Therapeutic Reviews

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Antidepressant Drugs *AHFS 28:16.04*

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Indications: Depression, anxiety and panic disorders, post-traumatic stress disorder, stress incontinence and urgency, †chronic pain, †agitated delirium, †sweating, †hot flashes, †insomnia, †pruritus, †bladder spasm, †pathological laughing and crying, †drooling.

Pharmacology

Depression: Antidepressants enhance transmission of one or more monoamines (Fig. 1, Box 1). Some have additional actions which may contribute towards their beneficial and/or undesirable effects (Table 1). Although increased monoamine transmission occurs within hours, the antidepressant effect is slower to appear because this requires normalization of receptor sensitivity *and* neuroplasticity. Many of the early-onset undesirable effects from antidepressant drugs are a consequence of enhanced monoamine transmission in the presence of receptors that have been upregulated to compensate for a relative monoamine deficit. As receptor sensitivity returns to normal, these undesirable effects generally resolve and beneficial effects begin to emerge.

Neuroplasticity is the ability of the CNS to adapt structurally and functionally in response to external stimuli and is mediated by nerve growth factors (e.g., brain derived neurotrophic factor). In depression, neuroplasticity is impaired in the limbic and prefrontal cortex circuits which regulate mood, attention, energy, appetite and sleep. By enhancing monoamine transmission, antidepressants help increase the production of nerve growth factors and restore neuroplasticity.[1]

Depression refractory to one antidepressant can respond following a switch to another antidepressant or to the use of combination treatment which targets different, or multiple, monoamines (see Titrating, switching and combining antidepressants).[2,3]

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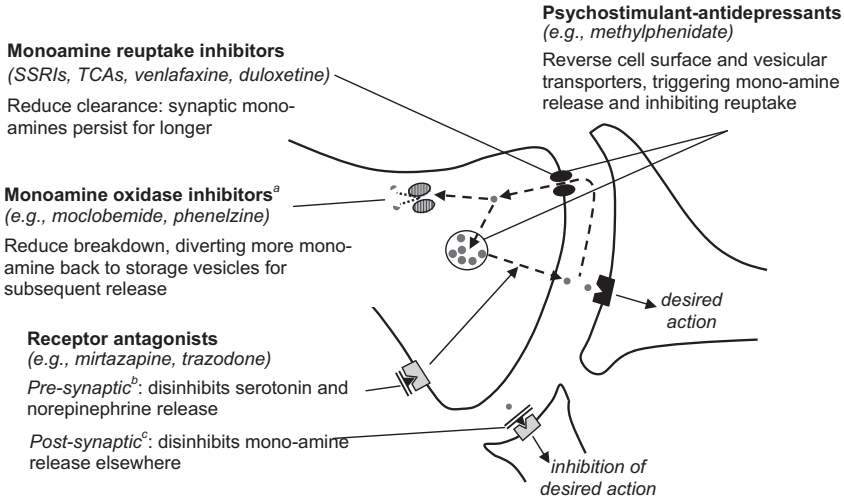

Fig. 1. Predominant mechanism of action of antidepressants. [a]Monoamine oxidase type A breaks down serotonin, norepinephrine (noradrenaline) and dopamine. Type B breaks down dopamine. Antidepressant-MAOIs are either non-selective (e.g., phenelzine) or type A selective (e.g., moclobemide). Antiparkinsonian MAOIs (e.g., selegiline) are Type B selective. [b]Blockade of pre-synaptic α-adrenergic receptors removes inhibition of serotonin and norepinephrine release. [c]Blockade of post-synaptic $5HT_{2A}$ and $5HT_{2C}$-receptors removes inhibition of dopamine and norepinephrine release from the post-synaptic neuron.

Anxiety and Panic Disorder: Antidepressants and benzodiazepines inhibit the amygdala's so-called fear circuits through $5HT_{1A}$ and $GABA_A$ receptors, respectively.[4,5] The amygdala is a "threat sensor" which integrates sensory information with contextual information (e.g., interpretations, memories). If a fear response is required, the amygdala's effector pathway activates the relevant circuits (respiratory and cardiovascular centers, pituitary-adrenal axis, sympathetic autonomic nervous system, and fear-related areas of the cerebral cortex).

Pain: The analgesic effects of antidepressants also are due to enhanced monoamine transmission, e.g., in descending pain modulation pathways.[6,7] These pathways can induce both analgesia (norepinephrinergic (noradrenergic) and serotoninergic activity) and hyperalgesia (serotoninergic activity).[8,9] The latter may explain the inconsistent analgesic effect of SSRIs and why SNRIs appear no more effective then NRIs.[10] Sodium-channel blockade and NMDA-glutamate-receptor antagonism also may contribute to the analgesic efficacy of some antidepressants,[7] including the modest effect of topical doxepin.[11,12]

The beneficial and undesirable effects of antidepressants vary for multiple reasons including differing:

- mechanisms of action (Fig. 1)
- monoamines affected (Box 1)
- effects on other receptors (Table 1)
- pharmacokinetic profiles (Table 2).

