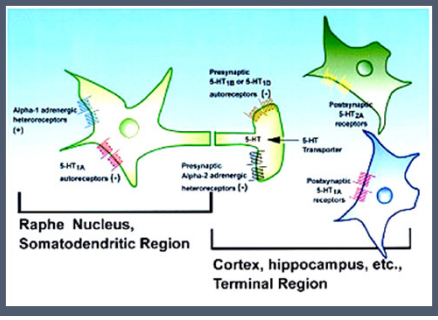
DEPRESSION



Dr K Outhoff

Basic Principles

- Common, debilitating, life-threatening, often chronic medical disease
- 15% of severely depressed people will ultimately commit suicide
- Diagnosis often missed / dismissed
- Depression can be treated successfully – recovery is the rule, not the exception
- Risk of recurrence is significant: 50% after 1st episode, 75% after 2 episodes, 90% after 3 episodes
- Aim of treatment is complete remission –getting and staying well
- Treat acute episodes, prevent future episodes by continuing medication at full dose for 6-12 months after remission
- Not possible to predict who will and who will not respond to a given antidepressant drug
- Onset of action of drugs typically 2-4 weeks
- Noradrenaline and serotonin and their receptors are key to understanding the pathophysiology of depression

Biological Basis of Depression Monoamine hypothesis

Deficiency / depletion of the monoamine neurotransmitters:

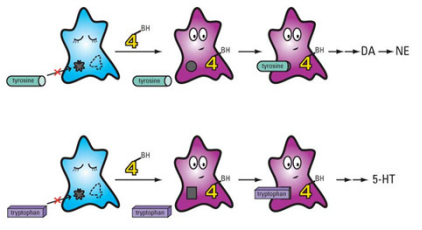
- Catecholamines: Noradrenaline (and its precursor, Dopamine)
- Noradrenaline:
  - is created by enzymes in nerve terminal (tyrosine, DOPA, DA)
  - Stored in storage vesicles
  - Released into synapse
  - Binds to post synaptic alpha-1 and beta receptors to exert its effects
  - Action terminated
    - by destructive enzymes:
      - MAO (mitochondria in pre-synaptic neuron)
      - COMT (largely outside neuron)
    - Re-uptake pump into presynaptic neuron
    - Bind to pre-synaptic alpha-2 autoreceptors and alpha-2 heteroceptors (negative feedback)

Monoamines

Indolamine: 5HT (serotonin)

- Synthesised in nerve terminals (tryptophan, 5HTP, 5HT)
- Stored in vesicles
- Released into synapse
- Bind to post-synaptic receptors (5HT1-5HT5) to exert its effects
- Action terminated
  - Destroyed by enzyme, MAO
  - Re-uptake pump
  - Bind to pre-synaptic 5HT-1a (terminal) and 5HT-1d (somatodendritic) autoreceptors (negative feedback)

FIGURE 3.
BH4 co-factor for trimonoamine neurotransmitter synthesis[48]



BH4=tetrahydrobiopterin; DA=dopamine; NE=norepinephrine; 5-HT=serotonin.

Stahl SM. *Essential Psychopharmacology.* 3rd ed. New York, NY: Cambridge University Press. In press. Reproduced with permission. Copyright Neuroscience Education Institute.

Stahl SM. *CNS Spectr.* Vol 12, No 10. 2007.

Neurotransmitter Receptor Hypothesis of Depression

- Something is wrong with the receptors for the monoamine neurotransmitters (NA, DA, 5HT)
- Deficiency of neurotransmitter causes compensatory up-regulation of post-synaptic receptors. ie. they proliferate
- Antidepressants eventually cause a down-regulation (decreasing numbers or desensitising) of key neurotransmitter receptors (hence delayed onset of action of antidepressants)

Theories combined

Immediate pharmacological action of antidepressants:

- Increase noradrenaline and/or serotonin and/or dopamine

Delayed pharmacological action of antidepressants:

- Down-regulation of post-synaptic receptors, especially
  - Beta-1 receptors (noradrenergic pathways)
  - 5HT-1 receptors (serotonergic pathways)

Antidepressant Drugs

1. Monoamine Oxidase Inhibitors (MAOI)
2. Tricyclic Antidepressants (TCA)
3. Serotonin and Noradrenaline re-uptake Inhibitors (SNRI)
4. Noradrenergic and specific Serotonergic Antagonists (NaSSA)
5. Selective Serotonin Re-uptake Inhibitors (SSRI)
6. Noradrenaline re-uptake Inhibitors (NARI)
7. Other

How do antidepressants work?

