

Terminology and categorization

Affect is emotional 'weather': the state right now. Mood is emotional 'climate': the recent average.

Abnormal mood states include depressed mood, elevated mood (termed hypomania when mild and mania when severe), and a curious thing called a mixed affective state that is a mixture of mania and depression.

Depression can come and go over a person's lifetime, and sometimes it alternates with mania, as part of bipolar affective disorder. More commonly, depression just occurs (and recurs) on its own; this is termed unipolar depression.

Under the ICD-10 classification system (used by most people except Americans and researchers), depression occurs as an 'episode' (i.e. the patient has depression now):

- depressive episode (further categorized as mild/moderate/severe)

You can have a one-off depressive episode, but depression is also the (or a) major feature of the following psychiatric diseases:

- recurrent depressive disorder
- bipolar affective disorder, current episode depressed

and

- organic depressive disorder (... due to a whole bunch of things such as hypothyroidism, Cushing's...)

plus a few rarer things, such as:

- schizoaffective disorder (a sort of no-man's-land between schizophrenia and bipolar affective disorder)

If the patient's gloomy but doesn't meet the criteria for depression, they may have:

- nothing much wrong;
- dysthymia (chronically low mood but not meeting the criteria for depression);
- cyclothymia (mood goes up and down gradually but mildly; a sort of not-quite-bipolar disorder);
- an emotionally unstable personality disorder (in which affect can bounce up and down very rapidly indeed: whereas bipolar affective disorder is considered 'rapid cycling' if ≥ 4 mood episodes occur in a year, in emotionally unstable personality disorders, mood can go up and down over minutes or hours);
- an adjustment reaction (recently bereaved, etc.).

Depression can co-occur with a host of other problems, and the boundaries can become blurred (e.g. a prolonged adjustment reaction can shade into depression; a person with an emotionally unstable personality disorder can have episodes of depression). It's important not to miss depression just because you can sympathise with the cause (e.g. they've just been diagnosed with lung cancer; you might think 'I'd be depressed too', but that's no reason not to identify and treat persistent depression).

In DSM-IV (the American system), things are much the same but there are *major depressive episodes* and disorders such as *major depressive disorder (single episode)* and *recurrent depressive disorder*. The Americans also make the useful distinction between

- bipolar I disorder (the patient has had a manic [or mixed] episode at some point);
- bipolar II disorder (the patient has only had *hypomanic* episodes, plus a depressive episode at some point).

So to a first approximation: mania at some point = bipolar I; hypomania only = bipolar II. This distinction gets used in the UK quite a lot too.

We'll now concentrate on unipolar depression.

Epidemiology

The lifetime prevalence of major depressive episodes is approximately 12%, and approximately 4% of people will have a depressive episode this month [1]. This is much more common than bipolar affective disorder (lifetime prevalence about 1% for bipolar I disorder, and up to 5% for bipolar I+II) [1].

Mood disorders in general have low prevalence until early teenage years; there is then a roughly linear increase in prevalence until late middle age, and a more gradual increase thereafter, with the median age of onset of mood disorders ranging between 29–43 across countries [2].

Unipolar major depression is approximately twice as common in women than men (a difference beginning in early adulthood and persisting) [1].

Psychosocial stressors are risk factors for depression, but (obviously) the role of acute social stressors is relatively less in people with high genetic risk for mood disorders [1] (see also gene \times environment interactions below).

Mood disorders underlie 50–70% of suicides [1]. The lifetime risk of death by suicide has been estimated as ~15–20% for bipolar disorder and ~10% for other mood disorders [1]. Suicide accounts for ~1.5% of all deaths [3].

Neurobiology

Briefly... Drug development tells a story of the *monoamine hypothesis of depression* ('monoamines' referring to catecholamines [e.g. noradrenaline, dopamine] and indoleamines [serotonin = 5-hydroxytryptamine]).

- Reserpine is an antihypertensive that depletes amine stores; it precipitates depression [4].
- CSF 5-HT metabolites were found to be abnormal in people who committed suicide [5].
- Drugs effective for depression elevate monoamine levels (in a range of ways).

