GENERAL PRINCIPLES OF PSYCHOPHARMACOLOGY

OUTLINE

- Background
- Pharmacokinetics
- Pharmacodynamics
- Classification of drugs in psychiatry
- Prescribing principles

History of treatments in psychiatry

1934 Insulin coma treatment (Sakel)

1936 Frontal leucotomy (Moniz)

1936 Metrazole convulsive therapy (Meduna)

1938 Electroconvulsive therapy (Cerletti and Bini)

1941 Amphetamine for hyperactivity in children (Bradley)

1949 Lithium (Cade)

1952 Chlorpromazine (Delay and Deniker)

1954 Benzodiazepines (Sternbach)

1957 Iproniazid (Crane and Kline)

1957 Imipramine (Kuhn)

1966 Valpromide (valproate) in bipolar disorder (Lambert *et al.*)

1967 Clomipramine in obsessive–compulsive disorder (Fernandez and Lopez-Ibor)

1971 Carbamazepine in bipolar disorder (Takezaki and Hanaoka)

1988 Clozapine in treatment-resistant schizophrenia (Kane *et al.*)

1999 Lamotrigine in bipolar depression (Calabrese *et al.*)

2001 Atypical antipsychotic augmentation in depression (Shelton *et al.*)

2005 Quetiapine in bipolar depression (Calabrese *et al.*)

Pharmacokinetics

- Before psychotropic drugs can produce their therapeutic effects, they must reach the brain in adequate amounts.
- The extent to which they do so depends on their;
  - ❖ Absorption
  - ❖ Distribution
  - ❖ Passage across the blood– brain barrier
  - ❖ Metabolism
  - ❖ Excretion.

Plasma half-life

- The half- life of a drug in plasma is the time taken for its concentration to fall by a half, once dosing has ceased.
- For most psychotropic drugs, the amount eliminated over time is proportional to the plasma concentration, and in this case it will take approximately five times the half- life for the drug to be eliminated from plasma.
- Equally, when dosing with a drug begins, it will take five times the half- life for the concentration in plasma to reach steady state.

Pharmacodynamics

- Psychotropic drugs interfere with neurotransmitter function in several ways:
  - ❖On neurotransmitter receptors
  - ❖Storage
  - ❖Release
  - ❖Reuptake
  - ❖Metabolism
- Drugs can be **agonists** (mimic endogenous neurotransmitters) or **antagonists** (bind receptors and block the action of agonists)

Pharmacodynamics

Major pharmacodynamic considerations include:

- Receptor mechanisms
- The dose-response curve
- The therapeutic index
- The development of tolerance, dependence, and withdrawal phenomena

Neurotransmitters

- Important neurotransmitters implicated in psychopharmacology include:
  - Acetylcholine: reduction implicated in Alzheimer's
  - Serotonin: regulates mood, anxiety and arousal
  - Dopamine: plays a role in Schizophrenia and Parkinson’s disease
  - Norepinephrine:
  - Epinephrine
  - Glutamate: Excitatory neurotransmitter
  - GABA: Inhibitory neurotransmitter

Drug interaction

- When two psychotropic drugs are given together, one may interfere with or enhance the actions of the other through;
  - ❖ **Pharmacokinetic interactions**: Alterations in absorption, binding, metabolism, or excretion
  - ❖ **Pharmacodynamics interactions:** By interaction between the pharmacological mechanisms of action.

Pharmacokinetic Interactions

- **Absorption**: Absorption of chlorpromazine is reduced by antacids.
- **Metabolism**: Inhibition of the metabolism of antipsychotic drugs by some SSRIs, and the stimulation of the metabolism of many psychotropic drugs by carbamazepine, which induces the relevant cytochrome P450 enzymes.
- Interactions that affect **renal excretion** are mainly important for lithium, the elimination of which is decreased by thiazide diuretics.

Pharmacodynamics Interactions

- These are exemplified by the **serotonin syndrome**, in which drugs that potentiate brain 5-HT function by different mechanisms (e.g. SSRIs and MAOIs) can combine to produce dangerous 5- HT toxicity.
- As a rule, **a single drug can be used to produce all of the effects required of a combination** e.g. many antidepressant drugs have useful antianxiety effects.
- Avoid combinations of psychotropic drugs whenever possible

Classification of drugs

- According to their major therapeutic use, however, the therapeutic effects of different classes of drugs may overlap considerably.
  - ❖Anxiolytics and hypnotics
  - ❖Antipsychotics
  - ❖Antidepressants
  - ❖Mood stabilizers
  - ❖Prescription stimulants

Antipsychotics

- Used to treat psychosis e.g. In schizophrenia and mania.
- Psychotic patients experience delusions and hallucinations.
- Also useful for sedation and tranquilisation.
- Non psychotic indications: Tic disorders

