ANTIDEPRESSANTS

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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

DIAGNOSIS

- 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
  I. Depressed mood most of the day
  II. Markedly diminished interest or pleasure
  III. Significant weight loss or weight
  IV. Insomnia or hypersomnia
  V. Psychomotor agitation or retardation
  VI. Fatigue or loss of energy
  VII. Feelings of worthlessness or excessive guilt
  VIII. Diminished ability to think or concentrate,
  IX. 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

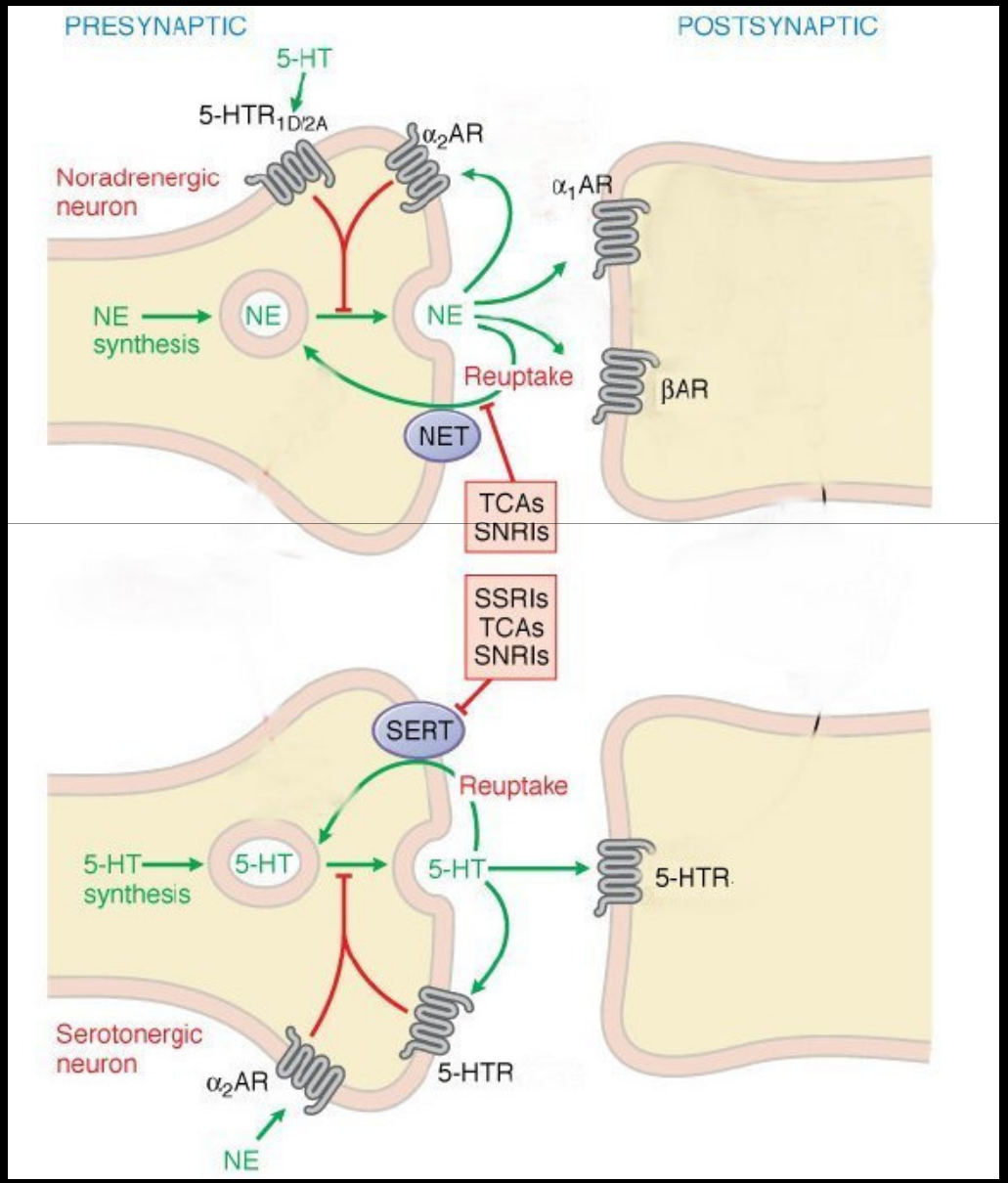
e.g. **amitriptyline, imipramine**, **nortriptyline**