Some other evidence supports this; e.g. acute depletion of tryptophan (which reduces central 5-HT synthesis) lowers mood and can re-precipitate depression [6-8].

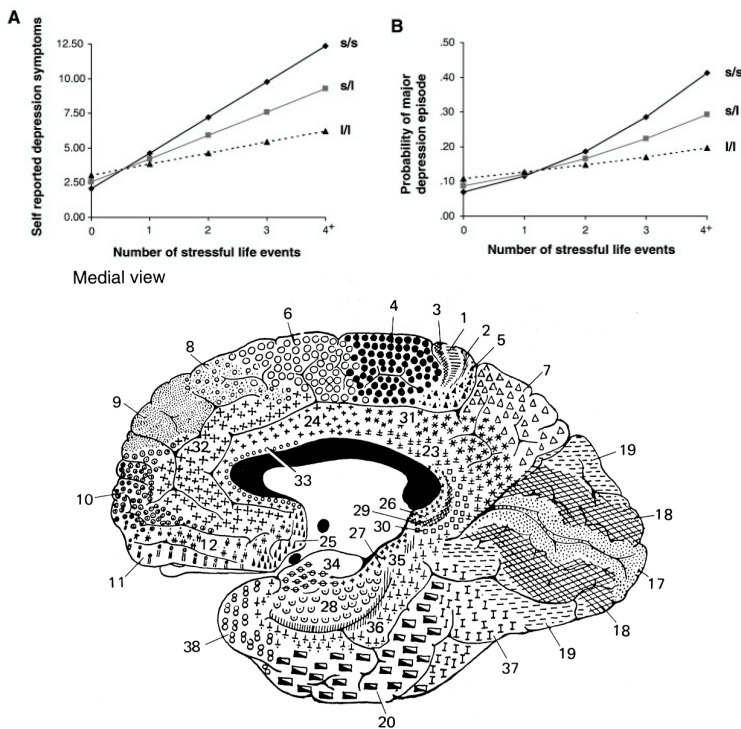
However, the story that 'depression is due to low serotonin' is not quite right.

- The pharmacological response to antidepressants (in terms of changes in synaptic monoamines) is rapid, but the clinical effect takes weeks. The reasons for this are still debated.
- No change in regional brain NA/DA/5-HT has been shown to be necessary and sufficient for depression [1].
- The view on CSF 5-HT metabolites has changed; maybe it's related to impulsive and violent behaviour, rather than depression [9].

More recently attention has focused on e.g. studies showing higher monoamine oxidase A (MAO-A) expression in depression [10, 11], though the overall chemical picture remains somewhat murky [12].

Part of the anterior cingulate cortex (ACC) is strongly implicated in the pathology of depression [13], as well as in the control of normal mood. Depressed show increased blood flow per unit volume in the ACC [14, 15]. Metabolic activity in the ACC is also unique in differentiating those depressed patients who eventually respond to antidepressant drug therapy from those that do not [16, 17]. If normal subjects think sad thoughts, metabolic activity increases here [18]. Hyperactivity of part of the ACC has been suggested to be a primary factor in sadness and depression.

Genetic predispositions to depression have been identified. Here's one that famously interacts a gene \times environment interaction:



Interaction of serotonin transporter (5-HTT) genotype with adverse life events in depression. 's', short allele (low transcriptional efficiency of the promoter); 'l', long allele (high transcriptional efficiency). From [19].

Brodmann's [20] areas of the human cerebral cortex. Abnormal activity in the part of area 24 below the genu (bendy bit at the front) of the corpus callosum, and area 25, both parts of the anterior cingulate cortex, is implicated in depression [14-18, 21].

Diagnosis

Depression is marked by persistent low mood, loss of interest and enjoyment in usually pleasurable activities (anhedonia), reduced energy, fatigue and fatigability, and diminished activity. Concentration, attention, self-esteem, and self-confidence are often reduced, and the patient may have ideas of guilt and unworthiness, bleak and pessimistic views of the future, ideas or plans or acts of self-harm or suicide, poor sleep, and poor appetite. Diurnal variation of mood is common (often worst in the morning), as is early-morning waking, psychomotor retardation or agitation, loss of appetite and weight, and loss of libido.

