WESTMEAD PRIMARY EXAM GROUP

PSYCHOTROPIC MEDICATIONS

CLASSIFICATION OF ANTIPSYCHOTIC DRUGS

Typical antipsychotics

- Phenothiazines
  - e.g. chlorpromazine, fluphenazine, thioridazine
- Butyrophenones
  - e.g. haloperidol, droperidol
- Thioxanthines
  - e.g. chlorprotixen, thiothixene

Atypical antipsychotics

- Clozapine
- Risperidone
- Sulpiride
- Sertindole
- Seroquel
- Olanzapine
- Quetiapine.

DOPAMINE HYPOTHESIS

- Excessive limbic dopamine is hypothesised to cause psychosis
- Many antipsychotics inhibit dopamine 2 receptors in mesolimbic and striatal frontal systems in the CNS
- Drugs that increase dopamine can aggravate schizophrenic psychosis
- Diminished dopamine activity in the cortex and hippocampus
- However dopamine hypothesis doesn't explain all aspects of psychosis

DOPAMINE HYPOTHESIS

- There are 5 important dopamine pathways in the brain
  - Meso-limbic/meso-cortical pathway - closely related to behaviour
  - Nigrostriatal system - invovled in coordination of voluntary movement
  - Tuberoinfubdibular system - inhibits prolactin secretion
  - Medullary periventricular system - involved in eating behaviours
  - Incertohypothalamic pathway - anticipatory movement
- Mesolimbic and mesocortical pathways are most targeted by antipsychotic agents
- Potency of antipsychotic agents seems to correlated with the affinity for the D2 receptor
- Most of the newer atypical antipsychotic agents and some traditional ones have affinity for 5HT-2a receptor, suggesting the importance of serotonin
- Extrapyramidal toxicity appears to be related to D2 affinity

BASIS OF ACTION

- Typical antipsychotics - dopamine blockade
- Atypical antipsychotics - e.g cloazpine and quetiapine are 5HT 2a receptor blockers (inverse agonists)
- Most are readily and completely orally absorbed
- Significant first pass metabolism
- Bioavailibility 25 - 35% (chlorpromazine), 65% haloperidol
- Highly lipid soluble, high portein binding - 92 - 99%
- Large volume of distribution
- Long duration of action
- 6 months post cessation of medications on average for relapse of symptoms - Cloapzine in exception

PHENOTHIAZINES

CHLORPROMAZINE

- Alpha 1 blockade = 5HT2a bloackade > D2 > D1
  - Antiadrenoreceptor blockade causes postural symptoms
  - Antimuscarinic effects - cause anticholinergic syndrome
- Pharmacokinetics:
  - A: well absorbed
  - D: Large VD
  - M: P450 system
  - E: Metabolism dependent elimination
- Side effects - Sedation, weight gain, decreased seizure threshold, QT prolongation, EPS

BUTYROPHENONES

HALOPERIDOL

- A commonly use typical antipsychotic
- Highly potent but with less autonomic side effects but more EPS than phenothiazines
- Sedation and rate of hypotension is low
- D2 > Alpha 1 action > D4 > 5HT2a > D1 > H1

ATYPICAL ANTIPSYCHOTICS

- Olanzapine, respiradone, clozapine, quetiapine, aripiprazole
- Respirdone is rapidly converted into paliperidone except in 10% who are poor metabolisers
- Primary action is 5HT blockade and some minor dopamine blockade
- Clozapine should never be stopped abruptly unless myocarditis or agranulocysotis
- Olanzapine - effective against negative as well as positive symptoms

LITHIUM

- Uses - manic bipolar disorder, prevention of recurrent manic or depressive episodes in bipolar disorder
- Pharmacodynamics - not completely understood
    - Suppresses inositol signaling and inhibits GSK - 3
- Pharmacokinetics
    - A: Complete absorption in 6 - 8 hours (peak plasma levels in 30 minutes to 2 hours)
    - D: Total body water, no protein binding, volume of distribution 0.7 - 0.9 L/kg
    - M: not metabolised
    - E: Excreted in urine with a half life of 30 minutes - 20 hours
        - Renal clearance reduced by 25% by diuretics and NSAIDs
- Side effects: Tremor, ataxia, dysarthria, confusion, decreased thyroid function, nephrogenic DI, oedema, weight gain
- OD: can be dialysed

ANTIDEPRESSANTS

- Basis of action - BIOGENIC AMINE THEORY
  - Depression is thought to be due to a deficiency of monoamines in the CNS as well as deficiencies in neurotrophic and endocrine factors
  - The aim of anti-depressants is to increase monoamines such as serotonin, NA, dopamine in the CNS

TRICYCLIC ANTIDEPRESSANTS

- Amitriptyline
- Act at serotonin, histamine and Ach and alpha receptors
- Pharmacokinetics
  - A: Well absored, long half life - 45% Bioavailability
  - D: 90% protein bound, half life 31 - 46 hours, 5 - 10L
  - M: hepatic, has an active metabolite
  - E: 5% excreted unchanged in the urine

SSRI

- Inhibit serotonin transport - the most common anti-depressant used
- Use: generalised anxiety disorder, PTSD, OCD, Panic disorder
- Fluoxetine
  - A: 70% bioavailability
  - D: 90% protein bound
  - M: Active metabolite - norfluoxetine, has a long half life, inhibits cytochrome P450
  - E:
- Side effects
  - sexual dysfunction, nausea, GI upset, diahorrea, serotonin syndrome

MAO INHIBITORS

- Inhibition of monoamine breakdown
- Phamacokinetcs - extensive first pass metabolism
- Overdose - autonomic instability, psychotic symptoms, confusion, delirium, fever, seizures
- Need to avoid cheese, tap beer, soy, dried sausages

TOXICOLOGICAL SYNDROMES