1. Increase synaptic serotonin levels:
   - SSRI (fluoxetine, escitalopram, paroxetine, etc)
2. Increase synaptic noradrenaline levels:
   - NARI (reboxetine)
3. Increase both serotonin and noradrenaline: (dual acting)
   - TCAs (amitriptyline, imipramine, lofepramine, etc)
   - SNRI (venlafaxine, duloxetine)
   - NaSSA (mirtazapine)
4. Inhibit breakdown of serotonin and noradrenaline:
   - MAOIs (phenelzine, tranylcypramine)
   - RIMA (moclobemide)
5. Agonists of serotonin 5HT1 receptors:
   - Agomelatine

Mono-amine Oxidase Inhibitors (MAOI)

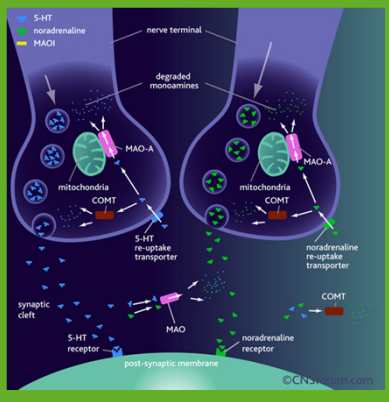
- Classical MAOIs - irreversible and non-selective:
  - Phenelzine
  - Tranylcypromine
  - Isocarboxacid
- RIMAs – reversible inhibitors of MAO –A:
  - Moclobemide
- Selective Inhibitors of MAO-B:
  - Selegiline (Parkinsons)

MAOIs

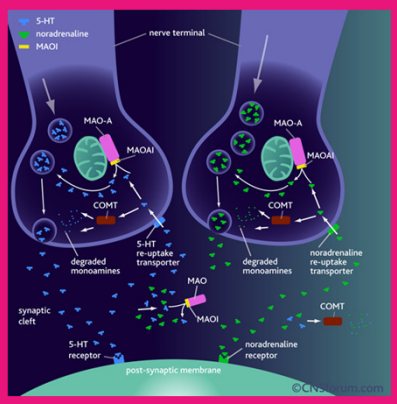
Therapeutic action:

- increase intracellular NA, 5HT, dopamine by inhibiting their breakdown
- Neurotransmitters escape into synapse
- Ultimate down regulation of receptors

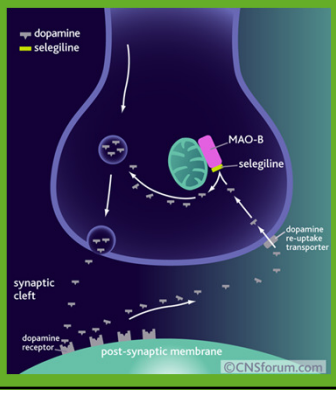
MAOI -physiology



Mechanism of Action of MAOIs



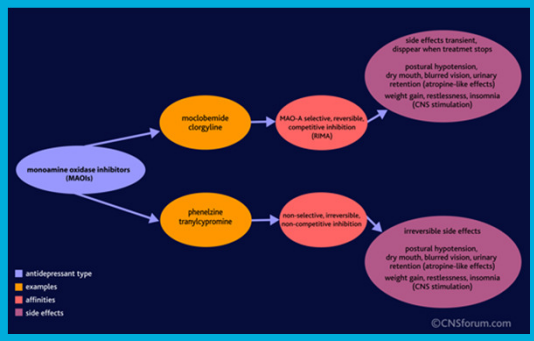
MAOI – B and Parkinsons Disease



MAOIs
adverse effects

- CNS stimulation:
  - Tremors
  - Excitement
  - Insomnia
  - Convulsions
- Increased appetite and weight gain
- Antimuscarinic:
  - Dry mouth
  - blurred vision
  - Urinary retention
  - Constipation
- Severe hepatotoxicity