Probe questions for depression and mania

The following are adapted from the PSE (ninth edition) [22], and ICD-10 criteria [23]. Feel free to use your own phrasing.

Always ask about thoughts of suicide (suggested phrasings below). There is no evidence that asking about suicidality triggers suicidality [1].

Always ask about a history of mood elevation: bipolar affective disorder can be missed, and its presence influences treatment.

Depression

- **Do you keep reasonably cheerful or have you been very depressed or low-spirited recently?**
 - Have you cried at all?
 - When did you last really enjoy doing anything?
- **How do you see the future?**
 - Has life seemed quite hopeless?
 - Can you see any future?
 - Have you given up or does there still seem some reason for trying?
- **Have you lost interest or pleasure in things you typically enjoy?**
- **How has your energy been recently?**
- **Have you been getting exhausted or worn out during the day or evening, even when you haven't been working very hard?**

If core symptoms of depression:

- **Have you had any trouble sleeping recently?**
 - Establish bedtime, time of falling asleep, sleep pattern across the night, whether the patient wakes early (and why).
- **What is your opinion of yourself compared to other people?**
 - Do you feel better, or not as good, or about the same as most?
 - Do you feel inferior or even worthless?
- **What has your appetite been like recently?**
- **Has your weight changed during the past few months?**
 - ... by how much?
- **Do you feel guilty or that you are to blame for something?**
 - Do you tend to blame yourself at all?
 - If people are critical, do you think you deserve it?
- **What has your concentration been like recently?**
 - Can you read an article in the paper or watch a TV programme right through?
 - Do your thoughts drift off so that you don't take things in?
- **Have you felt agitated, or worried, or more irritable than usual recently?**
How do you show it?
- **Have you felt slowed down in your thoughts or movements?** Do things seem to be moving too fast for you?
- **Have you felt that life wasn't worth living?**
 - Did you ever feel like ending it all?
 - What did you think you might do?
 - Did you actually try?
 - Have you been thinking of ending your life recently?
 - Are you thinking about it now?
 - Have you thought about specific ways to end your life?
 - Do you have plans to do so?
 - Have you made any preparations?
 - Are there things that would prevent you from acting on those plans?
 - Do you want to end your life?
- **Have you been having other thoughts about death recently?**

The rest of the somatic syndrome:


- **Is the depression worse at any particular time of day?**
- (if applicable) **Does the depression or tension vary with your menstrual period?**
- **Do you feel that you have lost your emotions in some way?**
 - That you are empty of all feeling, incapable of reacting emotionally?
 - Is this a definite change, or have you always been like that?
- **Has there been any change in your interest in sex?**

Mania

- **Have you sometimes felt particularly cheerful and on top of the world, without any reason?**
 - Too cheerful to be healthy?
 - How long does it last?
- **Have you felt more easily irritated lately?**
- **Have other people commented on a change in you?**
- **Have you had difficulty concentrating lately, or felt easily distracted?**
- **Have you felt particularly full of energy lately, or full of exciting ideas?**
 - Do things seem to go too slowly for you?
 - Have you felt your thoughts racing?
 - Do you find yourself extremely active but not getting tired?
 - Have you felt specially healthy?
 - Have you felt restless?
- **Do you need less sleep than usual?**

- Have you been buying any interesting things lately?
- Have you developed any new interests recently?
- Have you been reckless or taken any risks lately?
- Have you become more sociable recently?
- Has there been any change in your interest in sex?
- Have you seemed super-efficient at work, or as though you had special powers or talents quite out of the ordinary?

Criteria

Let's use the ICD-10 system. **It's very helpful to know the 10 symptoms of depression (A and B below), and which are the core 3 (A below).** Criteria for mild/moderate/severe depression (2–4–6 total symptoms with 2–2–3 core symptoms) are also reproduced below. It's less vital to know the criteria for the somatic syndrome. 

DEPRESSION. ICD-10 criteria for depressive episodes. Headings in bold are written so to as to approach an acronym; plain text and other diagnostic criteria are taken from ICD-10 [23].

