity
- Urticarial rash

Raised cholesterol
Blood dyscrasias: Leukopaenia, thrombocytopaenia, agranulocytosis
Sudden cardiac arrhythmias, arrest
Seizures
Impaired temperature regulation

Neuroleptic malignant syndrome:

Extreme:
- muscular rigidity,
- high fevers,
- coma,
- Death

Rx:
- dantrolene

Conventional antipsychotics pharmacokinetics

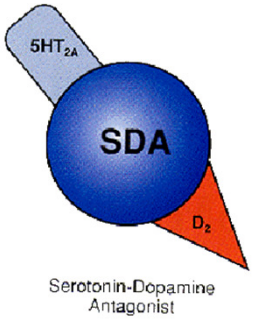
- Most are erratically absorbed after oral admin
- Relationship between [plasma] and clinical effect v. Variable
- Adjust dose on trial and error basis
- Half life: 15-30hrs
- Hepatic clearance

- Depot formulations given every 2-4 weeks; limit compliance problems (40%)

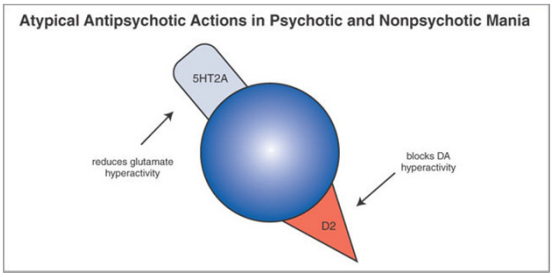
conventional antipsychotics with a twist

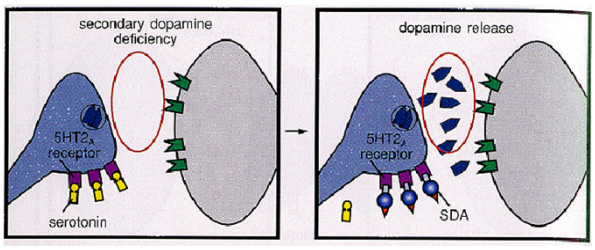
- More selective for mesolimbic dopamine receptors (therapeutic) than for nigrostriatal dopamine receptors (lessen EPSE profile)
- **Sulpiride** has relatively little extrapyramidal toxicity
- High doses control florid symptoms of schizophrenia
- Lower doses have an alerting effect on apathetic and withdrawn schizophrenics
- Other side effects similar to phenothiazines

Atypical antipsychotic drugs



Putative actions of SDAs





Atypical antipsychotics 'typical efficacy with atypical side effects'

<u>Serotonin and Dopamine Antagonists: SDA</u>

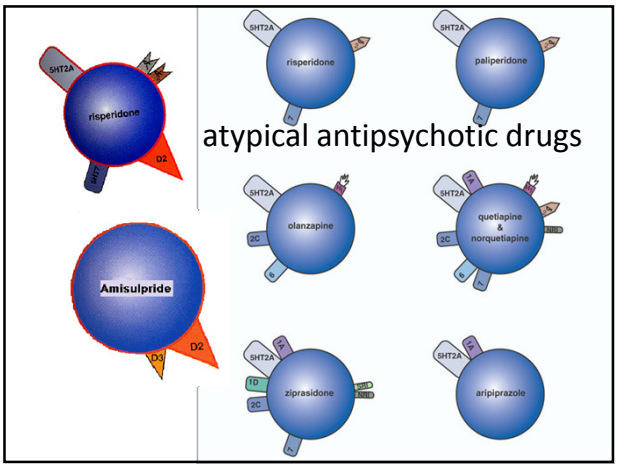
- Risperidone
- Olanzapine
- Ziprasidone
- Amisulpride
- Quetiepine
- Aripriprazole
- Sertindole (withdrawn – cardiac arrhythmias, sudden death)

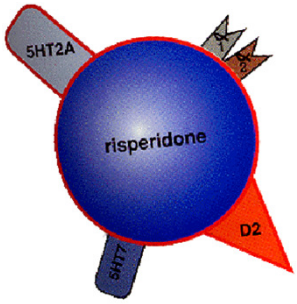
Atypical antipsychotics

Atypical side effects:
- Less EPSE
- Less galactorrhoea

- Appreciable weight gain

Also:
- Insomnia
- Agitation
- Anxiety
- Headaches
- Sedation mostly in kids

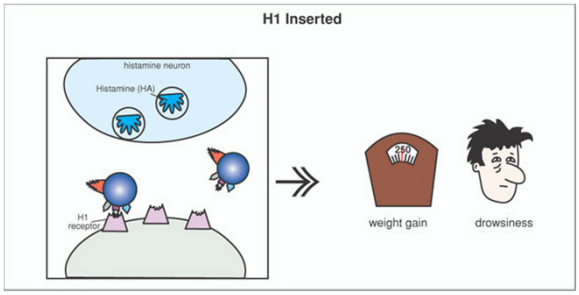




Risperidone , SDA

- Predominantly blocks 5HT2 receptors, but also potent blocker of dopamine 2 receptors
- Also antagonist at H1, alpha-1 and alpha-2 receptors
- Effective for positive and negative symptoms
- Extrapyramidal symptoms rare
- Neuroleptic Malignant Syndrome rare

