Depression

Types

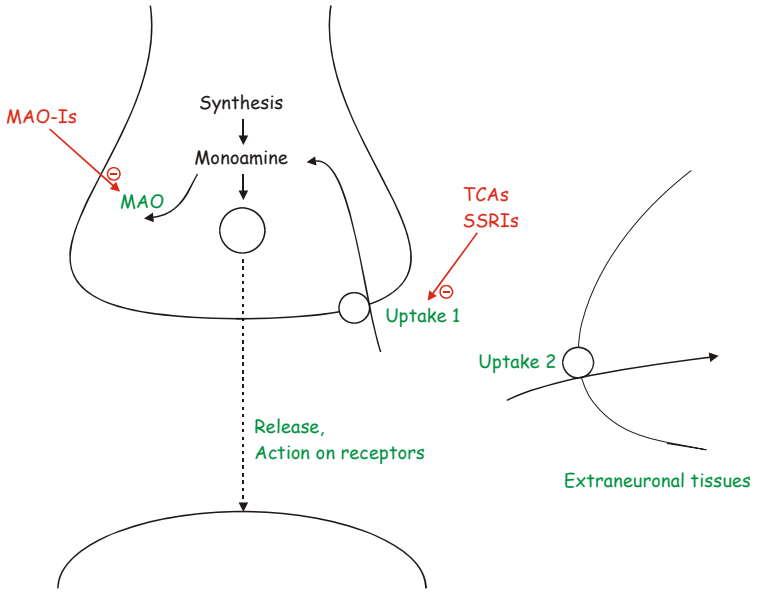
- Unipolar
  - Cut-off: 'major depressive episode' has 5 out of 8 ICD-10 criteria over a 2 week period
- Bipolar
  - Bipolar I disorder: major depressive episodes + manic episodes (3 out of 9 ICD-10 criteria plus >1 week or admission)
  - Bipolar II disorder: major depressive episodes + hypomanic episodes (3 out of 9 ICD-10 criteria plus >4 days)
  - Cyclothymic disorder: chronic mood fluctuations of hypomania and of depression insufficient to meet major depression criteria

Pathophysiology: monoamine hypothesis of depression

The dominant neurochemical theory of depression.

Proposes that depression is caused by functional underactivity of monoamine (NorAdr and 5HT) systems.

Antidepressants are thought to rectify this imbalance by
- Preventing re-uptake of monoamines from the synaptic cleft (TCAs, SSRIs)
- Preventing catabolism of monoamines in neurones and glia (MAOIs)



Evidence
- Low levels of monoamines in CSF and post-mortem specimens of depressed patients
- Effectiveness of typical antidepressants, which are known to affect monoamine levels

Limitations
- Does not explain the mode of action of atypical antidepressants, which do not act by the above mechanisms
  - Reconciliation: possible action on presynaptic adrenoceptors (autoreceptors) modulates release (e.g. mianserine)
- Does not explain delay between starting drug and clinical onset of action
  - Reconciliation: possible need to overcome compensatory feedback changes (e.g. β-receptor supersensitivity), or slow adaptive changes downstream of the monoamine systems

Differences between individual antidepressants of the same class are attributed to
- Differences in relative impact on NorAdr/5HT
- Differences in localisation of effect

Drug classes

Tricyclic antidepressants (TCAs)
Structural analogues of phenothiazines

Classification

Drug	Sedative effect
Dothiepine	More
Trazodone	↓
Amitriptyline	↓
Imipramine	Less
Lofepramine	None, but weakest effect

Indications
- Unipolar depression
- Chronic pain syndromes (low dose)
- Nocturnal enuresis in children

Mechanism of action
- Inhibit re-uptake of NorAdr and 5HT by uptake 1 into presynaptic neurones
    - Uptake of NorAdr is effectively blocked at therapeutic doses
    - Uptake of 5HT is only partially blocked at high doses