MAOI



MAOIs
Interactions with drugs and food

1. Fermented Cheese reaction:
   - Tyramine containing foods
   - Usually metabolised in Gut wall by MAO
   - Little reaches circulation.
   - With inhibition of MAO, tyramine is absorbed into the circulation
   - Sympathomimetic effect
     - Acute hypertension
     - Throbbing headache
     - Intracranial haemorrhage
   - Culprits
     - Cheese
     - yeast containing products like marmite
     - Indirectly acting sympathomimetics (ephedrine, amphetamines)
     - TCA

MAOIs
Interactions with drugs and food

2. Pethidine
   - Severe hyperpyrexia
   - Restlessness
   - coma

Tricyclic Antidepressants

- Clomipramine
- Imipramine
- Amitriptyline
- Nortriptyline
- Protriptyline
- Maprotiline
- Amoxapine
- Doxepin
- Desipramine
- Trimipramine
- Lofepramine

Tricyclic Antidepressants multi-potent blockers

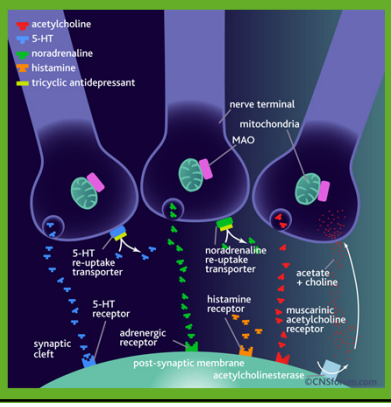
Therapeutic action:

1. Block the re-uptake pumps of Noradrenaline and Serotonin

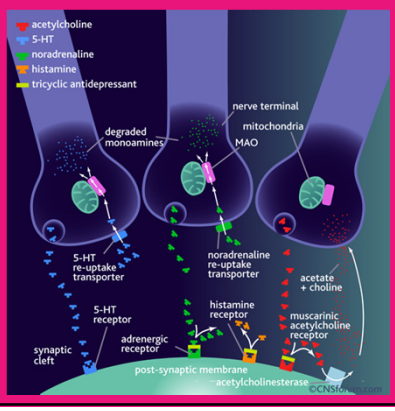
Side effects:

1. Block muscarinic cholinergic receptors
   - Dry mouth
   - Blurred vision
   - Urinary retention
   - Constipation
2. Block H1 histamine receptors
   - Sedation
   - Weight gain
3. Block alpha-1 receptors
   - Orthostatic hypotension, dizziness
   - Reflex tachycardia

TCA - therapeutic effects



TCAs adverse effects



TCAs other adverse effects

Lethal in overdose – assess suicide risk

- CNS
  - Excitement
  - Delirium
  - Coma
  - Respiratory depression
  - Antimuscarinic effects
- Cardiotoxic
  - Ventricular arrhythmias
  - Prolongation of QT interval
  - Sudden death
- Pro-convulsant

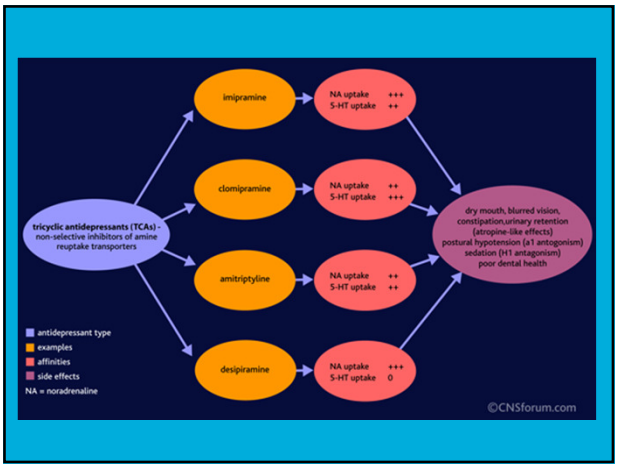
TCAs Drug interactions

- Potentiate effects of alcohol and may cause severe respiratory depression
- Fluoxetine and paroxetine inhibit TCA metabolism