- 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



MODE OF ACTION

- TCAs also block
  - muscarinic acetylcholine receptors
  - histamine receptors
  - 5-HT receptors
  - α_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
- α_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

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MONOAMINE OXIDASE INHIBITORS

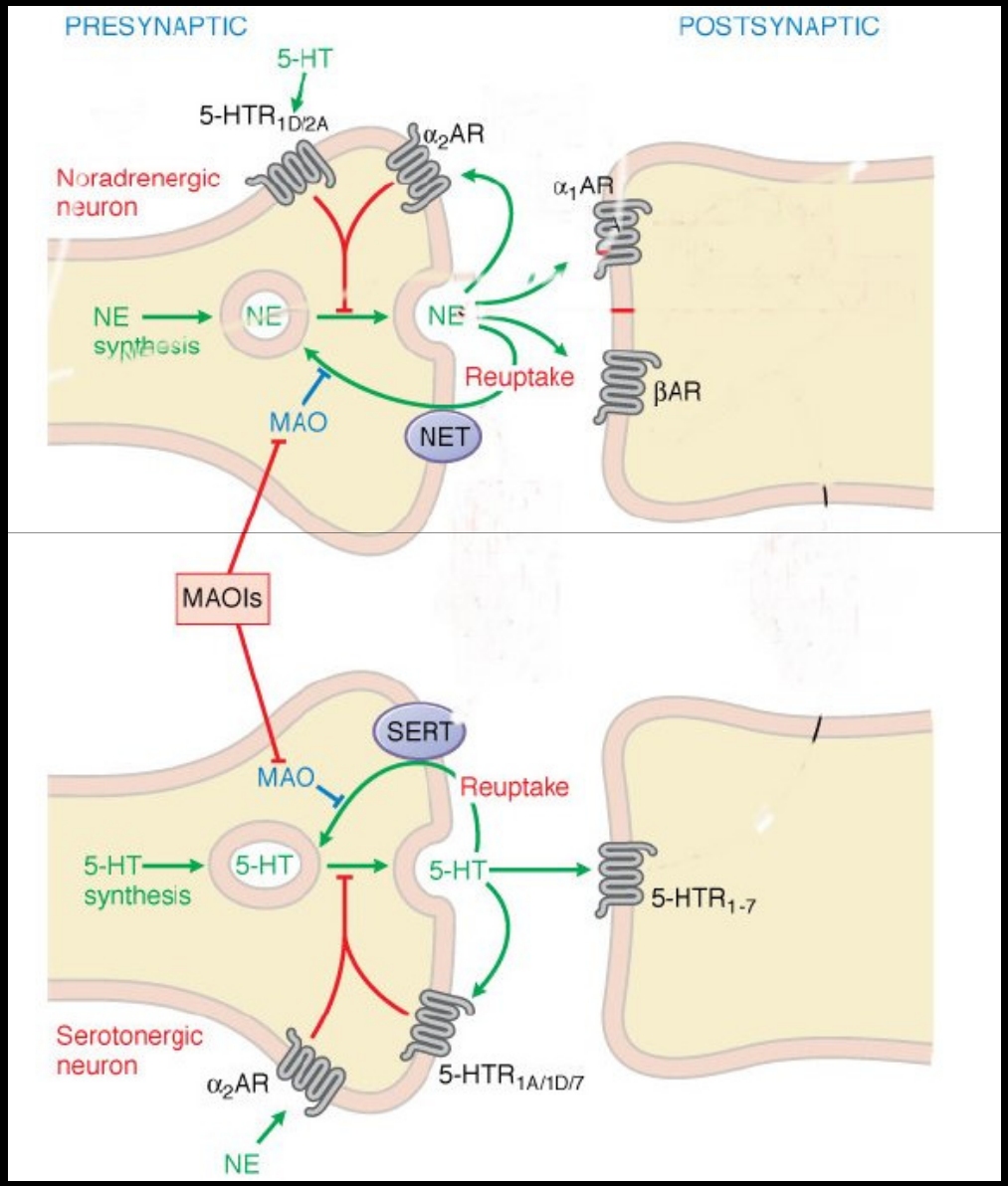
e.g. **phenelzine**, **tranylcypromine**, **moclobemide**