The clearance of many antidepressants is significantly affected by CYP2D6 metabolizer phenotype, and to a lesser extent by CYP2C19. Further, serotonin re-uptake transporter polymorphisms may influence SSRI efficacy.[13] However, clinical benefit from genotyping has yet to be demonstrated.[14]

St. John's wort (hypericum extract) is as effective as conventional antidepressants in treating mild–moderate depression and causes fewer undesirable effects.[29] However, NICE discourages its use because of:

- uncertainty about appropriate doses
- variation in the nature of products
- potential serious interactions with other drugs (including oral contraceptives, anticoagulants and anti-epileptics).[30]

Box 1. Classification of Antidepressants According to Principal Actions[a]

Monoamine re-uptake inhibitors (MARIs)

Serotonin and norepinephrine (SNRIs[b] or dual inhibitors)

Amitriptyline[c], venlafaxine, duloxetine

Serotonin (selective serotonin re-uptake inhibitors, SSRIs)

Sertraline, citalopram, paroxetine, fluoxetine

Norepinephrine (NRIs)

Nortriptyline[c], lofepramine, desipramine[c], reboxetine

Norepinephrine and dopamine (NDRIs)

Bupropion

Psychostimulant-antidepressants[d]

Dextroamphetamine, methylphenidate, modafinil

Receptor antagonists

Trazodone (α_1, $5HT_2$)

Mirtazapine (central α_2, $5HT_2$, $5HT_3$)

Monoamine oxidase inhibitors (MAOIs)[e]

Phenelzine, tranylcypromine

[a]Abbreviated names broadly reflect those found elsewhere;[15] confusion is inevitable because *S* is used for *Selective*, *Specific*, and *Serotonin*.
[b]SNRI is sometimes reserved for dual inhibitors without additional receptor binding affinities (e.g., venlafaxine and duloxetine).
[c]TCAs differ in their modes of action, and do not comprise a single discrete drug class.
[d]Reverse dopamine re-uptake transporters.
[e]MAOIs are included for completeness; their use by non-psychiatrists is *not* recommended.

Cautions

In patients with a history of mania, antidepressants may precipitate a recurrent episode, particularly when administered without a mood stabilizer.

Suicide Risk

The risk of antidepressant-related suicidal ideation needs to be balanced against the greater risk of non-fatal self harm and completed suicide from untreated depression.[31]

One in 1,000 patients attempt suicide in the six months after starting antidepressants: one-third are successful.[32] In those aged ≤25 years, antidepressants are associated with suicidal ideation and non-fatal self-harm (NNH 143).[33,34] The risk is greater with SSRIs than TCAs,[35] and is present even when an antidepressant is used for non-depressive illnesses.[34] In adults ≥25 years old, there is a smaller increase in the risk of non-fatal self-harm (NNH ca. 700), no increase in suicide or suicidal thoughts, and no difference between SSRIs and TCAs.[35–37]

Suicidal ideation should be evaluated when treating depression in all age groups. Consider the safety in overdose of both the antidepressant and concomitant medicines. In both the USA and Europe, regulators have emphasized the need for close monitoring of adherence to treatment, treatment response, and emergence of thoughts of self-harm, particularly during the first month after starting an antidepressant, and to encourage patients to report to their doctor any deterioration in mood or behavior.[38,39]

Epilepsy

Antidepressants cause a dose-dependent reduction in seizure threshold. The risk is lowest for SSRIs, higher with TCAs, and highest with clomipramine, bupropion and maprotiline.[40] There are fewer data

Table 1
Transporter and Receptor Affinities for Selected Antidepressants[16–19]

	Re-uptake Transporters			Receptor Affinities					
Drug	*5HT*	*NE*[a]	*DA*	$5HT_{2A}$	$5HT_{2C}$	H_1	α_1	α_2	ACh_M
Agomelatine (not USA)[b]				-	+	-	-		-
Amitriptyline	+++	++	-	+++	+++	+++	+++	+	+++
Bupropion	-	+	++	-	-		-	-	-
Citalopram	+++	-	-	-	-	-	-	-	-
Desipramine	+	+++	-	+	-	++	++	-	+
Duloxetine	+++	+++	+	-	-	-	-	-	-
Fluoxetine	+++	-	-	+	+	-	-	-	-
Imipramine	+++	+	-	+	+	+++	++	-	+/+++[c]
Lofepramine (not USA)	+	+++	-	-		+	+	-	-/++[c]
Methylphenidate	-	-	++	-	-		-	-	-
Mirtazapine	-	-	-	++	++	+++	-	+++	-
Nortriptyline	+	+++	-	+++	+++	+++	++	-	++
Paroxetine	+++	+	-	-	-	-	-	-	+
Reboxetine (not USA)	-	+++	-	-	-		-	-	
Sertraline	+++	-	+	-	-	-	+	-	-
Trazodone	-	-	-	++	+	-	++	+	-
Venlafaxine	+	+[d]	-	-	-	-	-	-	-

Affinity = +++ high, ++ moderate, + low, - negligible or none; blank = no data.
[a]The norepinephrine re-uptake transporter also clears dopamine in the prefrontal cortex where dopamine re-uptake transporters are absent. Reduced dopamine in the prefrontal cortex is related to anhedonia and inattention.
[b]Agomelatine is also a melatonin (type 1 and 2) receptor agonist. Although animal models raise this as a target of possible interest, the contribution which this makes towards its clinical effects in humans is unclear.
[c]Varies with different ACh_M receptor subtypes.
[d]Despite *in vitro* studies suggesting a relatively low affinity for serotonin and norepinephrine re-uptake transporters, *in vivo* studies suggest venlafaxine is a dual inhibitor. *In vitro* assays measure the ability of a drug to displace another compound of known affinity; it may be that venlafaxine binds to a different site on monoamine re-uptake transporters and so cannot displace the reference compounds.[18]

and less experience with mirtazapine and venlafaxine. In patients with epilepsy, antidepressants also may cause seizures by altering anti-epileptic drug levels as a result of a drug–drug interaction. Thus, citalopram is widely favored for use in patients with epilepsy because of the low risk of reduction in seizure threshold and lack of significant interactions with anti-epileptic drugs. Antidepressants also can cause seizures through hyponatremia.

