Antipsychotics

= neuroleptics

The first of them, chlorpromazine, was introduced for use in anaesthetic preparation since it induced a state of 'relaxed alertness'. It was soon tried in SZ and noted to reduce delusions and hallucinations without causing excessive sedation.

Indications

- Psychosis
  - SZ (mainly)
  - Delusional depression
  - Mania
  - Any acute psychosis, regardless of aetiology (even e.g. brain damage)
- Tourette's

Pathophysiology: dopamine hypothesis of schizophrenia

Proposes that schizophrenia is caused by functional overactivity of dopamine systems.

Evidence
- Increased levels of dopamine/dopamine receptors in both untreated and treated schizophrenics
- Effectiveness of typical antipsychotics, which are known to inhibit dopamine receptors
- Psychosis induced by amphetamines, which are known to cause dopamine release

Limitations
- Does not explain the mode of action of atypical antipsychotics, which act at a variety of receptors
- Does not explain relative lack of efficacy of typical agents against negative symptoms

Classification

Typical
Mechanism
- Mostly bind to D_2 receptors in mesolimbic system (mostly hippocampus, thalamus and hypothalamus)
  - Occupy 70% of D_2 receptors for maximum efficacy – occupancies above this level do not result in increased efficacy but cause a worsening of the side-effect profile
- Frequently cause extrapyramidal SEs by concomitant action on nigrostriatal tract

- May in turn be classified according to potency in blocking D_2 receptors
  - High potency – give a few mg (e.g. haloperidol): block D_2 very potently; hence mostly DA-related side-effects
  - Low potency – give hundreds of mg (e.g. chlorpromazine): block D_2 receptors badly, so high doses are required and there is increased block of other receptors ('dirty action'); hence mostly anticholinergic, antiadrenergic and antihistaminic side-effects

Types
- Phenothiazines:
  - Aliphatic side-chain: chlorpromazine
  - Piperazine side-chain: trifluoperazine (stellazine)
  - Piperidine side-chain: thioridazine
- Butyrophenones: haloperidol
- Thioxanthines: flupenthixol, cis-clopenthixol
- Diphenylbutylpiperidines: pimozide
- Substituted benzamides: sulpiride, amisulpiride (metabolite of sulpiride) - ?atypical

Atypical
Mechanism

- Act at broad range of receptors
- Rare extrapyramidal SEs

Types

- Dibenzodiazepines = broad-spectrum receptor antagonists ('non-dopaminergic'): clozapine, olanzapine, quetiapine
    - Clozapine: 'best drug we have' (better in 30-40%), works in 1/3 of refractory cases; very expensive, risk of agranulocytosis; little D_2 action, much $D_{1,3,4,5}$ (D_3 is autoreceptor controlling expression of other DA receptors) and 5-HT_2
    - Olanzapine: also 5-HT_3 (sedative)
    - Quetiapine: shorter half-life and needs to be given twice daily, unlike others
- Benzisoxasole = D_2/5-HT_2 antagonist: risperidone (becomes typical at high doses)
- Sertindole

- Ca. 50x more expensive than typicals as still patented, but now often used routinely
    - NICE guidelines – consider atypical if
        - Newly diagnosed SZ
        - Acute SZ when unable to discuss choice with patient
        - Unacceptable side-effects on typical
        - Poor control on typical
            - Clozapine should be introduced if control inadequate despite the sequential use of ≥2 antipsychotics (one of which should be an atypical)
- Effective against negative symptoms
- More likely to induce weight gain

Mode of administration

- Usually PO
- Short-acting IM or IV injection possible for many drugs
- Deep IM depot injection possible for some drugs; esp. useful if compliance in doubt
    - Phenothiazines: fluphenazine
    - Butyrophenones: haloperidol
    - Thioxanthines: flupenthixol (depixol), cis-clopenthixol
    - *There is no atypical depot*

- In acute psychosis in a neuroleptic-naïve patient
    - Give IM lorazepam
    - Then PO antipsychotic (safer and less irritant than parenteral formulations)

Adverse effects

Receptor interactions determine likely side-effects (see classification section).

Antidopaminergic side-effects:

- Nigrostriatal
    - Acute
        - Acute dystonic reaction: acute D_2 block[1]
            - Esp. in young men
            - Types
                - Buccolingual (pulling sensation of the tongue)
                - Torticollic (rigidity of neck and jaw muscles)
                - Oculogyric (deviated upward gaze, ocular muscle spasm)
                - Tortipelvic (abdominal rigidity)
                - Opisthotonic (whole body spasm)
            - Culprit drugs

Analgesics	Alfentanil
Antiarrhythmics	Flecainide

[1] DINGLI, K. ET AL. (2007): Tetanus versus acute dystonic reaction caused by metoclopramide. *BMJ* **334**:899-900.