- Belong to first generation antidepressants with TCAs
- Most MAOIs irreversibly inhibit the intraneuronal catabolism of norepinephrine and serotonin by MAO-A and MAO-B

increase brain levels of noradrenaline and 5-HT

- Moclobemide causes selective, reversible inhibition of MAO-A

MODE OF ACTION



INTERACTIONS

- “Cheese- reaction”:

  Tyramine in mature cheese, red wines and Marmite®

  ↓

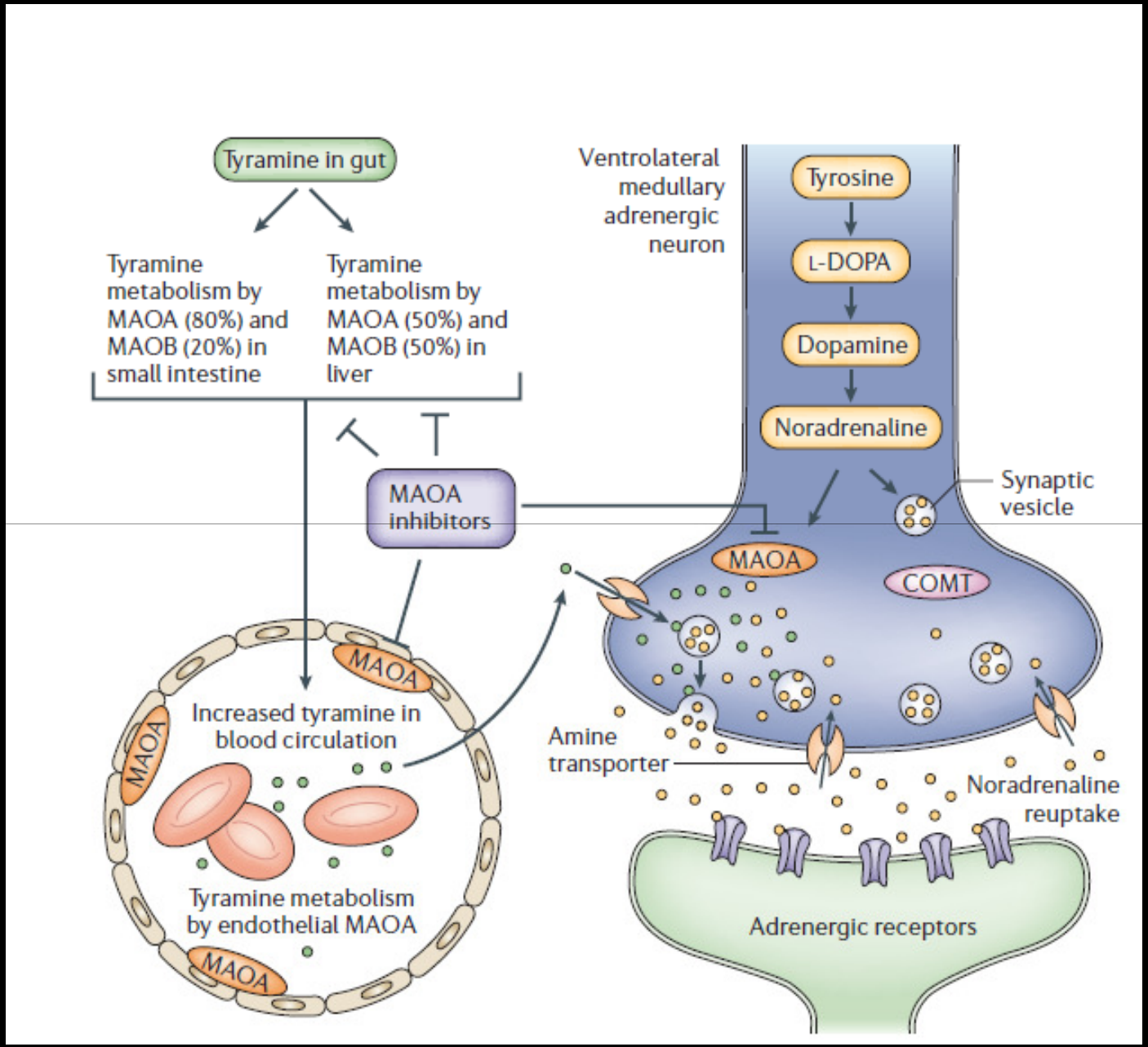
  escape metabolism by MAO in the gut wall and liver