Adverse effects
- Anticholinergic: dry mouth, blurred vision, mydriasis, acute glaucoma, tachycardia, constipation, urinary retention, erectile impotence
- Antiadrenergic: postural hypotension
- Antihistaminergic: sedation. 'Drugged' feeling for first few days. Affects compliance, so warn patient and say that transient. Recurs when dose is raised.
- Quinidine-like action: arrhythmias, long QT, -vely inotropic
- Lowered seizure threshold
- Weight gain

Contraindications
- Myocardial disease
- Epilepsy
- Suicide risk (overdose fatal through cardiac effects and convulsions)

Interactions
- MAOIs
- Potentiation of catecholamines and sympathomimetics
- Potentiation of methyldopa; other antihypertensives safe

Note
- Choice of agent depends on secondary psychotropic action: most TCAs are sedative, few are stimulant
- Lofepramine does not cause postural hypotension

Selective serotonin re-uptake inhibitors (SSRIs)
Classification

Fluoxetine/Prozac®	More stimulating
Sertraline/Lustral®	
Paroxetine/Seroxat®	More sedating
Citalopram/Cipramil®	

Mechanism
- The name says it; effect on NorAdr re-uptake is minimal at therapeutic doses

Comparison with TCAs

Advantages

- Better side-effects profile
- Safer in cardiovascular disease
- Safe in overdose
- Less likely to cause weight gain
- Original scare of paradoxical increase in suicide risk has not been substantiated

Disadvantages

- Smaller dose range
- Expensive (under license)

Choice depends on

- Age
- Likely ability to tolerate side-effects/likely compliance
- Cardiovascular disease
- Suicide risk
- Patient expectation (e.g. patients may demand Prozac or be demoralised by its stigma)
- Cost differential has decreased
    - 1 month amitriptyline 75mg £2.16
    - 1 month fluoxetine 20mg £7.72

Adverse effects

- Nausea, due to 5HT potentiation in the CTZ/vomiting centre
- Headache
- Sexual dysfunction
- Sleep disturbance (early)
- Weight loss (except paroxetine)
- ↓glycaemic control (fluoxetine)
- SIADH (fluoxetine)
- Impotence, ejaculatory failure

Contraindication

- Epilepsy

Note

- Citalopram: less P_{450} interaction, important in elderly

Monoamine oxidase inhibitors (MAOIs)

Classification

Hydrazines

- Phenelzine (non-selective)

Non-hydrazines

- Tranylcypromine (non-selective)
- Moclobemide (MAO-B selective)
- Selegiline (anti-Parkinsonian, MAO-B selective)

Mechanism

- Inhibition of MAO (see Parkinson's disease for details)
    - Irreversible except for moclobemide and tranylcypromine
- Non-hydrazine group: resemble amphetamine and thus have an indirect sympathomimetic effect

Adverse effects

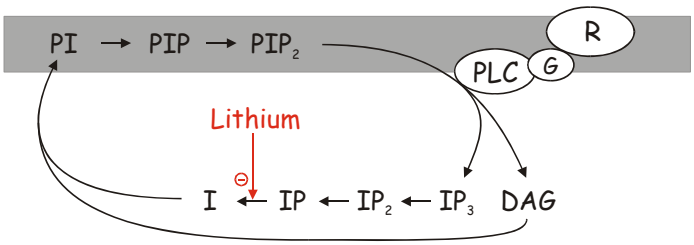
- Postural hypotension (sympathetic ganglion blockade)
- Hypertensive crisis with co-administered sympathomimetics
    - MAO in gut and liver normally protects against exogenous sympathomimetics by a strong first pass effect. MAOIs remove this protection.
        - Sympathomimetics include mature cheese (contains tyramine; hence dubbed 'cheese reaction'), broad beans, red wine, Marmite etc.
        - Moclobemide is safer: its reversible blockade of MAO can be surmounted

        - Note that hypertensive crisis can occur although the patient may have postural hypotension initially
    - α-mediated vasoconstriction → severe throbbing headache, hypertension
    - β-mediated cardiac stimulation → slow palpitations
    - Treatment
        - α-blockade ± β-blockade (only *after* α-blockade)
        - Consider vasodilatation with e.g. CCB
- Agitation
- Tremor
- GI disturbance