<i>A. Core symptoms (* = part of somatic syndrome)</i>	<i>Absent</i>	<i>Present</i>
Mood: depressed mood to a degree that is definitely abnormal for the individual, present for most of the day and almost every day, largely uninfluenced by circumstances, and sustained for at least 2 weeks.		
Anhedonia (*): loss of interest or pleasure in activities that are normally pleasurable.		
Energy: decreased energy or increased fatigability.		
<i>Total symptoms in category A:</i>		
<i>B. Other key diagnostic symptoms (* = part of somatic syndrome)</i>	<i>Absent</i>	<i>Present</i>
Sleep: sleep disturbance of any type.		
Worth: loss of confidence and self-esteem.		
Appetite (*): change in appetite (decrease or increase) with corresponding weight change.		
Guilt: unreasonable feelings of self-reproach or excessive and inappropriate guilt.		
Concentration: complaints or evidence of diminished ability to think or concentrate, such as indecisiveness or vacillation.		
Activity (*): change in psychomotor activity, with agitation or retardation (either subjective or objective).		
Death: recurrent thoughts of death or suicide, or any suicidal behaviour.		
<i>Total symptoms in category B:</i>		
<i>Total symptoms in categories A + B:</i>		
<i>C. Somatic syndrome of depression</i>	<i>Absent</i>	<i>Present</i>
Anhedonia (as above): marked loss of interest or pleasure in activities that are normally pleasurable.		
Psychomotor agitation/retardation ("activity" as above): objective evidence of marked psychomotor retardation or agitation (remarked on or reported by other people).		
Appetite (as above): marked loss of appetite.		
Weight (as above): weight loss (5% or more of body weight in the past month).		
Morning mood: depression worse in the morning.		
Unresponsive emotionally: lack of emotional reactions to events or activities that normally produce an emotional response.		
Libido: marked loss of libido.		
Early morning waking: waking in the morning 2 hours or more before the usual time.		
<i>Total symptoms in category C:</i>		
<i>General criteria for a depressive episode (F32)</i>	<i>False</i>	<i>True</i>
The depressive episode should last for at least 2 weeks. (<i>Diagnosis after a shorter period may still be reasonable if symptoms are unusually severe and of rapid onset.</i>)		
There have been no hypomanic or manic episodes in the individual's lifetime. (<i>If false, the diagnosis simply changes from a depressive episode to an episode of bipolar depression.</i>)		
The episode is not attributable to psychoactive substance use or organic mental disorder.		

- A **mild depressive episode** requires 2 symptoms from group A and a total of ≥ 4 symptoms from across groups A & B.
- A **moderate depressive episode** requires 2 symptoms from group A and ≥ 6 symptoms from across groups A & B.
- A **severe depressive episode** requires all 3 symptoms from group A and ≥ 8 symptoms from across groups A & B, or a clinical impression of "severe" in a patient with marked agitation or retardation who is unwilling or unable to describe their symptoms in detail.
- For **severe depressive episode without psychotic symptoms**, there must be no hallucinations, delusions, or depressive stupor.
- For **severe depressive episode with psychotic symptoms**, there may be any of these, other than "typically schizophrenic" symptoms.† ICD-10 is silent on what to call what appear to be depressive episodes with psychotic features of that kind; note that such symptoms can occur in severe depression with psychosis [24]. The depressive psychotic symptoms may be specified as **mood-congruent** or **mood-incongruent**.
- The **somatic syndrome** of depression requires 4 symptoms in category C.

MANIA AND HYPOMANIA. ICD-10 criteria for hypomanic and manic episodes. Layout as before. Some criteria are phrased almost identically for hypomania and mania, and have been combined below with the actual text shown [23].