  ↓

  displaces noradrenaline from presynaptic vesicles

  ↓

  hypertensive crises via increased sympathetic drive


Tyramine in gut
Tyramine metabolism by MAOA (80%) and MAOB (20%) in small intestine
Tyramine metabolism by MAOA (50%) and MAOB (50%) in liver
MAOA inhibitors
Ventrolateral medullary adrenergic neuron
Tyrosine
L-DOPA
Dopamine
Noradrenaline
Synaptic vesicle
MAOA
COMT
MAOA
MAOA
Increased tyramine in blood circulation
Tyramine metabolism by endothelial MAOA
MAOA
Amine transporter
Noradrenaline reuptake
Adrenergic receptors

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

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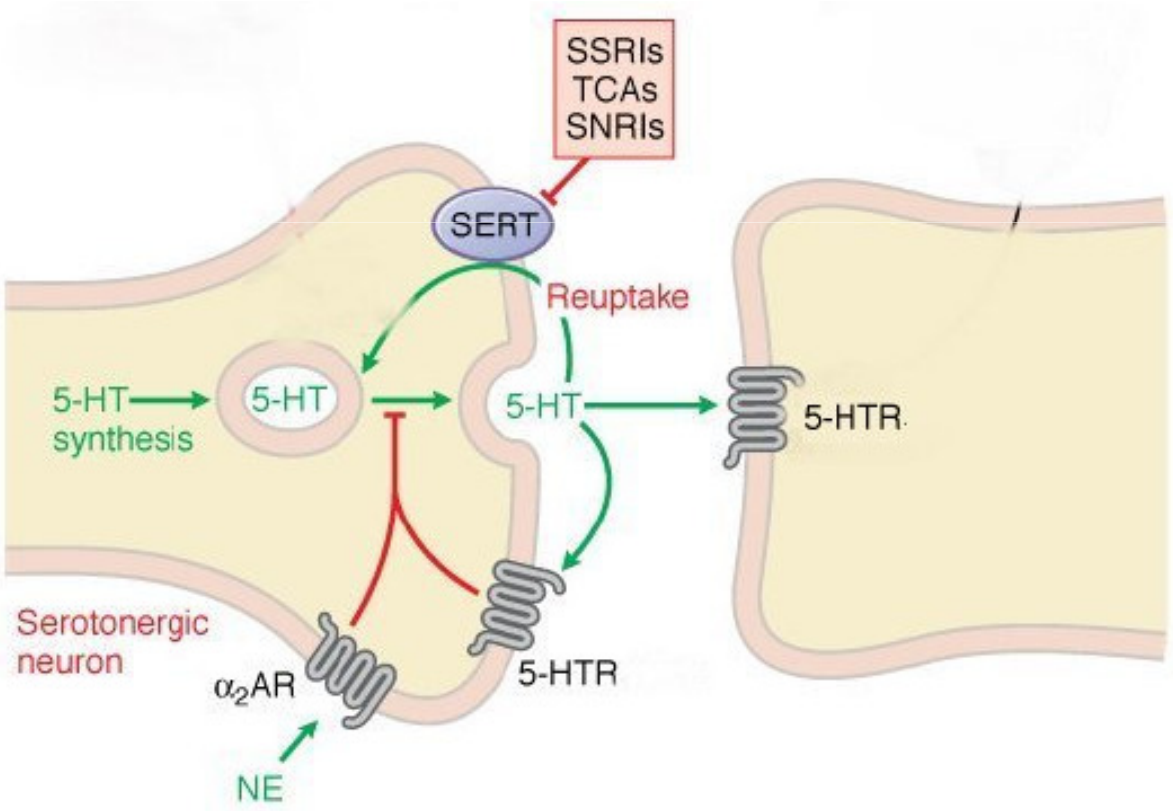
SELECTIVE SEROTONIN REUPTAKE INHIBITORS

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



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 interactions (Antidepressants, SSRI (related),Antidepressants, SSRI).

