LEARNING OUTCOMES

By the end of the lecture, students will be able to...

1. recall the biochemical basis of depressive illness.
2. classify the antidepressant drugs (with examples) based on their mechanism of action
3. describe the mechanism of action, pharmacokinetics, adverse drug effects, important drug/food interactions of antidepressants
4. list the clinical uses of antidepressants other than the treatment of depression
5. list the features of antidepressant drug overdose
OUTLINE....

A. Diagnosis
B. Monoamine hypothesis
C. Classification
D. Pharmacological Profile of Each Category
Affective disorders:

I. unipolar depression – depression alone
II. bipolar affective disorder – alternating depression and mania
DIAGNOSIS – DSM-IV

- At least five of the following for 2 weeks
  1. Depressed mood most of the day
  2. Markedly diminished interest or pleasure
  3. Significant weight loss or weight
  4. Insomnia or hypersomnia
  5. Psychomotor agitation or retardation
  6. Fatigue or loss of energy
  7. Feelings of worthlessness or excessive guilt
  8. Diminished ability to think or concentrate,
  9. Recurrent thoughts of death
MONOAMINE HYPOTHESIS

- Proposed by Schildkraut in 1965

“Underlying biological basis for depression is a deficiency of the monoamine neurotransmitters norepinephrine and/or serotonin in the brain.”
ANTIDEPRESSANTS

- Monoamine uptake inhibitors
  1. Tricyclic antidepressants (TCAs)
  2. Selective serotonin reuptake inhibitors (SSRIs)
  3. Serotonin-norepinephrine reuptake inhibitors (SNRIs)
  4. Norepinephrine reuptake inhibitor

- Monoamine oxidase inhibitors (MAOIs)

- Monoamine receptor antagonists
TRICYCLIC ANTIDEPRESSANTS

e.g. amitriptyline, imipramine, nortriptyline

- Belong to first generation antidepressants
- Inhibit 5-HT (5-hydroxytryptamine) and norepinephrine reuptake

slow clearance of norepinephrine & 5-HT from the synapse

enhance norepinephrine & 5-HT neuro-transmission
MODE OF ACTION

PRESYNAPTIC

5-HT

5-HTR₁DR₂A

α₂AR

Noradrenergic neuron

NE

NE synthesis

Reuptake

NET

NE

POSTSYNAPTIC

α₁AR

βAR

TCAs

SNRIs

SSRIs

TCAs

SNRIs

SERT

Reuptake

5-HT synthesis

SERT

5-HT

5-HTR

5-HTR

Serotonergic neuron
MODE OF ACTION

• TCAs also block
  - muscarinic acetylcholine receptors
  - histamine receptors
  - 5-HT receptors
  - $\alpha_1$ adrenoceptors

• Onset of antidepressant activity takes 2-3 weeks
PHARMACOKINETICS

- Readily absorbed from the gastro-intestinal tract
- Bind strongly to plasma albumin
- Has a large volume of distribution (as a result of binding to extravascular tissues)
- Undergo liver CYP metabolism into biologically active metabolites
- These metabolites are inactivated via glucuronidation and excreted in urine
ADVERSE DRUG REACTIONS

- Antimuscarinic - dry mouth, blurred vision, constipation and urinary retention
- Antihistamine – drowsiness
- $\alpha_1$ adrenoceptor blockage (+/- central effect) - postural hypotension
- Reduce seizure threshold
- Testicular enlargement, gynaecomastia, galactorrhoea
- AV-conduction blocks and cardiac arrhythmias
TOXICITY

- Fatal in toxicity
- Most important toxic effect is,
  slowing of depolarisation of the cardiac action potential by blocking fast sodium channels ("quinidine-like" effect)
  delays propagation of depolarisation through both myocardium and conducting tissue
  prolongation of the QRS complex and the PR/QT intervals
  predisposition to cardiac arrhythmias
DRUG INTERACTIONS

- Pharmacodynamic:
  - ↑ sedation with antihistamines, alcohol
  - ↑ antimuscarinic effects with anticholinergics
  - Hypertension and arrhythmias with MAOIs- should be given at least 14 days apart

- Pharmacokinetic (via altering CYP metabolism)
  - ↓ plasma concentration of TCA by- carbamazepine, rifampicin
  - ↑ plasma concentration of TCA by- cimetidine, calcium channel blockers, fluoxetine
OTHER CLINICAL USES OF AMITRIPTYLINE