Table 2
Pharmacokinetic Details for Selected Antidepressants[20–28]

Drug	Bio-availability PO (%)	T_{max} (h)	Plasma Half-life (h)	Metabolism
Agomelatine (not USA)	>80	1–2	1–2	CYP1A2[a]
Amitriptyline	45	4	13–36	Multiple pathways[b] (nortriptyline[b])
Bupropion	>87	1.5	21	CYP2B6[b]
Citalopram	80[c]	3	36	Multiple pathways[b]
Desipramine	30–50	4–6	7–77	CYP 2D6[a,b]
Duloxetine	90	6	12	CYP1A2, CYP2D6
Fluoxetine	90	4–8	1–4 days 7–15 days[b]	Multiple pathways[b]
Imipramine	45	3	21	Multiple pathways[b] (desipramine[b])
Methylphenidate	30	1–3	2	Non-CYP hepatic carboxylesterase[a]
Mirtazapine	50	2	20–40	CYP1A2, CYP2D6, CYP3A4
Nortriptyline	60	7–8.5	15–39	CYP2D6[a,b]
Paroxetine	50[d]	5	15–20	Multiple pathways
Reboxetine (not USA)	95	2–4	12	CYP3A4
Sertraline	>44	6–8	26	CYP3A4
Trazodone	65	1	7	CYP2D6, CYP3A4[b]
Venlafaxine	13 (45)[e]	2.5 (4.5–7.5)[e]	5 (11)[b]	CYP2D6, CYP3A4[b]

[a]Significant first-pass metabolism.
[b]Active metabolite(s); listed in table if can be administered separately.
[c]Tablet product: bioavailability of drops 25% higher.
[d]Increases with multiple dosing.
[e]m/r product.

Table 3
Tyramine-Containing Foods Associated With MAOI-Related Syndrome

Alcohol	Fava Beans
Red wine (white wine is safe)	Meat (smoked or pickled)
Beer	Meat or yeast extracts
Broad bean pods	Pickled herring
Cheese (old)	

It is hard to quantify the risk of using low-dose TCAs for neuropathic pain in patients with previous seizures because the risk is dose-related and animal studies even suggest a possible anti-epileptic action at low doses.[41]

Epilepsy is associated with both mood disorders and psychosis. Symptoms may occur in between (inter-ictal), during (ictal), or in the days or weeks after (post-ictal) seizures. Optimization of anti-epileptic medication should be considered alongside antidepressant treatment, particularly for ictal and post-ictal mood-related symptoms.[42] Further, anti-epileptic drugs can cause (and treat) mood disorders: seek specialist advice if symptoms develop after their introduction or titration.[40]

Parkinson's Disease

SSRIs can worsen extrapyramidal symptoms because serotonin reduces nigrostriatal dopamine release via inhibitory $5HT_2$ receptors. However, the risk appears small; few RCTs report any worsening.[43] SSRIs are thus still often used in preference to TCAs which can worsen autonomic dysfunction (α blockade) and cognitive impairment (ACh_M blockade).

$5HT_2$ antagonist antidepressants might be expected to avoid serotonin-mediated exacerbations. In small pilot RCTs, Parkinsonian symptoms improved with nefazodone[44] but not mirtazapine.[45]

Antiparkinsonian D_2 agonists can themselves improve mood. In RCTs evaluating pramipexole for motor symptoms, mood and motivation also improved.[46] Further, in an RCT, pramipexole was more effective than sertraline for depression in patients with Parkinson's disease.[47]

Monoamine Oxidase Inhibitors (MAOIs)

Included for general information. MAOIs are *not recommended* in palliative care. They can cause serious adverse events when prescribed concurrently with various other drugs. Seek advice from a psychiatrist if caring for a patient already receiving an MAOI; their previous mental illness is likely to have been difficult to treat and switching or adding other psychotropics is difficult and risky.

MAOIs are potentially dangerous because of the risk of serious dietary and drug interactions. Hypertensive crises are mainly associated with the consumption of tyramine-containing foods (Table 3). Typically, the patient experiences severe headache, and may suffer an intracranial hemorrhage. Drug interactions occur with sympathomimetics (e.g., ephedrine, pseudoephedrine, dextroamphetamine, nefopam), serotoninergics (see below) and levodopa.

Toxicity has been reported with serotoninergic opioids (e.g., fentanils, meperidine [pethidine], tramodol). However, although pharmaceutical companies marketing morphine and oxycodone also advise against concurrent use, their affinity for the serotonin re-uptake transporter is negligible,[48] and toxicity has not been reported.[49] Further, insisting on a two-week washout before treating pain is impracticable.

Drug Interactions

MAOIs have numerous clinically significant drug interactions, which may result in hypertensive crises and serotonin toxicity.

Several pharmacodynamic interactions (e.g., serotonin toxicity, bleeding risk, antimuscarinic effects, QT prolongation with citalopram and escitalopram) can be predicted from the mode of action of antidepressants (see Box 1 and Table 1).

In addition, potentially serious interactions may result from induction or inhibition of hepatic metabolism. Some antidepressants inhibit cytochrome P450 enzymes:

- CYP1A2 inhibition by fluvoxamine: e.g., tizanidine levels increased ≤33 times
- CYP2D6 inhibition by fluoxetine and paroxetine: e.g., TCA levels increased ≤10 times; paroxetine may reduce the efficacy of tamoxifen (a pro-drug).[50]

The metabolism of others is affected by P450 inhibitors and inducers:

- CYP2D6: most TCAs
- CYP3A4: mirtazapine.

Serotonin Toxicity ("Serotonin Syndrome")

Serotonin toxicity results from the ingestion of drug(s) which increase brain serotonin to levels sufficient to cause severe symptoms necessitating hospital admission and medical intervention (see Box 2 and Box 3).[51] It has been characterized as a triad of neuro-excitatory features:

- *autonomic hyperactivity*: sweating, fever, mydriasis, tachycardia, hypertension, tachypnea, sialorrhea, diarrhea
- *neuromuscular hyperactivity*: tremor, clonus, myoclonus, hyperreflexia, and hypertonia (advanced stage)
- *altered mental status*: agitation, hypomania, and delirium (advanced stage).