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

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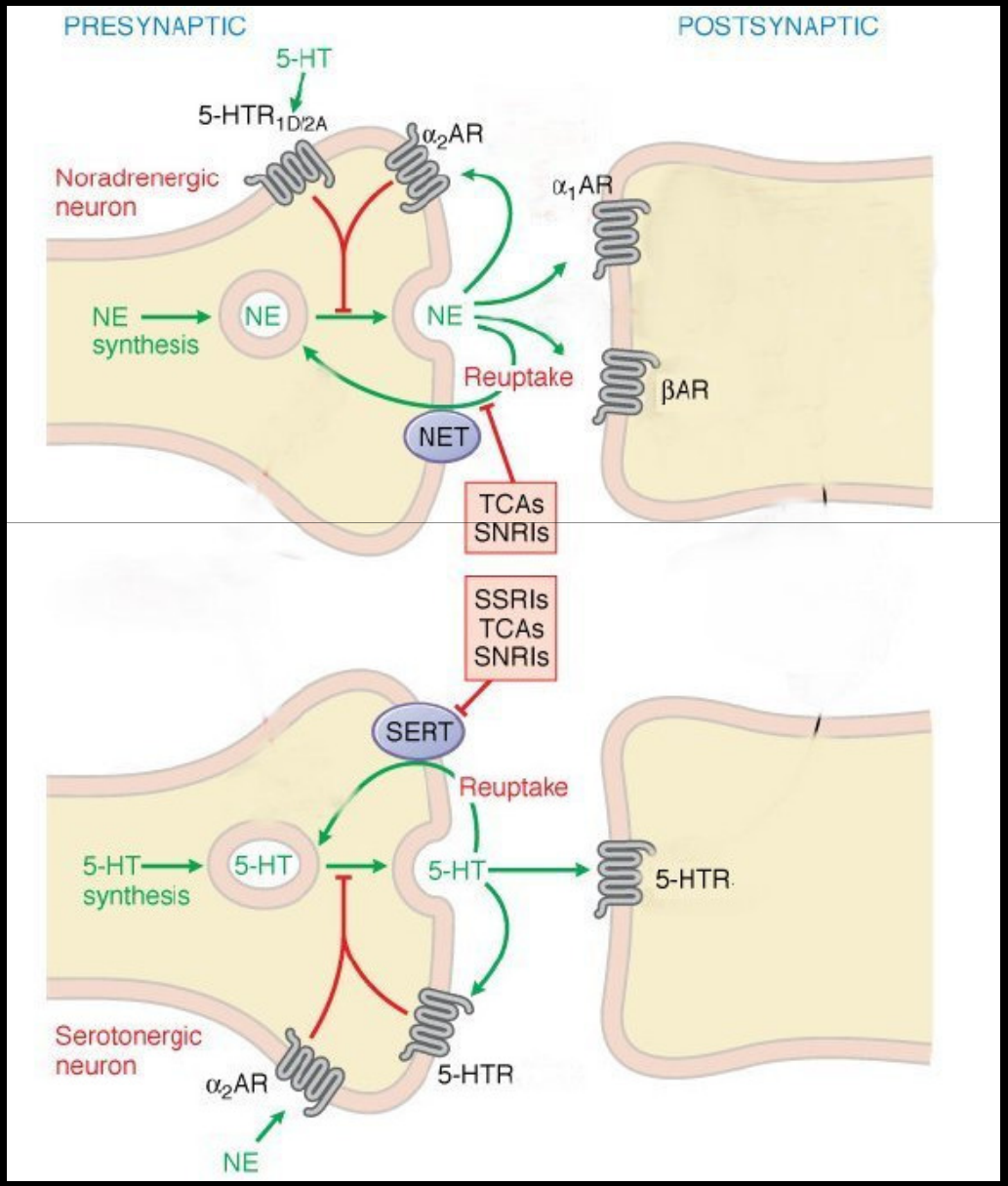
SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS

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



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  e.g. **bupropion**, **reboxetine**

- Monoamine receptor antagonists

  e.g. **mirtazapine**, **trazodone**, **mianserin**