<i>A. Core symptom of hypomania and mania</i>	<i>Absent</i>	<i>Present</i>
Mood: The mood is "elevated or irritable" [hypomania] or "predominantly elevated, expansive or irritable" [mania] to a degree that is definitely abnormal for the individual concerned.		
<i>B. Other symptoms of hypomania and mania</i>	<i>Absent</i>	<i>Present</i>
Distractible: difficulty in concentration or distractibility [from the criteria for hypomania]; distractibility or constant changes in activity or plans [from the criteria for mania].		
Activity: increased activity or physical restlessness;		
Sleep: decreased need for sleep.		
Talkative: increased talkativeness (pressure of speech).		
Recklessness: mild spending sprees, or other types of reckless or irresponsible behaviour [hypomania]; behaviour which is foolhardy or reckless and whose risks the subject does not recognize e.g. spending sprees, foolish enterprises, reckless driving [mania].		
Disinhibition socially: increased sociability or over-familiarity [hypomania]; loss of normal social inhibitions resulting in behaviour which is inappropriate to the circumstances [mania].		
Sexual energy: increased sexual energy [hypomania]; marked sexual energy or sexual indiscretions [mania].		
<i>Total symptoms in category B:</i>		
<i>C. Other symptoms of mania</i>	<i>Absent</i>	<i>Present</i>
Grandiosity: Inflated self-esteem or grandiosity.		
Flight of ideas: Flight of ideas or the subjective experience of thoughts racing.		
<i>Total symptoms in category C:</i>		
<i>Total symptoms in category B + C:</i>		

- *Hypomania* requires mood symptom A for at least 4 days, at least 3 symptoms from group B, and some interference with personal functioning in daily living.
- *Mania* requires mood symptom A for at least 7 days (unless it is severe enough to require hospital admission), plus at least 3 symptoms from across groups B and C (or at least 4 symptoms from those groups if the mood is merely irritable), plus severe interference with personal functioning in daily living.
- *Mania without psychotic symptoms* may include perceptual changes (e.g. hyperacusis, visual hyperaesthesia) but not hallucinations or delusions.
- *Mania with psychotic symptoms* requires delusions or hallucinations, other than those that are "typically schizophrenic".[†]
- Exclusion criteria apply (including psychoactive substance use, organic mental disorder, schizophrenia, and schizoaffective disorder).

MIXED AFFECTIVE STATE. ICD-10 criteria for mixed affective episode [23].

<i>Criteria for mixed affective episode (F38.00)</i>	<i>False</i>	<i>True</i>
A. Mixed state: There is either a mixture or a rapid alternation (within a few hours) of hypomanic, manic, and depressive symptoms		
B. Duration/severity: Both manic and depressive symptoms must be prominent most of the time during a period of at least two weeks.		

[†] "Typically schizophrenic" symptoms that are excluded are (a) delusions of control, influence, or passivity, clearly referred to body or limb movements or specific thoughts, actions, or sensations, and delusional perception; (b) hallucinatory voices giving a running commentary on the patient's behaviour, or discussing him between themselves, or other types of hallucinatory voices coming from some part of the body; (c) persistent delusions of other kinds that are culturally inappropriate and completely impossible. Note, however, that Schneiderian first-rank symptoms can occur in manic psychosis [25].

Diagnosing depression in the presence of other significant diseases

This can obviously be tricky: things like weight loss, sleep disruption, and changes in energy might be due to a host of medical disorders. The cognitive symptoms of depression (mood, thoughts about self/the world/the future) are often more useful than the 'biological' symptoms in this context.

Depressive psychosis (psychotic depression)

Psychosis originally meant any kind of disordered mental state [26], and subsequently a severe mental disorder involving loss of contact with reality [27, 28]. Nowadays it means one of:

1. *delusions and/or hallucinations without insight;*
2. *delusions and/or hallucinations (with or without insight);*
3. *(2) and/or disordered thought or speech;*
4. *(3) and/or severe behavioural abnormalities including behavioural disorganization, gross excitement and overactivity, or psychomotor retardation and catatonia [29, 30].*

When (usually severe) depressive symptoms precede the development of delusions or hallucinations, depressive psychosis is diagnosed. Typically, but not necessarily, the psychotic symptoms are mood-congruent (i.e. affectively negative; unpleasant), with delusions of guilt, sin, evil, poverty, death, or imminent disaster, and hallucina-

tions such as of defamatory or accusatory voices or the smell of rot or decomposing flesh [29, 31]. Sometimes they are mood-incongruent [32] or include Schneiderian first-rank symptoms [24].

Psychotic symptoms are seen in ~15% of cases of major depression [33, 34], the DSM-IV category. A direct survey found a lifetime prevalence of psychotic depression of 0.35% [35].