Box 2. Drugs With Clinically Relevant Serotoninergic Potency[48,51,53]

Antidepressants

Monoamine oxidase inhibitors (MAOIs) All types

Selective serotonin re-uptake inhibitors (SSRIs) All

Serotonin and norepinephrine re-uptake inhibitors (SNRIs)
Clomipramine and imipramine (but not reported with other TCAs), duloxetine, milnacipran (not UK), venlafaxine

Psychostimulants (serotonin releasers)
Dextroamphetamine, MDMA (methylenedioxymethamphetamine, Ecstasy) (but not methylphenidate)

Other drugs

H_1 antihistamines (serotonin re-uptake inhibitors)
Chlorpheniramine, brompheniramine (but not other H_1 antihistamines)

Opioids (serotonin re-uptake inhibitors)
Dextromethorphan, propoxyphene, fentanils, methadone, pentazocine, meperidine (pethidine), tramodol (but not other opioids)

Miscellaneous

MAOIs
Furazolidone, linezolid (antibacterials)
Methylene blue
Procarbazine (antineoplastic)
Selegiline (antiparkinsonian)

SNRI
Sibutramine (anorectic)

The onset of toxicity is generally rapid and progressive, typically as a second serotoninergic drug reaches effective blood levels (e.g., after one or two doses). Occasionally, recurrent mild symptoms may occur for weeks before the development of severe toxicity. Clonus (inducible, spontaneous or ocular), agitation, sweating, tremor and hyperreflexia are essential features. Spontaneous clonus, in the presence of a serotoninergic drug, is the most reliable indicator of serotonin toxicity.[52] Neuromuscular signs are initially greater in the lower limbs, then become more generalized as toxicity increases. Other symptoms include shaking, shivering (and chattering of the teeth), and sometimes trismus. It can be distinguished from neuroleptic (antipsychotic) malignant syndrome by its faster onset and pyramidal rather than extrapyramidal neuromuscular findings.

Different drugs increase serotonin levels to differing degrees. An overdose of the older irreversible MAOI tranylcypromine alone will produce hyperpyrexia, and even death,[54] whereas overdoses of reversible MAOIs or SSRIs alone will cause serotoninergic effects but rarely (if ever) life-threatening serotonin toxicity.[55,56] Thus death from serotonin toxicity is generally associated with the combination of two different types of drug which elevate serotonin levels via different mechanisms of action (an MAOI combined with either an SSRI or a serotonin releaser).[55]

Opioids are relatively weak serotonin re-uptake inhibitors and may only cause symptoms in higher doses or susceptible individuals. Fatalities from serotonin toxicity involving opioids have been seen with dextromethorphan, pethidine (meperidine), tramodol, and possibly fentanyl.[48]

Undesirable Effects

A synopsis is contained in Table 4. Overall, discontinuation with SSRIs is marginally less than with TCAs (NNT 33).[60]

GI Bleeding and Platelet Function

SSRIs and SNRIs (e.g., amitriptyline, duloxetine, imipramine, venlafaxine) decrease serotonin uptake from the blood by platelets. Because platelets do not synthesize serotonin, the amount of serotonin in platelets is reduced.[64] This adversely affects platelet aggregation.[65] After confounding factors have been controlled for, serotonin re-uptake inhibitors triple the risk of GI bleeding.[66,67] This may be important in already high-risk patients. If an antidepressant is indicated in such patients, safer alternatives would include an NRI (e.g., desipramine [not UK], nortriptyline) or mirtazapine.

QT Prolongation

Citalopram and escitalopram exhibit dose-related QT prolongation. Regulators recommend correction of hypokalemia and hypomagnesemia and advise ECG monitoring in those with cardiac disease or receiving other QT prolonging drugs.[68] The dose of citalopram should not exceed 40 mg daily, with the FDA recently recommending an even smaller maximum dose of 20 mg daily in patients >60 years, those with hepatic impairment, CYP 2C19 poor metabolizers, or with concurrent use of a CYP 2C19 inhibitor.[69] Other SSRIs appear less affected, at least in overdose.[70]

Fracture Risk

The European Medicines Agency highlighted a consistently increased fracture risk with SSRIs and TCAs across a number of observational studies.[71] The mechanism is uncertain; data regarding both the risk of falls and bone density are conflicting.

Use of Antidepressants in Palliative Care

Note. Generic formulations of a number of antidepressants are available, e.g., citalopram, escitalopram, fluoxetine, paroxetine, sertraline and venlafaxine, which are about one-third of the cost of the brand name formulations.

Neuropathic Pain

Amitriptyline and nortriptyline are commonly used for neuropathic pain.[72] Most RCTs have been of amitriptyline, although nortriptyline was better tolerated when compared with amitriptyline.[10] Their

Box 3. Treatment of Serotonin Toxicity[57]

In severe cases (e.g., rigidity, hemodynamic instability, temperature > 38.5°C, deteriorating blood gases) seek urgent advice from a critical care specialist: ventilation and paralysis ± inotropic support may be required.

Discontinue causal medication (toxicity generally resolves within 24 h).
Provide supportive care, e.g., IV fluids, oxygen.
Symptomatic measures in mild–moderate cases:
- benzodiazepines for agitation, myoclonus and seizures, e.g., midazolam 5–10 mg SC p.r.n.
- $5HT_{2A}$ antagonist[a], e.g.:
  - ➢ chlorpromazine 50–100 mg IM *or*
  - ➢ olanzapine 10 mg IM *or*
  - ➢ cyproheptadine 12 mg PO stat followed by 8 mg q6 h and 2 mg q2 h p.r.n. until symptoms resolve; ts can be crushed and given by enteral feeding tube.

[a]Prevents deaths from hyperpyrexia in animals and probably in humans. Generally give IM; the PO route is suitable only for mild toxicity and, in the case of overdose, in patients who have *not* received oral activated charcoal.[58,59]

efficacy and tolerability appear comparable to alternatives (e.g., anti-epileptic drugs and other SNRI and NRI antidepressants),[73–76] although few have been directly compared.