Antipsychotics

- Typical antipsychotics
  - ❖(typically) Produce extrapyramidal side effects (EPSE)- Parkinsonism (muscle rigidity, tremor, bradykinesia), acute dystonic reactions, dyskinesia, akathasia, tardive dyskinesia
- Atypical antipsychotics
  - ❖Lower propensity to produce EPSE

Antipsychotics

- Examples of typical antipsychotics include:
  - ❖Phenothiazines:
    - Chlorpromazine
    - Thioridazine
    - Fluphenazine
  - ❖Thioxanthines:
    - Flupenthixol
  - ❖Butyrophenones:
    - Haloperidol

Antipsychotics

- Atypical (2nd generation):
  - ❖Lower incidence of extrapyramidal side effects and prolonged elevated prolactin levels
- Greater effects on negative symptoms of schizophrenia
- Include: Clozapine, Risperidone, Olanzapine, Quetiapine, Aripiprazole, Sertindole, Amisulpiride, Ziprasidone

Antipsychotics

- Mechanism of action:
  - ❖Dopamine receptor blockade (D2)
  - ❖This accounts for antipsychotic activity and propensity to cause extra-pyramidal side effects
  - ❖Some atypical anti psychotics have low D2 receptor occupancy and high 5HT receptor occupancy

Antipsychotics

- Depot antipsychotic drugs
  - ❖Slow release preparations
  - ❖Where compliance cannot be assured
  - ❖Given I/M
  - ❖Include: fluphenazine decanoate, flupenthixol decanoate, zuclopenthixol decanoate, Haloperidol decanoate

Antipsychotics

Side effects include:

- Extra pyramidal side effects (anti-dopeminergic)
  - Acute dystonia, akathasia, parkinsonian syndrome, tardive dyskinesia
- Anticholinergic effects:
  - dry mouth, urinary retention, constipation, blurred vision
- Antiadrenergic effects:
  - Sedation, postural hypotension, inhibition of ejaculation
- Cardiac: arrhythmias, prolongation of QT interval
- Metabolic effects
- Sensitivity reactions
- Neuroleptic malignant syndrome
  - Muscle rigidity, breakdown of muscle fibres, fever, altered consciousness, death)
- Amenorrhoea
- Galactorhoea

Choosing antipsychotic medication

- The choice of antipsychotic medication should be made by the **service user** and **healthcare professional together**, taking into account the views of the carer if the service user agrees. Provide information and discuss the likely benefits and possible side effects of each drug.

Baseline investigations

- **Before starting antipsychotic medication**, undertake and record the following baseline investigations:
- Weight (plotted on a chart)
- Waist circumference
- Pulse and blood pressure
- Fasting blood glucose, HbA1c, blood lipid profile and prolactin levels
- Assessment of any movement disorders
- Assessment of nutritional status, diet and level of physical activity.

Baseline investigations

- **Before starting antipsychotic medication**, offer the patient an **ECG** if:
- Specified in the summary of product characteristics
- A physical examination has identified specific cardiovascular risk (e.g. high blood pressure)
- A personal history of cardiovascular disease or the patient is being admitted as an inpatient.

How to use antipsychotics

- Discuss and record the side effects that the person is most willing to tolerate.
- Record the indications and expected benefits and risks of oral antipsychotic medication, and the expected time for a change in symptoms and appearance of side effects.
- At the start of treatment give a dose at the lower end of the licensed range and slowly titrate upwards within the dose range given in the BNF or SPC.

How to use antipsychotics

- Justify and record reasons for dosages outside the range given in the BNF or SPC.
- Record the rationale for continuing, changing or stopping medication, and the effects of such changes.
- Carry out a trial of the medication at optimum dosage for 4–6 weeks.
- 'As required' (p.r.n.) prescriptions of antipsychotic medication should reviewed.

How to use antipsychotics

- Frequency of administration, therapeutic benefits and side effects as appropriate. Check whether **'p.r.n.'** prescriptions have led to a dosage above the maximum specified.
- Do not use a loading dose of antipsychotic medication (often referred to as 'rapid neuroleptisation').
- Do not initiate regular combined antipsychotic medication, except for short periods (for example, when changing medication).
- If prescribing chlorpromazine, warn of its potential to cause skin photosensitivity. Advise using sunscreen if necessary.

Monitoring antipsychotic medication use

- Monitor and record the following regularly throughout treatment, and especially during titration:

✓ **Response to treatment**, including changes in symptoms and behavior.