A single episode of depressive psychosis is classified under ICD-10 as a severe depressive episode with psychotic symptoms (F32.3). A repeated episode, with no history of mania, is classified as recurrent depressive disorder, current episode severe with psychotic symptoms (F33.3); a similar episode in the context of bipolar affective disorder would be classified as bipolar affective disorder, current episode severe depression with psychotic symptoms (F31.5).

Depression with psychotic features is not *always* severe depression [32]. Current diagnostic systems (ICD-10, DSM-IV) do not recognize this; this may change.

Causes of depression

These are legion [1] and include

- hypothyroidism, hyperthyroidism
- hyperparathyroidism (via hypercalcaemia)
- Cushing's disease
- cerebrovascular disease
- Parkinson's disease
- infectious mononucleosis
- SLE
- drugs (most famously reserpine; calcium channel antagonists, beta blockers are others)
- ... etc...

Treatment of depression

Some guidelines

NICE guidelines [36] recommend watchful waiting, guided self-help, or psychological therapy (e.g. brief cognitive-behavioural therapy) for mild depression; to begin with antidepressants for moderate depression; to use SSRIs as first-line antidepressant therapy; to use antidepressants plus CBT for severe, treatment-resistant, or recurrent depression.

Assess suicide risk in all patients [36].

Warn patients about the treatment effect delay of antidepressants (see below), potential side effects, and potential discontinuation reactions [36]

When getting an effective drug is of overriding importance, consider tricyclics, venlafaxine, and escitalopram [37].

Picking an antidepressant is partly about considering the side effect profiles [37] and trying to pick a drug whose side effect profile may be helpful or minimal.

Assess response regularly, including after 4 weeks of antidepressant use at a therapeutic dose (after which, if there is minimal improvement, consider a dose increase, a change of antidepressant, or sometimes adding a second agent) [37].

When considering response, you may encounter the following terms [38, 39]:

- *non-response*: $\leq 25\%$ decrease in symptom severity, relative to baseline
- *partial response*: 26–49% decrease
- *response*: $\geq 50\%$ decrease
- *remission*: following a depressive episode, absence of symptoms
- *recovery*: sustained remission
- *relapse*: response without sustained remission → exacerbation
- *recurrence*: recovery → new episode

Treat properly: aim for full remission. Aim to continue antidepressants (if tolerated) for at least 6–9 months after remission, or 1 year if any risk factors for relapse, or 2 years, or lifelong treatment, in higher risk patients [37].

Psychological

- **Cognitive-behavioural therapy** is effective for depression [40] and the standard psychotherapeutic approach in the UK.
 - Developed by Beck and colleagues in 1979. Designed to change negative views of the self, world, and future (Beck's 'cognitive triad' in depression: e.g. I'm worthless, the world is unfair, the future is hopeless). Involves self-monitoring of thoughts and behaviour, and evaluation of one's own thoughts for logical errors (e.g. in depression: dichotomous thinking [things are wonderful or they're awful], selective abstraction [taking a detail out of context and believing in just the detail], etc.) [40].
- **Behaviour therapy** and **interpersonal psychotherapy** are also effective [40].
- Combined psychosocial and pharmacological treatment is more effective than either on its own for chronic and recurrent depression [40].

Pharmacological

- **Selective serotonin reuptake inhibitors (SSRIs)**. There are 6. They're widely used and much safer in overdose than the drugs they followed (e.g. tricyclics).

citalopram	<i>a common choice</i>
escitalopram	<i>active isomer of citalopram; the most selective SSRI</i>
fluoxetine	<i>long half life; may be more 'activating' (alerting)</i>
fluvoxamine	<i>many pharmacokinetic interactions; less often used</i>
paroxetine	<i>somewhat sedating/more antimuscarinic effects; discontinuation symptoms common</i>
sertraline	<i>first line after myocardial infarction (best safety record here)</i>