Bupropion, duloxetine, venlafaxine and most other TCAs are also superior to placebo. In head-to-head comparisons, both duloxetine vs. amitriptyline,[77] and venlafaxine vs. imipramine[78] were comparable. SSRIs are modestly effective (three of four RCTs),[79–82] but inferior to imipramine.[82] The benefit reported with mirtazapine[83] has *not* been confirmed in RCTs.

Alternatives to antidepressants include anti-epileptics[84] and opioids. In head-to-head comparisons, the efficacy of TCAs (amitriptyline or nortriptyline) was similar to gabapentin or pregabalin. Overall, tolerability also was comparable; although one RCT found fewer withdrawals due to adverse effects with TCAs, one found a greater number and one found similar numbers.[85–87] They are also often used together: nortriptyline combined with gabapentin was more effective than either drug alone.[88] Nortriptyline was as effective as morphine.[89]

Other Pain Syndromes

Antidepressants are of benefit for various other pain syndromes including migraine and tension headache (TCAs),[90] chronic low back pain (TCAs),[91] fibromyalgia (duloxetine),[92] and osteo-arthritis (duloxetine).[93]

Depression

See also Palliativedrugs.com Quick Practice Guide: Depression (p.782).

Treatment is tailored to the severity of symptoms, their functional impact and patient preference (Fig. 2). First-line drug treatment is generally with sertraline or citalopram. They have fewer drug interactions, lower risk in overdose, and are marginally better tolerated than alternatives.[30] Efficacy has been confirmed in palliative populations.[94] Frequent re-evaluation of response, adherence, and alternative and concurrent sources of distress is required throughout.

Methylphenidate, with its rapid onset, may be preferable in patients with a very short prognosis, e.g., 2–4 weeks. This is shorter than suggested by consensus guidance[95] because of the recognition that conventional antidepressants act faster than previously thought.[96] However, trials of psychostimulants are generally of short duration and with outcome measures of uncertain clinical significance. Thus, conventional antidepressants should be used if the patient has a sufficient prognosis for a response to manifest.[95,97,98] Concurrent use with a conventional antidepressant may hasten the response compared with the latter alone, particularly in relation to fatigue.[98] Modafinil can be used if methylphenidate is poorly tolerated.

Although an SNRI or NRI may be considered if depression and neuropathic pain co-exist, slower titration is required to avoid higher rates of discontinuation.[30] They are therefore often treated separately (e.g., with an SSRI plus either gabapentin or nortriptyline).

Titrating, Switching and Combining Antidepressants

If there is no response after four weeks, or only a partial response after 6–8 weeks:

- increase the dose, particularly if there has been a partial response and minimal undesirable effects *or*
- switch antidepressants, particularly if there has been minimal improvement or bothersome undesirable effects *or*
- combine with a second antidepressant or adjuvant psychotropic drug, particularly if a previous switch was unhelpful.[30]

Dose titration is straightforward but, for SSRIs, of uncertain value. A systematic review found dose titration in patients not responding to SSRIs taken for 3–6 weeks no more effective than continuing the dose unaltered.[100] Nonetheless, many guidelines highlight individual variation in effective doses and therefore recommend dose titration if the existing drug is well tolerated.[30,62] A dose-response effect is more clearly established with TCAs and venlafaxine.[62]

The efficacy of second-line antidepressants appears comparable regardless of mode of action.[62,101,102] Options include an alternative SSRI or mirtazapine. One SSRI can be directly substituted for another without cross-tapering or a washout period.[62,102] Mirtazapine 15 mg can be directly substituted for SSRIs at usual doses (fluoxetine, citalopram or paroxetine 20 mg; sertraline 50 mg).[62,103] Opinion varies on the need to taper higher SSRI doses before switching.[101,103] Switching SSRIs is most effective when the first SSRI is poorly tolerated but benefit also is seen in non-responders,[102] perhaps because of differing additional actions (see Table 5). The effect of mirtazapine on additional monoamines is theoretically advantageous; its onset may be faster.[104] Venlafaxine has a marginally higher response rate (NNT = 10) compared with switching to a second SSRI[102] but is less well tolerated. Switching to or from TCAs and MAOIs requires additional care because of the potential for clinically significant pharmacokinetic or pharmacodynamic drug interactions, respectively (see above).[105]

A partial response to an antidepressant can be increased ("augmented") by adding a second psychotropic drug. This avoids potential loss of the initial improvement but is generally less well tolerated than monotherapy.[30] Options include:

- an antipsychotic (e.g., aripiprazole, quetiapine or olanzapine added to an SSRI)
- mirtazapine (added to an SSRI or venlafaxine)
- a range of options used only by psychiatrists (e.g., lithium, tri-iodothyronine).

NICE suggests primary care clinicians seek advice before adding a second drug.[30] Palliative care specialists using some of the above for other indications should be aware of their potential benefit when concurrent depression has only partially responded to an antidepressant.[62,106]

Duration of Treatment

Consider stopping treatment six months after full remission in those without risk factors for relapse. Risk factors include previous depression and the severity, duration, degree of treatment resistance, and the presence of residual symptoms. Treatment is tapered slowly (see below). Treat those with risk factors for longer: one year if full remission but one risk factor; and ≥2 years if ≥2 risk factors.[30,62] In palliative care, the latter is likely to mean lifelong/indefinitely.

Anxiety and Panic Disorders

The efficacy of cognitive behavioral and drug therapy is comparable.[112] Drug treatment is tailored to the likely duration of use:

- benzodiazepine, if prognosis is days to weeks
- SSRI (+/- a benzodiazepine initially), if prognosis is months.

Although supporting evidence (and licensing) for SSRIs varies for different anxiety disorders,[113] a class effect is plausible. Citalopram and sertraline are licensed for panic disorder, well tolerated, have fewer drug interactions, and are generally more familiar to prescribers. All SSRIs can initially exacerbate anxiety: start low and consider a concurrent benzodiazepine for the first few weeks.