✓ **Side effects of treatment**, taking into account overlap between certain side effects and clinical features of schizophrenia (for example, the overlap between akathisia and agitation or anxiety) and **impact on functioning.**

- The emergence of **movement disorders.**

Monitoring antipsychotic medication use

- Weight, weekly for the first 6 weeks, then at 12 weeks, at 1 year and then annually (plotted on a chart)
- Waist circumference annually (plotted on a chart)
- Pulse and blood pressure at 12 weeks, at 1 year and then annually
- Fasting blood glucose, HbA1c and blood lipid levels at 12 weeks, at 1 year and then annually
- Adherence
- Overall physical health.

Treating first and subsequent episodes

- For patients with **first episode psychosis** offer: Oral antipsychotic medication in conjunction with psychological interventions (family intervention and individual CBT).
- For people with an **acute exacerbation or recurrence** of psychosis or schizophrenia, offer oral antipsychotic medication or review existing medication. The choice of drug should be influenced by the same criteria recommended for starting .
- Take into account the clinical response and side effects of the service user's current and previous medication.

Non response to treatment

For people with schizophrenia whose illness has not responded adequately to pharmacological or psychological treatment:

- Review the diagnosis.
- Establish that there has been adherence to antipsychotic medication, prescribed at an adequate dose and for the correct duration.
- Review engagement with and use of psychological treatments

Non response to treatment

- Consider other causes of non-response, such as comorbid substance misuse (including alcohol), the concurrent use of other prescribed medication or physical illness.
- Offer clozapine to patients whose illness has not responded adequately to treatment despite the sequential use of adequate doses of at least 2 different antipsychotic drugs.
- For patients whose illness has not responded adequately to clozapine at an optimized dose, consider adding a second antipsychotic to augment treatment with clozapine for up to 8–10 weeks.

Antidepressants

- Indicated to treat the various symptoms of depressive disorders
- According to the biogenic monoamine theory, depression results from a deficiency of **monoamines** (norepinephrine, serotonin) in certain brain areas
- Exert antidepressant activity by increasing the availability of monoamines via:
  - ❖ Presynaptic inhibition of reuptake of 5HT, NE, Dopamine
  - ❖ Inhibition of monoamine oxidase reducing neurotransmitter breakdown
  - ❖ Increasing the availability of neurotransmitter precursors

Antidepressants

- Initial resolution of depressive symptoms generally takes 10-20 days
- Other uses: Anxiety, Sleep disorders, OCD, Eating disorders, Neuropathic pain, Migraines, ADHD

Antidepressants

Tricyclic antidepressants

- Inhibit reuptake of both 5HT & noradrenaline
- Include: amitryptiline, clomipramine, imipramine
- S/E: autonomic, psychiatric, cardiovascular, neurological, withdrawal effects
- Toxic effects in overdose

Antidepressants

Monoamine oxidase (MAO) inhibitors & reversible monoamine oxidase inhibitors (RIMAs)

- Inactivate enzymes that oxidise noradrenaline, 5HT, dopamine, tyramine (MAO A and MAO B)
- Include: Phenelzine, Isocarboxazid, Tranylcypromine
- Moclobemide- RIMA
- Interactions with food and drugs
- S/E: hypertensive crises, antimuscurinic, hepatotoxicity, insomnia, anxiety, weight gain, hypotension, ankle oedema

Antidepressants

Selective Serotonin Reuptake Inhibitors (SSRIs)

- Inhibit the reuptake of 5-HT with high potency and selectivity leading to increased 5-HT in the synaptic cleft
- Include: paroxetine, sertraline, fluoxetine, fluvoxamine, citalopram, escitalopram
- Easier dosing
- Better tolerance than TCAs & MAOs
- Fewer anticholinergic side effects, low toxicity in overdose, not sedating
- S/E: gastrointestinal, sexual dysfunction, suicidal behaviour
- Serotonin syndrome

Antidepressants

Other antidepressants:

- Serotonin/noradrenaline reuptake inhibitors(SNRIs)
  - ❖Venlafaxine, duloxetine
- Tetracyclic antidepressants
  - ❖MOA similar to TCA but with less anticholinergic side effects
  - ❖Mianserin
- Serotonin antagonist/ reuptake inhibitors (SARIs)
  - ❖Trazodone

Antidepressants

- Noradrenergic and specific serotonergic antidepressants (NaSSA)
  - ❖ Mirtazepine
- Noradrenaline reuptake inhibitor (NARI)
  - ❖ Reboxetine
- Noradrenergic and doperminergic reuptake inhibitor (NDRI)
  - ❖ Bupropion
- Melatonin agonist and specific serotonin antagonist (MaSSA)
  - ❖ Agomelatine

Choice of Antidepressant

- Anticipated adverse events and discontinuation symptoms.
- Potential interactions with concomitant medication or physical illness.
- The patients perception of the efficacy and tolerability of any antidepressants they have previously taken.
- First line is an SSRI. Taking into account that:
- SSRIs are associated with an increased risk of bleeding. Therefore consider prescribing a gastro protective drug in older people who are taking NSAIDs or aspirin.