Notable potential side effects include

- the common ones of GI side effects (esp. nausea), agitation/anxiety (SSRIs are useful for anxiety but increase the dose very slowly in this situation); headache, insomnia, tremor, sexual dysfunction (male and female; very common; SSRIs are a therapy for premature ejaculation);
- withdrawal may precipitate a discontinuation syndrome (e.g. 'flu-like symptoms, 'shock'-like symptoms, dizziness, insomnia, vivid dreams);
- bleeding (serotonin is important in platelet function), particularly in combination with NSAIDs;
- hyponatraemia (true of most psychotropic drugs!);
- serotonin syndrome (rare but dangerous CNS hyperstimulation with mental state changes, autonomic hyperactivity, and neuromuscular abnormalities; most commonly results from the combination of serotonergic agents at high doses);
- **Serotonin/noradrenaline reuptake inhibitors.**
 - **Venlafaxine.** At high doses this blocks both serotonin and noradrenaline reuptake (at low doses, it only blocks serotonin reuptake). Side effects are a combination of 'serotonergic' and 'noradrenergic' side effects; in particular, it can cause hypertension.
 - **Duloxetine.** More potent noradrenaline reuptake inhibition than venlafaxine [1].
- **Noradrenaline reuptake inhibitors.**
 - **Reboxetine** [37].
- **Tricyclic antidepressants.**
 - Amitriptyline, clomipramine, dosulepin (formerly dothiepin), doxepin, imipramine, lofepramine, nortriptyline, trimipramine.
 - Pharmacologically 'dirty': block the reuptake of noradrenaline and serotonin, and block muscarinic acetylcholine, histamine, and α_1 -adrenoceptors (to varying degrees) [40].
 - Minimum effective dose at least 75–100 mg/day; many need higher doses (e.g. ~200 mg/day or more). Doses are relatively independent of the spe-

cific drug. Undertreatment is common (e.g. amitriptyline 25mg nocte isn't an antidepressant dose).

- Side effects often anticholinergic (sedation, tachycardia, dry mouth, blurred vision, constipation, urinary retention) though there are others (e.g. postural hypotension).
- *Cardiotoxic in overdose* so no longer first-line (see [41]). Beware in those with other cardiac disease [37].
- **Monoamine oxidase inhibitors (MAOIs).**
 - Phenelzine, tranylcypromine (irreversible inhibitors), and moclobemide (reversible MAO-A inhibitor).
 - MAO breaks down serotonin (mostly MAO-A), noradrenaline (mostly MAO-A), dopamine (MAO-A and -B), and other monoamines.
 - *Tyramine reaction*: dangerous hypertensive crisis when tyramine ingested by patients on MAOIs (most notably ripe cheeses and some red wines, but also avocados, matured liver and meats, soy... patients need a detailed food avoidance list). So this is a potentially dangerous class of drugs.
 - Moclobemide probably the most commonly used of this class, as tyramine interactions are rarer and milder.
- **Other antidepressants of note.**
 - **Mianserin.** 5-HT₂ receptor antagonist. Quite sedating. Can cause agranulocytosis [42].
 - **Mirtazapine.** Inhibitor of alpha-2-adrenergic receptors, and antagonist of 5-HT₂ and 5-HT₃ receptors; almost no effect on monoamine uptake. Also antihistamine. Side effects include early sedation and appetite stimulation [1].
 - **Trazodone/nefazodone.** 5-HT_{2A} receptor antagonists (and serotonin reuptake inhibitors). Nefazodone causes less postural hypotension (less alpha-1 blockade) than trazodone [1, 37]. Trazodone can cause dangerous priapism.
- **Other therapies.** When other things fail...
 - **Bupropion.** Noradrenaline reuptake inhibitor and nicotinic acetylcholine receptor antagonist licensed in the UK for smoking cessation but in the USA also as an antidepressant, and widely used as an add-on to SSRIs in the USA.
 - **Buspiron.** 5-HT_{1A} receptor agonist licensed for anxiety.
 - **Lamotrigine.** More often used in bipolar depression.
 - **Lithium.** Used as an add-on ('lithium augmentation').
 - St John's wort (*Hypericum* extracts): mentioned here because patients may be keen and this can be effective for mild/moderate depression, if a standardized preparation is used [37], but it interacts pharmacokinetically with many things: BNF advice is to not to prescribe it, and never to add other antidepressants to it [42].
 - **Tri-iodothyronine (T3).** Even in those with normal thyroid function.
 - **Tryptophan.** (Compare tryptophan depletion, which lowers central serotonin.)
 - **Combinations and other things.** Quite a few of these, used occasionally in refractory depression. Some combinations are fairly frequently seen (e.g. venlafaxine + mirtazapine, a.k.a. 'California rocket fuel'!).