- Treatment of nocturnal enuresis in children
- Treatment of neuropathic pain
- Migraine prophylaxis
ANTIDEPRESSANTS

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- Monoamine oxidase inhibitors (MAOIs)

- Monoamine receptor antagonists
e.g. phenelzine, tranylcypromine, moclobemide

- Belong to first generation antidepressants with TCAs
- Most MAOIs irreversibly inhibit the intraneuronal catabolism of norepinephrine and serotonin by MAO-A and MAO-B
- Moclobemide causes selective, reversible inhibition of MAO-A

increase brain levels of noradrenaline and 5-HT
INTERACTIONS

- "Cheese-reaction":
  Tyramine in mature cheese, red wines and Marmite®
  escape metabolism by MAO in the gut wall and liver
  displaces noradrenaline from presynaptic vesicles
  hypertensive crises via increased sympathetic drive
DRUG INTERACTIONS

- Hypertensive crises similar to cheese reaction with OTC cough/cold preparations containing indirect-sympathomimetics
e.g. ephedrine

- Other antidepressants should not be started at least 2 weeks after stopping MAOIs and vice versa due to risk of serotonin syndrome

- Similar interaction with pethidine
ADVERSE DRUG REACTIONS

- Antimuscarinic side effects (e.g. dry mouth, blurred vision, urinary retention)
- Excessive central stimulation causes tremors, excitement and insomnia
- Postural hypotension
- Increased appetite with weight gain
ANTIDEPRESSANTS

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- Monoamine oxidase inhibitors (MAOIs)

- Monoamine receptor antagonists
SELECTIVE SEROTONIN REUPTAKE INHIBITORS

e.g. fluoxetine, paroxetine, citalopram, and sertraline

- Most commonly used antidepressant category
- Less likely to cause anticholinergic side effects
- Relatively safest antidepressant group in overdose
- Selectively inhibits reuptake of serotonin (5-HT)
MODE OF ACTION

[Diagram showing the mode of action of SSRIs, TCAs, SNRIs, and NE with 5-HT and 5-HTR]
SELECTIVE SEROTONIN REUPTAKE INHIBITORS

- Well absorbed when given orally
- Plasma half-lives of 18-24 h allowing once daily dosage
- Metabolised through CYP450 system and most SSRIs inhibit some CYP isoforms
- Therapeutic effect is delayed for 2-4 weeks
ADVERSE DRUG REACTIONS

- Insomnia, increased anxiety, irritability
- Decreased libido
- Erectile dysfunction, anorgasmia, and ejaculatory delay
- Bleeding disorders
- Withdrawal syndrome
4.3.3 Selective serotonin re-uptake inhibitors

Additional information

Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline selectively inhibit the re-uptake of serotonin (5-hydroxytryptamine, 5-HT); they are termed selective serotonin re-uptake inhibitors (SSRIs). For a general comment on the management of depression and on the comparison between tricyclic and related antidepressants and the SSRIs and related antidepressants, see section 4.3.

Cautions

SSRIs should be used with caution in patients with epilepsy (avoid if poorly controlled, discontinue if convulsions develop), cardiac disease, diabetes mellitus, susceptibility to angle-closure glaucoma, a history of mania or bleeding disorders (especially gastro-intestinal bleeding), and if used with other drugs that increase the risk of bleeding. They should also be used with caution in those receiving concurrent electroconvulsive therapy (prolonged seizures reported with fluoxetine). SSRIs may also impair performance of skilled tasks (e.g. driving). Interactions: see below and Appendix 1 (antidepressants, SSRI).
OTHER INDICATIONS FOR SSRIs

- Obsessive Compulsive Disorder
- Bulimia Nervosa
- Panic Disorder
Antidepressants

- Monoamine uptake inhibitors
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- Monoamine oxidase inhibitors (MAOIs)

- Monoamine receptor antagonists
SEROotonIN-NOREpinePHRINE
reuptake inhibitors

e.g. venlafaxine and duloxetine

- Inhibit the reuptake of both 5-HT and norepinephrine
- Has a more favourable adverse effect profile than TCAs
MODE OF ACTION
ANTIDEPRESSANTS

● Monoamine uptake inhibitors
  1. Tricyclic antidepressants (TCAs)
  2. Selective serotonin reuptake inhibitors (SSRIs)
  3. Serotonin-norepinephrine reuptake inhibitors (SNRIs)
  4. Norepinephrine reuptake inhibitor
    e.g. bupropion, reboxetine

● Monoamine receptor antagonists
  e.g. mirtazapine, trazodone, mianserin