TCAs pharmacokinetics

- Rapid absorption
- Protein binding high
- Large Vd
- Hepatic metabolism
- Metabolites often active
- Long half lives esp. In elderly (accumulation)
- Excreted in urine

- Start low dose, increase dose every 3-7 days to allow adjustment to adverse effects
- target dose to minimum of imipramine 125mg dose equivalence
- Limit total amount to reduce risk of overdose



Selective Serotonin Re-uptake Inhibitors (SSRI)

- Fluoxetine
- Paroxetine
- Citalopram
- Escitalopram
- Sertraline
- Fluvoxamine

Advantages of SSRIs

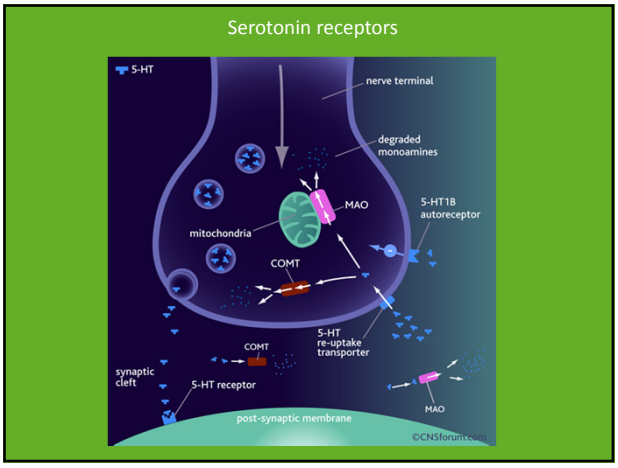
- Now most widely prescribed antidepressants in the world – experience and data available
- Much improved safety and tolerability
  - Not necessarily lethal in overdose
  - Acceptability of long term treatment better
  - Compliance higher
- Breadth of therapeutic profile
  - Depression (prefrontal cortex pathway)
  - Panic disorder (limbic cortex and hippocampus pathway)
  - Obsessive compulsive disorder (basal ganglion pathway)
  - Bulimia (hypothalamic pathway)
  - Social phobia, PTSD, Pre-menstrual dysphoria, Migraine

- But ? As effective as dual acting anti-depressants in severe depression
- To be avoided in children under 18 years (increase suicidal ideation)

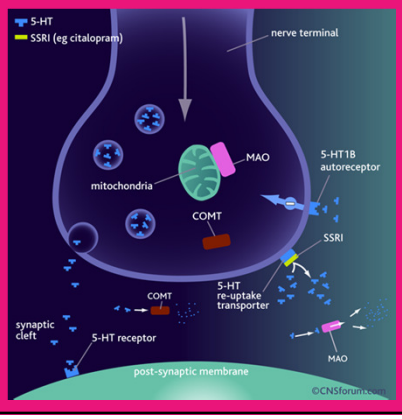
SSRI

<u>Therapeutic action: antidepressant, anxiolytic:</u>

- Blocks re-uptake of serotonin
- 5HT-1 receptor stimulation and ultimate down-regulation



SSRI m.o.a



Effects of stimulating other 5HT receptors – adverse effects of SSRIs

5HT-2	5HT-3
Agitation Akathisia Anxiety Panic attacks Insomnia Sexual Dysfunction	Nausea (CETZ) Diarrhoea (gut wall) Headache

SSRIs

- All taken orally
- All inhibit CYP 2D6 to varying degrees
- Paroxetine inhibits its own metabolism
- Fluoxetine has an active metabolite (norfluoxetine), therefore long half life
- Withdrawal effects common, esp. with paroxetine