Indications
- Third-line to TCAs/SSRIs
- Atypical depression
- Hypochondriacal features
- Resistant phobic states

Atypical antidepressants
- Serotonin and noradrenaline reuptake inhibitor (SNRI): venlafaxine
    - SE: nausea, HT, exacerbation of CV disease, wt loss
- Noradrenaline reuptake inhibitor (NARI): reboxetine
- Noradrenergic and specific serotonergic antidepressants (NaSSA): mirtazepine
    - Good for sleep
    - SE: weight gain
- 5-$HT_{2,3}$ antagonists and reuptake inhibitors (SARI): trazodone (*very* good for sleep – sleep is mostly 5-HT controlled, 5-HT stimulation disturbs sleep)

Lithium
Mechanism
- CNS
    - Inhibition of inositol monophosphatase
        - Reduces synthesis of phosphatidylinositides (IP_3/DAG), which are involved in intracellular calcium regulation



    - Partial depolarisation
        - Enters cells through Na^+ channels, but poorly pumped out by Na^+/K^+-ATPase → accumulates → partial loss of potassium → partial depolarisation → facilitated 5-HT and NA release
- Kidney, thyroid
    - Interference with cAMP-linked receptors underlies adverse effects

Indications
- Control of acute mania in conjunction with a neuroleptic (lithium itself has too slow an onset of action)
- Prophylaxis of chronic bipolar depression
- Augmentation

Administration
- Only used under specialist guidance
- Taken PO, excreted renally
- Linear dose-related increase in plasma levels

Pre-initiation screening

- Check thyroid function (induces hypothyroidism)
- Check renal function (causes ADH resistance and thus polyuria)
- Check for pregnancy (teratogenic)

- Serum levels are first monitored weekly, then every 3 months
- Thyroid and renal function tests every 6 months

- Plasma levels decreased by antacids, theophylline, acetazolamide
- Risk of toxicity increased by diuretics, NSAIDs; or antidepressants, antiepileptics, antipsychotics

Interactions
↑level with ACE-Is, diuretics, NSAIDs

Adverse effects
Very narrow therapeutic range
- 0.5-1.0 mmol/l
- 1 – therapeutic, 2 – toxic, 3 – lethal

Early
- Fine tremor
- Dry mouth, metallic taste
- Weakness, fatigue

Later
- Nephrogenic polyuria/polydipsia; interstitial nephritis
- Hypothyroidism
- Teratogenicity (controversial)
- Impaired memory
- Hypokalaemia, hypercalcaemia
- Weight gain

Toxicity
- Coarse tremor
- Slurred speech (dysarthria), ataxia
- Renal failure, cardiovascular collapse
- D&V
- Confusion, hyperreflexia, convulsions, coma

- Treatment: cessation of lithium, forced diuresis (IV mannitol), haemodialysis and peritoneal dialysis

Contraindications
- Thyroid, renal, cardiac disease
- Addison's
- Pregnancy, breastfeeding

Antiepileptics
E.g. carbamazepine, valproate; can be combined.

Indications
- Augmentation
- Esp. cyclic bipolar, lithium intolerance

Adverse effects/contraindications
- See epilepsy

Thyroxine
Also used for augmentation.

Principles of treating depression

Diagnosis
Consider

- Is the depression an 'illness' or 'normal unhappiness'?
    - Beck's triad
        - Pervasive lowering of mood
        - Anhedonia
        - Negative thinking
    - Physical symptoms
    - Also consider ICD-10 criteria
- If it is an illness:
    - How severe is it?
    - Are there psychotic features such as delusions or psychomotor retardation?
    - Is it a primary psychiatric disorder or secondary to a physical illness, alcohol or drugs which may themselves be amenable to treatment?
    - If it is a primary psychiatric illness, is it unipolar or bipolar?