Time course of response: important

Antidepressants don't work immediately (even ECT, which is quicker than most). *Warn patients about this.* Side effects come early; benefits are delayed. A trial of an antidepressant means using a drug, at a dose that's known to work, for at least 4 weeks. However, most patients who eventually respond show some improvement after 2–4 weeks [37].

The reason is debated. Theories include:

- slow adaptations in receptor sensitivity (\pm firing rates of serotonergic neurons);
- changes in levels of neurotrophic factors such as brain-derived neurotrophic factor (BDNF), and consequent changes in neuronal number and/or connectivity [43];

- rapid changes in the emotional processing of positive and negative events, with subsequent re-learning and cognitive restructuring that takes a while to have an impact on overt mood [44].

In practice

Which do people start with? Usually citalopram!

Which should people start with? In a meta-analysis [45] of ‘new-generation’ antidepressants (bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, mirtazapine, paroxetine, reboxetine, sertraline, venlafaxine),

- escitalopram and sertraline were the best tolerated (and very effective);
- mirtazapine and venlafaxine were very effective.

See also e.g. [37, 46].

Physical

- **Electroconvulsive therapy (ECT).**
 - The most effective treatment for major depression [1].
 - Consider as a first-line treatment for major depression in emergencies (e.g. not eating or drinking, depressive stupor, extreme distress, suicidality) [37]. NICE are somewhat more restrictive [36].
 - Under anaesthesia and paralysis, an electric current is passed between two electrodes placed bilaterally or unilaterally on the head (if unilaterally, normally on the right). Most current goes to the scalp. A course of treatments is needed (typically 6–12 sessions).
 - Problems include acute cardiovascular stress, transient headache, and cognitive side effects (acute brief retrograde and anterograde amnesia with some disorientation is common; there is debate as to the frequency of longer-term memory deficits, partly because severe depression also impairs concentration and memory). Cognitive side effects are less with unilateral ECT [1].
- **Vagal nerve stimulation.** Not common [47].
- **Neurosurgery.** Rarely used, but surgical destruction of the subgenual anterior cingulate cortex (or adjacent white matter) is a therapy for refractory depression [47]. Deep brain stimulation has the advantage of being reversible and work on this is in progress [48].

When psychosis is present

Typical treatment is the combination of an antipsychotic and an antidepressant (which is better than just an antipsychotic, but not clear if it’s better than just an antidepressant). Tricyclics and ECT may be particularly helpful [46].

In young people

In under-18s: only fluoxetine has been shown to have benefit [42]. Monitor especially for self-harm and suicidality.

Suicidality on antidepressant therapy has been somewhat controversial (given the condition they’re used for). The risk of suicidal thinking or behaviour induced by antidepressants appears to relate to age: an increased risk for children, adolescents, and adults under 25, but a moderate protective effect for adults aged 25–64, and a more strong protective effect for adults over 65 [49]. Warn young people about this risk.

In pregnancy

Antidepressants and depression may both cause harm. Best evidence of safety for SSRIs (but avoid paroxetine) and tricyclics. For breastfeeding, sertraline and nortriptyline are undetectable in babies; fluoxetine and citalopram may lead to significant levels in the infant [37].

In the context of bipolar affective disorder

We won't cover this in detail, but an important thing to remember is that antidepressants can precipitate mania in those with bipolar affective disorder, so a 'mood stabilizer' is usually used together with the antidepressant.

Of historical interest

1934. Convulsive therapy for catatonic psychosis, by von Meduna. Chemical. (Prior reports exist from the late 1700s) [1].

1938. First electroconvulsive therapy, by Cerletti & Bini.

1953. First antidepressant drug, isoniazid [50].

1957. Discovery of tricyclics' utility.

1977. First widely used SSRI, fluoxetine, submitted to FDA for approval.

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