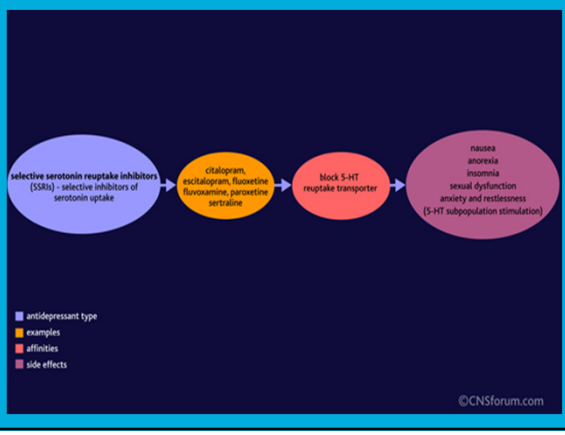
SSRIs

- Usual maintenance dose is the starting dose
- Usual onset of antidepressant response is 2-4 weeks
- Usual onset of adverse effects more immediate
- Target symptoms do not worsen initially
- Usual response is a complete response

Serotonin Syndrome

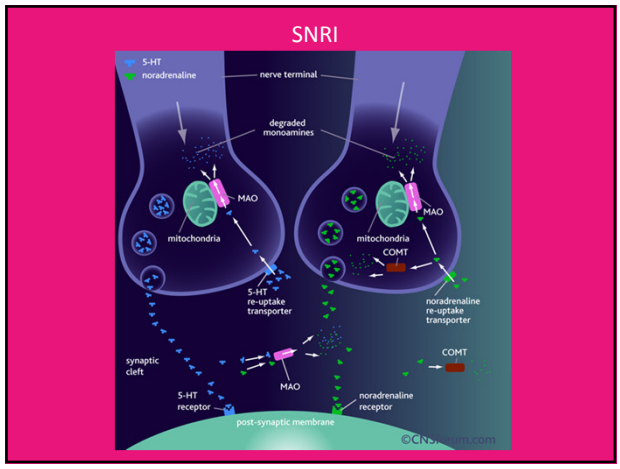
- Tremor
- Hyperthermia
- Cardiovascular collapse
- Death
- Usually in association with MAOIs, TCA's, other SSRI's

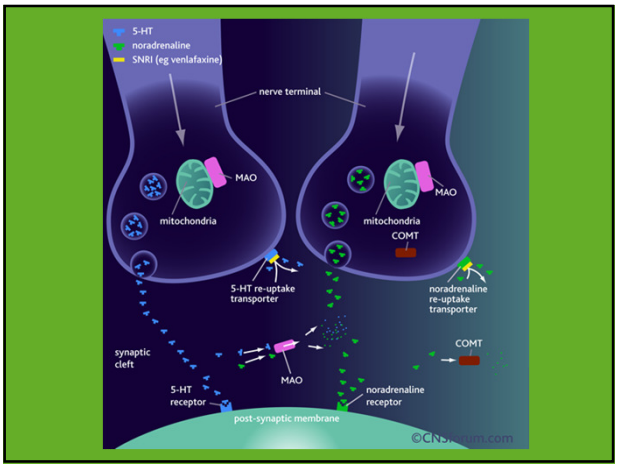
SSRI



SNRI Venlafaxine

- Serotonin and Noradrenaline re-uptake inhibitor ie dual acting antidepressant
  - Inhibits 5HT re-uptake at lower doses
  - Inhibits 5HT and NA re-uptake at higher doses
  - Inhibits 5HT and NA and Dopamine re-uptake at even higher doses
- Dose titration possible to v. high doses
- Adverse effects similar to SSRIs
- Withdrawal effects prominent





NaSSA Mirtazapine

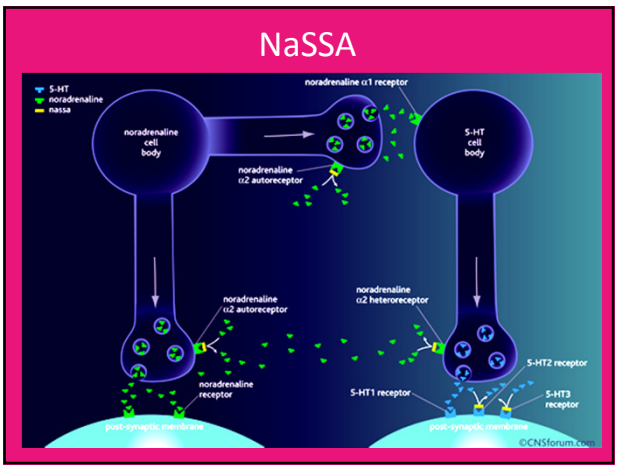
Noradrenergic and Specific Serotonergic Antidepressant