The answers to the above questions enable a decision to be made regarding:

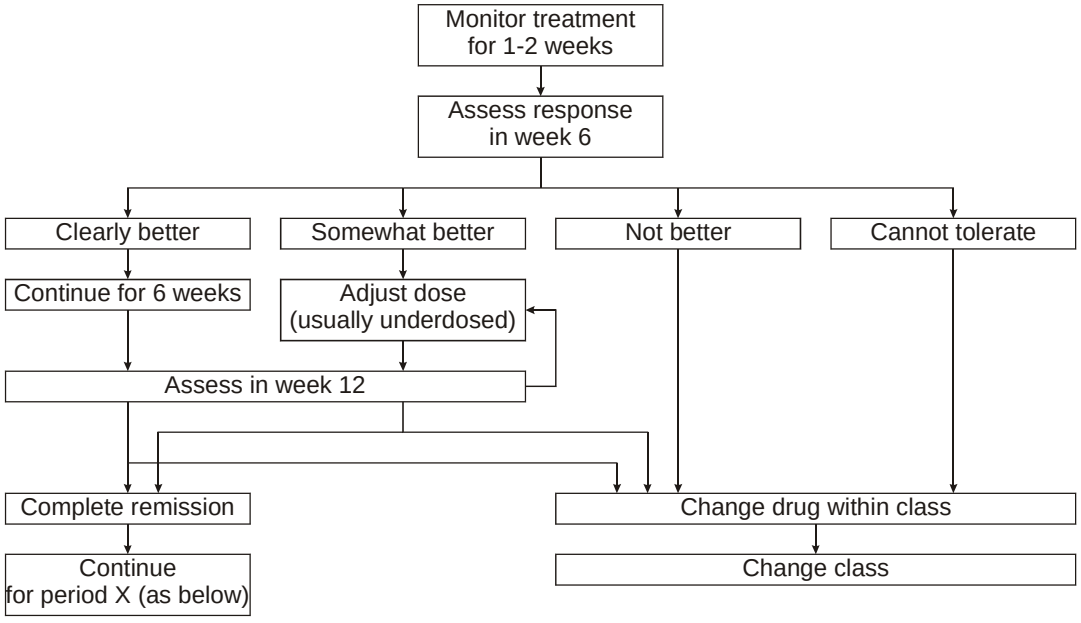
- Consider potential causes: β-blockers, CCBs, steroids, OCP
- Is any treatment indicated?
- If treatment is indicated:
    - Should treatment involve antidepressants/lithium/ECT/psychotherapy?
    - Is hospital referral required?

Initiating pharmacological therapy
Consider

- Initial choice of therapy lies between TCAs and SSRIs
    - Advantages/disadvantages as above
- Likely to be drug-responsive if normal pre-morbid personality, biological Sx
- Always consider indication for ECT

Start with a low dose and rapidly escalate over a week while monitoring side-effects

- This empirical approach is necessary due to marked differences in bioavailability between individuals



Failure to respond
Allow adequate time before considering a change in medication.

- TCAs better than SSRIs in resistant cases
- If unresponsive after ≥2 trials of antidepressants, consider referral for
    - MAO-Is, esp. if atypical (phobic, hysterical)
    - Augmentation with lithium/antiepileptics/T_4
    - ECT
- Never forget: psychiatric conditions have biopsychosocial origins, hence Rx should mirror this (antidepressants, psychotherapy, address situation)

Duration of pharmacological therapy
Duration of treatment depends on the number of episodes and the age of the patient.

	Age <40	Age 40-50	Age >50
First episode	6-9 months	6-9 months	Indefinitely
Second episode	6-9 months	4-5 years	Indefinitely
Second episode with complications	4-5 years	Indefinitely	Indefinitely
Third+ episode	Indefinitely	Indefinitely	Indefinitely

Withdrawal of treatment

- Remember about half of patients with a depressive illness will never have a further episode
- Natural history of reactive depression is to improve in 3-4 months
- Withdrawal should be gradual and patient monitored for symptom recurrence

Inability to tolerate side-effects

- TCAs differ in their side-effect profiles with regard to
    - Sedative or stimulant action
    - Anticholinergic effects
- Could substitute for another TCA or change to a SSRI, which generally lack such effects