Anticonvulsants	Carbamazepine, phenytoin
Antidepressants	MAO-Is, SSRIs, TCAs
Antiemetics	Metoclopramide, domperidone
Calcium channel blockers	Diltiazem
Antipsychotics (typical)	
Sedatives	Midazolam
Stimulants	Cocaine

        - Give antimuscarinic as below; continue 24-48h (Sx may recur for up to 2w after cessation of offending drug!)
    - Chronic
        - Pseudo-parkinsonism: chronic D_2 block
            - Esp. in old people
            - Bradykinesia, lead-pipe rigidity, pill-rolling tremor (latter two → cog-wheeling)
            - Festinating gait, difficulty turning around, mask-like facies
            - Give antimuscarinics (procyclidine, benztropine) to restore the DA-ACh balance in the substantia nigra, or use antipsychotic agent with marked anticholinergic action (e.g. chlorpromazine). DA agonists would cause psychosis.
        - Akathisia
            - In 30-40% on typical antipsychotics
            - Uncontrollable restlessness (feeling of having to move or pace all the time, unable to sit still)
            - Has been associated with suicide
            - Less responsive to antimuscarinics; give β-blocker (propranolol), swap to atypical
        - Tardive dyskinesia: chronic D_2 block causing DA supersensitivity after many years
            - Slow orofacial movement, e.g. grimacing and slow masticatory movements, protruding tongue, lip smacking
            - Seen in >30% on chronic typical antipsychotics; irreversible in 50%
            - Option 1: swap to atypical agent. Unmasking of supersensitive DA receptors causes short-term worsening
            - Option 2: tetrabenazine (depletes presynaptic dopamine)
            - Option 3: BZs

- Tuberoinfundibular, causing hyperprolactinaemia (dopamine = prolactin release inhibitory factor)
    - Decreased libido
    - Men: galactorrhoea, impotence
    - Women: galactorrhoea, amenorrhoea

- Mesocortical
    - ?Increase in negative symptoms

In summary:

System	***D_2 agonist***	***D_2 antagonist***
Mesolimbic	Excitation up to psychosis	Treatment of SZ
Nigrostriatal	Treatment of Parkinson's	Movement disorders
Tuberoinfundibular	Treatment of hyperprolactinaemia	Hyperprolactinaemia
CTZ	Emesis	Anti-emetics

Dictates that drugs acting at D_2 receptors *will* have side-effects – in case of antagonists, those in the right-hand column.

Anticholinergic side-effects: dry mouth, blurred vision, mydriasis, acute glaucoma, tachycardia, constipation, urinary retention, erectile impotence

Antiadrenergic side-effects: bradycardia, postural hypotension, ejaculatory impotence, sedation

Antihistaminergic side-effects: sedation

Neuroleptic malignant syndrome (NMS):

- Caused mostly by dopamine-blocking drugs
    - Commonest culprit is haloperidol; rarely, TCAs, L-dopa, dopamine agonists, metoclopramide or domperidone are implied
- Similar to malignant hyperpyrexia caused by anaesthetic agents
- Insidious onset, usually within first 10 days of initiation or ↑dose, but may occur at any time. Esp. with depots, thus not given as first dose. Dehydration predisposes.
- Features
    1. Autonomic instability (tachycardia, HT)
    2. Motor (hyperpyrexia, muscle rigidity, hyperreflexia)
    3. Mental (increasing confusion/mutism → coma → death)
- Diagnostic criteria have been formulated[2]
- NMS vs. serotonin syndrome

	NMS	Serotonin syndrome
Mechanism	DA receptor blockade, or abrupt agonist withdrawal	Increased serotonergic tone
Clinical	Variable onset Severe muscular rigidity Autonomic instability	Rapid onset Muscular rigidity not always present Myoclonus, tremors, hyperreflexia
Bloods	↑CK	Non-specific

    - Causes of serotonin syndrome
        - SSRIs – incl. venlafaxine, fluvoxamine, tramadol, trazodone, St John's wort
        - ↑serotonin synthesis – tryptophan
        - ↓serotonin metabolism – selegiline, moclobemide
        - ↑serotonin release – ecstasy, amphetamine, cocaine, fenfluramine
        - Serotonin receptor agonists – triptans

- Often mistaken for meningoencephalitis
- Raised CK, WBC often also increased
- Conservative management. Stop drug. Keep hydrated and cool. Some give DA agonists (bromocriptine) or muscle relaxants (dantrolene – prevents calcium release from SR)
- 20% mortality, 30% risk of recurrence

Lowered seizure threshold

Specific drug groups:

- Phenothiazines: photosensitivity, contact dermatitis, cholestatic jaundice, arrhythmias (long QT), agranulocytosis
- Atypicals: arrhythmias, weight gain, insulin resistance
- Clozapine: agranulocytosis in 3%, myocarditis/cardiomyopathy, hypersalivation (give Quels – anticholinergic sweets), seizures (dose dependent; treat with sodium valproate, not carbamazepine which can also cause agranulocytosis); withdrawn but back since often effective in resistant SZ
- Risperidone: used to be a favourite treatment for aggression/agitation in dementia – however now known to be associated with ↑mortality and 3x ↑risk of stroke

[2] LEVENSON, J.L. (1985): Neuroleptic malignant syndrome. *Am J Psychiatry* **142**:1137-45. Mentioned in BMJ Lesson of the week, **329**:1333-4.