Antihistamine effects of risperidone



Risperidone dosing

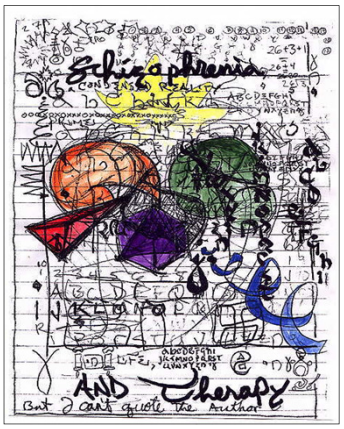
- Dose requires careful titration to maximise beneficial effects and minimise side effects
- Available in oral: tablets, solution, quicklet orodispersible tablets
  - 2mg od on day 1
  - 4mg od on day 2—maintain at this dose or increase to max 8mg od gradually
- and depot (25-50mg intramuscularly every 2 weeks) formulations

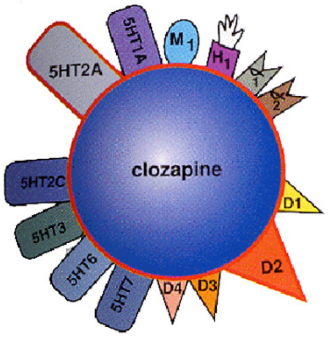
Risperidone pharmacokinetics

- Completely absorbed after oral administration
- Peak [plasma] attained after1-2 hrs
- Half life 3hrs
- Metabolised by CYP2D6, with active metabolite (half life 24hrs)

Risperidone indications

- Acute and chronic schizophrenia
- Behavioural disturbances in dementia
- Disruptive behaviour disorders in children aged 5-12 years
- Contra-indications/ warnings:
  - Hyperglycaemia and DM
  - Parkinsons disease (increased risk NMS)
  - Pregnancy; if benefits outweigh the risks





Clozapine

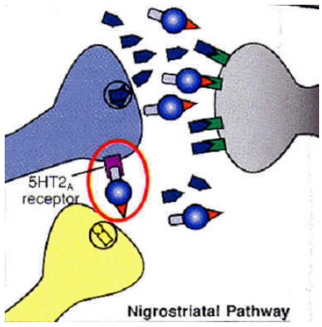
a drug class in itself for refractory psychosis

- One of most complicated drugs in psychopharmacology
- Interacts with at least 9 neurotransmitter receptors
- Simultaneous blocking of D-2 and 5HT2 (SDA's) accounts for therapeutic action
- 3 receptors : H-1, Ach, alpha-1 account for side effects
- Other receptors : dopamine and serotonin subtypes: which ones account for efficacy?

Clozapine the prototype SDA

- Relative amount of D-2 vs 5HT-2 receptors are blocked at a given dose
- Possibility of less D-2 blockade required when 5HT-2 blocked simultaneously
  - Only 30-60% D-2 receptors blocked
  - 85-90% 5HT-2 blocked
- Blockade of 5HT -2 receptors in nigrostriatal pathways increases dopamine release here (only in this pathway) ie much fewer EPSEs or tardive dyskinesia

5HT2a receptors blocked by clozapine in nigrostriatal pathway



Clozapine cont...

Other potential sites for targeting schizophrenia:

1. D-1 antagonists
2. Dopamine 4 antagonists
3. Dopamine partial agonists
4. Dopamine auto-receptor selective agonists
5. 5HT3 antagonists
6. 5HT2c antagonists

Clozapine effects

- Effective against negative symptoms too
- **Risk of fatal agranulocytosis 3%:** Regular blood counts required
- Makes this drug cumbersome to prescribe
- Seizures
- Sedation
- Weight gain

Some more thoughts:
conventional antipsychotics vs atypical antipsychotics

<u>Conventional antipsychotics:</u>

- Common side effects are dose related
- Efficacy reaches a plateau, and increasing the dose beyond this point, decreases the efficacy of the drug
- Recommended optimal dose is thus no more than 6-12mg haloperidol or its equivalent
- At this dose, efficacy and drop out rates (overall tolerability) similar to novel / atypical antipsychotics
- Although, extrapyramidal side effects more prevalent with conventional antipsychotics

Overall recommendations

- Start patient on conventional antipsychotic, but no more than 6-12mg Haloperidol
- If patient does not respond to this dose or develops intolerable extrapyramidal side effects, (relatively high proportion), switch to atypical antipsychotic
- Reserve Clozapine for treatment resistant schizophrenia (3rd line after conventional and atypical antipsychotics)

Pharmacological management of disturbed /agitated/ aggressive patient with acute psychosis

1) Haloperidol 2-5mg im
- Repeat after 60 min if necessary
- Monitor vital signs
- Beware acute dystonia
- Do not use more than 10mg haloperidol

2)Benzodiazepines preferably imi
- Lorazepam 2mg imi or
- Clonazepam 2mg imi or
- Diazepam 10mg ivi CAUTION respiratory depression
- Monitor patient+++

3)Anticholinergic:
Biperiden 2mg imi when dystonic reactions develop
Prophylactic: Orphenadrine 50mg oral bd

In summary

1. Conventional antipsychotics effective, but troublesome intractable acute (reversible)or chronic (often irreversible)EPSE may limit their long term use. Still recommended first line. Block D2 receptors in all 4 dopamine pathways. Increasing dose beyond 12mg Haloperidol confers NO therapeutic advantage.
   Sulpiride preferentially blocks D2 in mesolimbic pathway, so fewer EPSE and more 'alerting.'
2. Atypical antipsychotics block serotonin and dopamine receptors (SDA). Effective, superior effects on cognition and negative symptoms, much fewer EPSEs but many responsible for weight gain. Usually used second line because of cost implications.
3. Clozapine blocks at least 9 receptors including serotonin and dopamine receptors. Need careful and regular blood monitoring for fatal agranulocytosis. Weight gain is appreciable. EPSE rare. Used for treatment resistant schizophrenia third line.

- Anticholinergics prescribed to prevent/treat EPSE
- Benzodiazepines for violent, aggressive patients imi with close monitoring