Table 4
Relative Frequency and Mechanisms of Undesirable Effects of Antidepressants[61–63]

		Relative Frequency				
		SNRI				
Undesirable Effect	Putative Mechanism	Amitriptyline	Clomipramine	Duloxetine	Imipramine	Venlafaxine
GI (nausea, diarrhea)	↑Serotonin (acting on $5HT_3$)	−	+	++	−	++
CNS (agitation, restlessness, anxiety, insomnia)	↑Serotonin (acting on $5HT_2$)	−	+	+	+	+
Weight gain	$5HT_2$ and H_1 antagonism	++	+	−	+	−
Sedation	H_1, ACh_M and α_1-adrenergic antagonism	++	+	−	+	−
Postural hypotension	α_1-adrenergic antagonism	++	++	−	++	−
Sexual dysfunction	↑Serotonin (acting on $5HT_2$)	+	++	++	+	++
Dry mouth, constipation	ACh_M antagonism	++	++	−	++	−
SIADH	↑Serotonin (acting on $5HT_2$); ↑norepinephrine (acting on α_1)	+	+	+	+	+

Key: ++ = relatively common or strong; + = may occur or moderately strong; − = absent or rare/weak.
SNRI = serotonin and norepinephrine re-uptake inhibitor; NRI = norepinephrine re-uptake inhibitor; SSRI = selective serotonin re-uptake inhibitor; RA = receptor antagonist.

If response is inadequate, combine with cognitive behavioral therapy (evidence best for panic disorder)[112] or switch to an alternative SSRI or SNRI.[113,114] In general psychiatry, switching is not advocated within three months because benefit can take longer to manifest than in depression.[113,114] However, in patients with a short prognosis, consider adding a benzodiazepine to obtain more rapid benefit. Pregabalin also acts quickly but is reserved for patients not responding to antidepressants; supporting trials

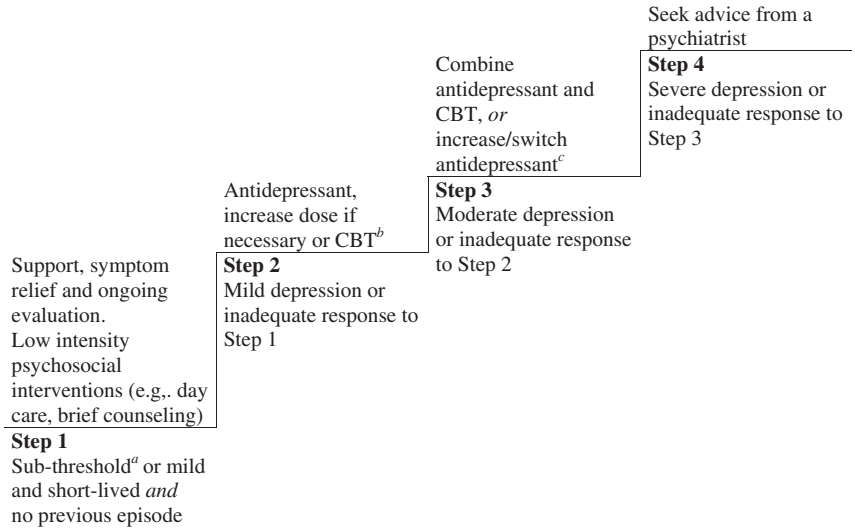

Fig. 2. Overview of the management of depression.[30,99] [a]Sub-threshold symptoms = patients with <5 DSM IV symptoms required for a diagnosis of depression. [b]CBT = cognitive behavioral therapy. [c]See below, managing an inadequate initial response.

Relative Frequency								
NRI			SSRI				RA	
Desipramine	Lofepramine	Nortriptyline	Citalopram	Fluoxetine	Paroxetine	Sertraline	Mirtazapine	Trazodone
−	−	−	++	++	++	++	−	−
+	+	+	+	+	+	+	−	−
−	−	−	−	−	−	−	++	+
+	−	+	−	−	−	−	++	++
+	+	+	−	−	−	−	−	++
+	+	+	++	++	++	++	−	−
+	+	+	−	−	−	−	−	−
+	+	+	++	++	++	++	+	+

are fewer, mainly confined to generalized anxiety disorder and response rates appear lower than for SSRIs and benzodiazepines.[113,115]

Agitated Delirium

The benefit reported with trazodone[116] remains unconfirmed in clinical trials. Treatment of underlying causes, non-drug management (e.g., orientation strategies, correction of sensory deprivation) and prevention of complications are central to delirium management. Antipsychotics are generally used first-line when medication is needed.[117]

Table 5
Differences Between SSRIs[107–111]

Drug	Additional Actions	Hepatic Enzyme Inhibition					Discontinuation Reaction Risk[a]
		CYP 1A2	CYP 2C9	CYP 2C19	CYP 2D6	CYP 3A4	
Citalopram	H_1 antagonist (*R*- enantiomer)				+		Low
Escitalopram	None				+		Low
Fluoxetine	$5HT_{2C}$ antagonist[b]		++	++	+++	+	Minimal
Fluvoxamine	Sigma-1 agonist[c]	+++		+++		++	Moderate
Paroxetine	Norepinephrine re-uptake inhibitor[b]				+++		High
Sertraline	Dopamine re-uptake inhibitor[b]				+		Low

Key: + = weak inhibition; ++ = moderate inhibition; +++ = marked inhibition
[a]Approximates to half-life (see Table 1)
[b]These actions theoretically contribute to their antidepressant effects but the affinity, and overall contribution of these additional actions is much less than the predominant serotonin re-uptake inhibition
[c]The action of sigma-1 receptors is poorly defined, but sigma-1 receptor agonists may have antidepressant, pro-seizure, euphoric and/or dysphoric effects.