Choice of Antidepressant

- Fluoxetine, fluvoxamine and paroxetine have a higher propensity for drug interactions.
- For people who also have a chronic physical health problem, consider using citalopram or sertraline as these have a lower propensity for interactions.
- Paroxetine is associated with a higher incidence of discontinuation symptoms.
- Take into account toxicity in overdose for people at significant risk of suicide. Be aware that: Venlafaxine is associated with a greater risk of death from overdose
- The greatest risk in overdose is with TCAs, except for Lofepramine.

Choice of Antidepressant

- There is increased likelihood of the patient stopping treatment because of side effects, therefore need to increase the dose gradually, with SSRIs, venlafaxine, duloxetine and TCAs.
- Consider the specific cautions, contraindications and monitoring requirements for some drugs.
- That non-reversible MAOIs, such as phenelzine, combined antidepressants and lithium augmentation of antidepressants should normally be prescribed only by specialist mental health professionals.

Mood stabilizers

Effective for treating both mania and depression in bipolar patients.

- **Lithium**
  - MOA: Intracellular signalling effects through second messengers. (inhibits formation of cAMP and attenuates formation of inositol lipid derived mediators)
  - S/E: polyuria, polydypsia, weight gain, cognitive problems, tremor, hypothyroidism, GI problems, teratogenic
  - Narrow therapeutic index
  - Toxicity: marked tremor, nausea, diarrhoea, ataxia, drowsiness, confusion, seizures, coma,

Mood stabilizers

Anticonvulsants

- Valproate/Valproic acid:
  - ❖ Acute mania, mixed episodes, prophylactic agent, rapid cycling bipolar
  - ❖ S/E: nausea, tremor, sedation, hair loss, weight gain, deranged LFTs. is teratogenic
  - ❖ Wide therapeutic index though can be fatal in overdose
- Carbamazepine
  - ❖ Acute mania, bipolar depression; prophylactic agent
  - ❖ Interacts with many drugs: decreases plasma levels of antipsychotics, benzodiazepines, TCAs, hormonal contraceptives; levels can be decreased by: erythromycin, calcium channel blockers

Mood stabilizers

Anticonvulsants…

- Lamotrigine
  - ❖maintenance treatment
  - ❖Especially for bipolar depression
- Gabapentin
  - ❖Used in non response

Anxiolytics

- Used to curb anxiety

Benzodiazepines

- Reduce anxiety, agitation and tension
- Uses: anxiolytic, sedative, muscle relaxant, anticonvulsant
- MoA: Enhance GABA neurotransmission
- Are addictive
- Should not be routinely prescribed for longer than a two weeks

Anxiolytics

Benzodiazepines…

- Long acting compounds preferable for management of anxiety. (half life more than 12 hours)
  - Include: diazepam, chlordiazepoxide, alprazolam, clonazepam
- Side effect: headache, confusion, ataxia, blurred vision, GI disturbance, jaundice, paradoxical excitement……
- Potentiate effects of alcohol
- Cause dependence which is associated with a withdrawal syndrome- apprehension, insomnia, nausea, tremor heightened sensitivity to perceptual stimuli

Anxiolytics

Azapirones

- Buspirone
  - ❖ Useful in treatment of Generalised Anxiety Disorder
  - ❖ Effects take several days to develop
  - ❖ MoA: stimulates 5-HT_{1A} receptor
  - ❖ Not sedative but associated with light headedness, nervousness headache

Anxiolytics

- **Antidepressant drugs:**
  - ❖TCA, SSRIs, MAOIs
  - ❖Onset of effect much slower than of the benzos
- **Beta-adrenoceptor antagonists**
  - ❖Relieve autonomic symptoms of anxiety
  - ❖Especially if main symptoms are tremors and palpitations
  - ❖Include propranolol
  - ❖Contraindicated in hypotension, bradycardia, heart block, bronchospasms

Hypnotics

- Are used to improve sleep
- Primary chronic insomnia is rare
- Comorbidity is the rule
- Non pharmacological methods tried first- Sleep Hygiene
- The ideal hypnotic would increase the length and quality of sleep without residual effects the next morning.
- Many anxiolytic drugs also act as hypnotics
- Antihistamines and low doses of sedating anti depressants e.g. amitriptyline are also used to facilitate sleep

Psychostimulants

- Include:
  - ❖Amphetamines- dextroamphetamine
  - ❖Methylphenidate
- MoA: increase the release and block the reuptake of dopamine and noradrenaline
- Indications:
  - ❖Narcolepsy
  - ❖ADHD
- Side effects: restlessness, insomnia, poor appetite, dizziness, tremor, palpitations, arrhythmias