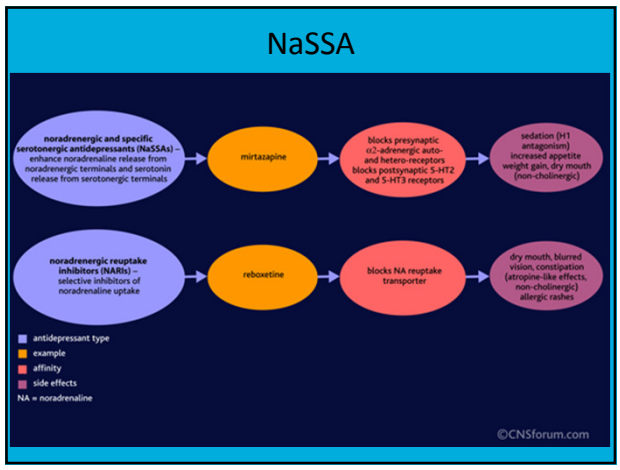
Therapeutic action:

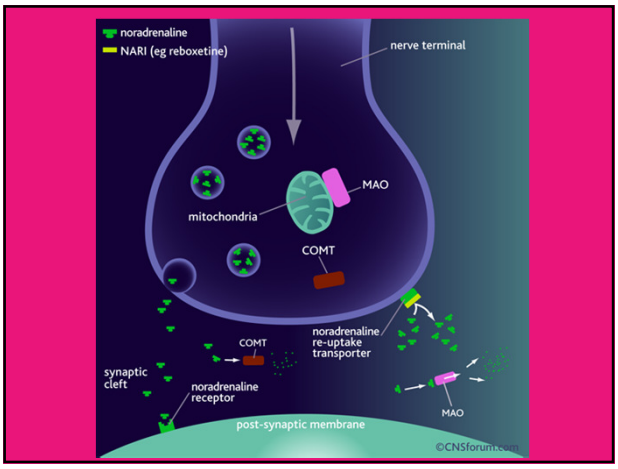
- Alpha-2 inhibition (pre-synaptic)
- 5HT2 and 5HT3 blockade

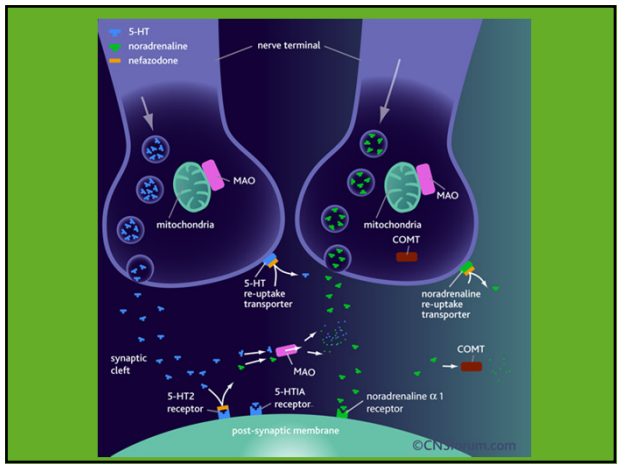
Adverse effects:

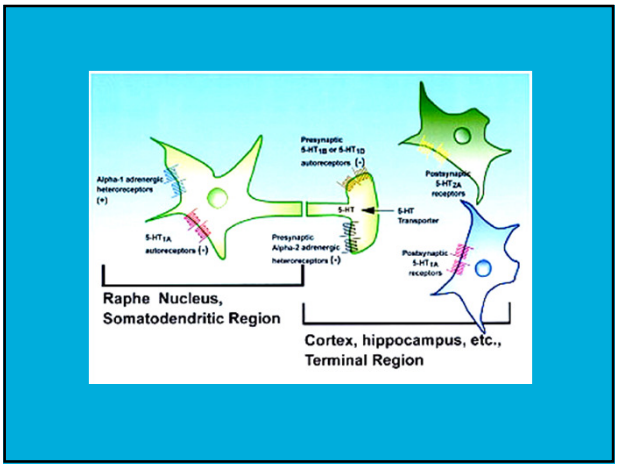
- Histamine H1 blockade
  - Sedation
  - Weight gain











Mood stabilisers - Lithium

- Prophylactic control of mood swings in Bipolar Affective Disorder
- Given over long periods (years)
- Onset of action: 3-4 weeks
- May be used as an adjunct in depression
- Narrow therapeutic window: 0.5-1.0mmol/l
- Long duration of action
- Mimics Na, enters voltage gated Na channels, generating action potential
- not pumped out of cell by Na/K ATPase
- Therefore low intracellular K

Lithium

therapeutic effects related to second messenger systems, which alter signal transduction pathways

Inhibition of inositol monophosphatase:

- Depletion of phosphatidyl inositol
- Diminished ITP
- Diminished receptor effects

Inhibition of glycogen synthase kinase:

- Phosphorylates key enzymes involved in apoptosis and amyloid formation

Lithium toxicity

- Nausea, vomiting, diarrhoea
- Cerebellar:
  - tremor
- Renal:
  - Nephrogenic Diabetes insipidus (inhibition of antidiuretic hormone)
  - Na retention (increased aldosterone secretion)
  - Renal failure
- Thyroid enlargement (hypothyroidism)
- Weight gain

Acute toxicity: 3-5mmol/l

- confusion, motor impairment, , coma, convulsions, death
- May be precipitated by diuretics (reduced proximal tubular reabsorption)

Other mood stabilising drugs

Anticonvulsants:

- Carbamazepine
- Oxcarbazepine
- Valproate: most frequently prescribed drug for BAD in USA
- Lamotrigine
- (Gabapentin + Topiramate: sparse evidence)

Antipsychotics:

- Olanzapine

Depression: acute treatment

Antidepressants are the first line treatment for moderate to severe depression irrespective of environmental factors and depression type.

First line drug therapy: Drugs well tolerated and safer in OD:

- SSRIs and other newer antidepressants

Second line:

- TCAs

Third line: Specialist

- MAOIs

Severe illness:

- Dual acting antidepressant
- TCA, Venlafaxine

Psychotic depression:

- Combine with antipsychotic

Treatment failure / resistance options

1. Dose increase
2. Switching antidepressants
    1. Within class: no washout
    2. Between class: consider washout period
3. Augmentation / combination therapy
    1. Other antidepressants
    2. Lithium
    3. Lamotrigine etc

Stopping treatment

- Minimum period of four weeks taper required
- Some patients require months of tapering
- If discontinuation reaction occurs, restart antidepressant and taper down more slowly.
- For SSRIs and Venlafaxine, consider switching to fluoxetine which can then be stopped after discontinuation symptoms have subsided

Special considerations Age

- Increased incidence of deliberate self harm in adolescents and young adults
- Decreased tolerability in the elderly
- High risk of relapse in elderly who have co-morbid medical illness

Special considerations Comorbid medical illness

- Increasing severity of comorbid conditions associated with a greater risk of depression relapse
- Drug-drug interactions
- Avoid TCAs in those at high risk of cardiovascular disease, arrhythmias, cardiac failure
- Acute coronary syndromes: best to use SSRIs, mirtazapine, bupropion
- Bleeding disorders: do not use SSRIs
- Patients on Aspirin / NSAIDs: do not use SSRI

Special considerations
Pregnancy and breastfeeding

- Choose antidepressant with most evidence for lack of adverse outcomes in foetus
  - TCA
  - SSRIs
  - But avoid paroxetine
- Breastfeeding:
- Drugs which do not accumulate in baby:
  - Sertraline
  - Nortriptyline
  - Avoid fluoxetine, citalopram, Lithium