Agitation and Challenging Behaviors in Dementia

Evidence for antidepressants is even more limited than for antipsychotics, and certainly insufficient to justify routine use.[118,119] Larger studies have not replicated the earlier benefit reported for trazodone.[118]

Sweating

Like other antimuscarinics, amitriptyline is used for paraneoplastic sweating unresponsive to NSAIDs.[120] However, like all monoamine reuptake inhibitors, it can also *cause* sweating.[121]

Hot Flashes

Venlafaxine and SSRIs are of benefit in hot flashes associated with the menopause, hormone therapy and androgen ablation therapy for prostate cancer.[122,123]

Insomnia

When insomnia co-exists with other indications, sedating antidepressants (e.g., TCAs, mirtazapine, trazodone) are often selected. Doxepin 3–6 mg at bedtime PO improves both sleep latency and fragmentation in primary insomnia. Benefit is sustained for ≥12 weeks without rebound insomnia after discontinuation.[124] Trazodone is commonly used although evidence is limited.[125]

Pruritus

Two small RCTs suggest benefit within a few days from sertraline (cholestatic pruritus)[126] and paroxetine (pruritus of mixed cause in cancer patients).[127] Benefit also is reported in pruritus associated with polycythemia vera.[128] Mirtazapine is reported to improve pruritus of mixed cause in advanced disease.[129] Like other H_1 antagonists, doxepin can be used for histamine-mediated pruritus and/or for night sedation.

Bladder Spasm, Stress Incontinence and Urgency

Antimuscarinic antidepressants (e.g., amitriptyline) reduce detrusor contractions associated with urgency, although licensed alternatives have additional direct effects on the detrusor muscle.[130] Duloxetine has a limited role in stress incontinence.[131]

Pathological Laughter and Crying

Frequent brief uncontrollable laughter and/or crying, incongruent with external events, can complicate numerous neurological disorders, including Parkinson's disease, cerebral tumors, multiple sclerosis, strokes, ALS/MND, and dementia. It can be socially disabling. Functional imaging suggests dysregulation of serotoninergic and other monoaminergic pathways. The differential diagnosis includes:

- seizures: generally complex partial seizures and thus an alteration of consciousness during/after episodes
- depression or other mood disorders: mood alteration is persistent whereas the emotion that may accompany pathological laughter and crying is short-lived.

Validated assessment tools are available to aid diagnosis.[132] First-line treatment is with citalopram or sertraline; doses can be lower than those required for depression. Benefit is often seen within days. Second-line options include amitriptyline, imipramine, nortriptyline and levodopa.[133]

Drooling and Sialorrhea

Like other antimuscarinics, amitriptyline reduces salivation.[134]

Stopping Antidepressants

Abrupt cessation of antidepressant therapy (particularly an MAOI) after regular administration for >8 weeks may result in a discontinuation reaction (withdrawal syndrome).[110] Discontinuation reactions depend on the class of antidepressant, and are more common with drugs with shorter half-lives (Box 4). Thus, with SSRIs, they are most common with paroxetine and least common with fluoxetine.

Box 4. Antidepressant Discontinuation Reactions[110]

SSRIs and venlafaxine: "*FINISH*" [135]
Flu-like symptoms (fatigue, lethargy, myalgia, chills)
Insomnia (including vivid dreams)
Nausea
Imbalance (ataxia, vertigo, dizziness)
Sensory disturbances (paraesthesia, sensations of electric shock)
Hyperarousal (restlessness, anxiety, agitation)

TCAs
Flu-like symptoms (fatigue, lethargy, myalgia, chills)
Insomnia (including vivid dreams)
GI disorders (nausea, diarrhea)
Mood disorders (depression or mania)
Movement disorders (rare: akathisia, parkinsonism)

Trazodone
Flu-like symptoms (fatigue, lethargy, myalgia, chills)
GI disorders (nausea, diarrhea)
Restlessness
Tremor
Headache

Mirtazapine
Nausea
Dizziness
Hyperarousal (anxiety, agitation)
Headache

MAOIs
Insomnia
Movement disorders (ataxia, athetosis, catatonia, myoclonus)
Mood disorders (lability, depression, agitation, aggression)
Paranoia
Hallucinations
Seizures
Altered speech (pressured, slow)

Discontinuation reactions differ from a depressive relapse or a panic disorder. They generally start abruptly within a few days of stopping the antidepressant (*or reducing its dose*). In contrast, a depressive relapse is uncommon in the first week after stopping an antidepressant, and symptoms tend to build up gradually and persist. Discontinuation reactions generally resolve within 24 h of re-instating antidepressant therapy, whereas the response is slower with a depressive relapse.

Ideally, antidepressants taken for >8 weeks should be progressively reduced over four weeks. If a mild discontinuation reaction is suspected, re-assurance alone may be adequate. If distressing, restart the antidepressant and reduce more gradually.

Some patients experience discontinuation symptoms even during tapering. When this happens, increase the dose and, before continuing with tapering, consider:

- using a liquid formulation and reducing the dose in smaller steps *or*
- switching from venlafaxine or a short half-life SSRI to fluoxetine.[110]

Abbreviations/Key

$5HT_{1A}$, $5HT_2$, $5HT_3$, etc.	5-hydroxytryptamine-1A, -2, and -3 receptors, etc.
α, α_1, α_2	Alpha, alpha-1 and -2 receptors
ACh_M	Anticholinergic (muscaric) receptor
ALS/MND	Amyotrophic lateral sclerosis/motor neuron disease
b.i.d.	Bis in die, twice daily
CBT	Cognitive behavioral therapy
CNS	Central nervous system
CYP	Cytochrome P450
D_2	Dopamine-2 receptor
DA	Dopamine
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECG (EKG)	Electrocardiogram
GABA	Gamma-aminobutyric acid
GI	Gastrointestinal
H_1	Histamine-1 receptor
IM	Intramuscular
IV	Intravenous
MAOI	Monoamine oxidase inhibitor
MARI	Monoamine re-uptake inhibitor
NDRI	Norepinephrine and dopamine re-uptake inhibitor
NE	Norepinephrine (noradrenaline)
NICE	National Institute for Health and Clinical Excellence
NMDA	*N*-methyl-D-aspartate
NNH	Number needed to harm, i.e., the number of patients needed to be treated in order to harm one patient sufficiently to cause withdrawal from a drug trial
PO	Per os, by mouth
p.r.n.	Pro re nata, as needed
q2 h, q6h	Every 2 hours, 6 hours, etc.
RA	Receptor antagonist
RCT	Randomized controlled trial
SC	Subcutaneous
SNRI	Serotonin and norepinephrine re-uptake inhibitor
SSRI	Selective serotonin re-uptake inhibitor
TCA	Tricyclic antidepressant
t.i.d.	Ter in die, three times daily
T_m	Time to reach maximum plasma concentration

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Palliativedrugs.com Quick Practice Guide: Depression

Sadness and tears, even if associated with transient suicidal thoughts, do not justify the diagnosis of depression or the prescription of an antidepressant. Often they are part of an adjustment reaction, and improve with time. Other patients are demoralized rather than medically depressed and respond to symptom management and psychosocial support.

Evaluation

1. Screening: about 5–10% of patients with advanced cancer develop a major depression. Cases will be missed unless specific enquiry is made of all patients:
   "What has your mood been like lately?…. Are you depressed?"
   "Have you had serious depression before? Are things like that now?"

2. Assessment interview: if depression is suspected, explore the patient's mood more fully by encouraging the patient to talk further with appropriate prompts. Symptoms suggesting clinical depression include:
   - sustained low mood (i.e., most of every day for several weeks) } core symptoms
   - sustained loss of pleasure/interest in life (anhedonia) } core symptoms
   - diurnal variation (worse in mornings and better in evenings)
   - waking significantly earlier than usual (e.g., 1–2 h) and feeling "awful"
   - feelings of hopelessness/worthlessness
   - excessive guilt
   - withdrawal from family and friends
   - persistent suicidal thoughts and/or suicidal acts
   - requests for euthanasia.

3. Differential diagnosis: the symptoms of depression and cancer, and of depression and sadness overlap. If in doubt whether the patient is suffering from depression, an adjustment reaction or sadness, review after 1–2 weeks of general support and improved symptom management. If still undecided, seek advice from a psychologist/psychiatrist.

4. Medical causes of depression: depression may be the consequence of:
   - a medical condition, e.g., hypercalcemia, cerebral metastases
   - a reaction to severe uncontrolled physical symptoms
   - drugs, e.g., antineoplastics, benzodiazepines, antipsychotics, corticosteroids, antihypertensives.

Management

5. Correct the correctable: treat medical causes, particularly severe pain and other distressing symptoms.

6. Non-drug treatment:
   - explanation and assurance that symptoms can be treated
   - depressed patients often benefit from the ambience of a Palliative Care Day Center
   - specific psychological treatments (via a clinical psychologist, etc.)
   - other psychosocial professionals, e.g., chaplain and creative therapists, have a therapeutic role, but avoid overwhelming the patient with simultaneous multiple referrals.

7. Drug treatment:
   - if the patient is expected to live for >4 weeks, prescribe a conventional antidepressant; if <4 weeks, consider a psychostimulant
   - the starting and continuing doses of antidepressants are generally lower in debilitated patients than in the physically fit
   - all antidepressants can cause withdrawal symptoms if stopped abruptly; generally withdraw gradually over 4 weeks
   - at usual doses, one SSRI can be directly substituted for another without cross-tapering or a washout period. Mirtazapine 15 mg can be directly substituted for SSRIs (fluoxetine, citalopram or paroxetine 20 mg; sertraline 50 mg)
   - taper higher SSRI doses before switching
   - switching to or from TCAs and MAOIs requires additional care – seek advice or see reference texts[105]

PCF preferred antidepressants

First-line

Psychostimulant, e.g., methylphenidate

Particularly if prognosis <2–4 weeks:

- start with 2.5–5 mg b.i.d. (on waking/breakfast time and noon/lunchtime)
- if necessary, increase by daily increments of 2.5 mg b.i.d. to 20 mg b.i.d.
- occasionally higher doses are necessary, e.g., 30 mg b.i.d. or 20 mg t.i.d.

SSRI, e.g., sertraline or citalopram

Particularly if prognosis >2–4 weeks, and if associated anxiety:

- no antimuscarinic effects, but may cause an initial increase in anxiety
- if necessary prescribe diazepam at bedtime
- start with sertraline 50 mg or citalopram 10 mg once daily, increasing the latter to 20 mg after 1 week
- if no improvement after 4 weeks, or only a partial improvement after 6–8 weeks, either:
  - ➢ increase dose by sertraline 50 mg or citalopram 10 mg *or*
  - ➢ switch to a second-line antidepressant
- maximum daily dose sertraline 200 mg or citalopram 40 mg (20 mg in patients >60 years, those with hepatic impairment, CYP 2C19 poor metabolizers, or concurrent use of a CYP 2C19 inhibitor)
- low likelihood of a withdrawal (discontinuation) syndrome.

Second-line

Alternative SSRI, e.g,. sertraline or citalopram

Dose as above

Mirtazapine

Acts on receptors; it is not a MARI. A good choice for patients with anxiety/agitation:

- start with 15 mg at bedtime
- if little or no improvement after 2 weeks, increase to 30 mg at bedtime
- concurrent H_1-receptor antagonism leads to sedation but this decreases at the higher dose because of noradrenergic effects.
- fewer undesirable effects than TCAs.

If no response after 4 weeks, consider third-line options.

Third-line options

- seek advice from a psychiatrist
- dose escalation
- switch antidepressant
- combine an SSRI with mirtazapine, olanzapine or quetiapine.