Antidepressants in clinical practice

Mark Agius[1,*], Hannah Bonnici[2]

[1] Clare College Cambridge, University of Cambridge, Cambridge, UK

[2] Hospital Pharmacy St. James Hospital Malta, Malta

***Corresponding author email: ma393@cam.ac.uk**

This paper is an updated version of 'Antidepressants in use in clinical practice' previously published in Psychiatria Danubina, 2017; 29 (Suppl. 3): 667-671

Abstract

Rather than to provide new information, the objective of this paper is to produce simple guidance for doctors prescribing antidepressants by giving useful information for when they are being prescribed. Antidepressants should always be seen as part of a package of treatment for the patient with depression. Such a package also should include psychological treatments and social interventions. Here the main antidepressant groups, including the selective serotonin reuptake inhibitors, the tricyclics and other classes are described, together with their mode of action, adverse effects and dosages. Antidepressants should usually be prescribed for six months in the case of a patient diagnosed with unipolar depression. The efficacy of antidepressants is similar between classes, despite their different mechanisms of action. The choice is usually based on avoiding adverse effects, or sometimes on beneficial side effects. No single antidepressant is beneficial without any adverse effects. Increasing knowledge of what exactly causes depression should enable researchers not only to create more effective antidepressants rationally, but also to understand the limitations of existing drugs.

Keywords: antidepressants, depression, psychological therapies, social therapies

Introduction

Depression may be described as a mood disorder that negatively and persistently affects the way a person feels, thinks and acts. Common signs include low mood, loss of interest in activities that were once enjoyable and changes in appetite and sleep patterns. Treating depression may involve a single drug or combinations of drugs, psychotherapy and electroconvulsive therapy, alongside medical and family support. The type of antidepressant treatment chosen is dependent on numerous factors, including the type of depression, whether it is acute, chronic or recurrent, past positive responses to treatment, the severity of the depression and other factors (1).

The pathophysiology of depression is known to involve a reduction or functional deficiency of the neurotransmitters noradrenaline, serotonin and dopamine in the central nervous system. Other factors that may contribute to depression include changes in hormones, circadian rhythm and neuropeptides. This article focuses on the antidepressants that are currently available to doctors (2).

Antidepressants should usually be prescribed for six months to treat a patient with a single episode of unipolar depression. The efficacy of antidepressants is similar between classes, despite their different mechanisms of action. The choice is therefore based on the adverse effects to be avoided. There is no single ideal drug capable of exerting its therapeutic effects without any adverse effects.

Classes of Antidepressants

Antidepressants may be divided into the following classes:

- **Monoamine uptake inhibitors**
  - Tricyclic antidepressants (TCAs)
  - Selective serotonin reuptake inhibitors (SSRIs)
  - Noradrenaline reuptake inhibitors (NARIs)

- Serotonin-noradrenaline reuptake inhibitors (SNRIs)
- Noradrenaline-dopamine reuptake inhibitors (NRDIs)

- **Monoamine oxidase (MAO) inhibitors**
  - Non-selective monoamine oxidase inhibitors
  - Selective monoamine oxidase type A inhibitors
- **Atypical antidepressants and other classes**

Tricyclic and tetracyclic antidepressants

Mechanism of action

Tricyclic antidepressants (TCAs) and tetracyclic antidepressants inhibit the neuronal reuptake of noradrenaline and serotonin, thereby increasing their concentration within the synapses and enhancing neurotransmission. Their efficacy for the two types of neurotransmitter receptors varies and this results in different frequencies and intensities of adverse effects (3).

- The onset of action is delayed by 7 - 14 days. It is usual practice to start on low doses which are gradually increased until the patient is stable. Patients are advised not to stop taking antidepressants suddenly due to the risk of withdrawal symptoms.
- TCAs are more likely to be discontinued than SSRIs due to adverse effects. They can be fatal in overdose.
- TCAs are contra-indicated in patients with cardiac defects due to their quinidine-like effects and prolongation of the QT interval. They also have a relatively high likelihood to cause seizures.
- TCAs may be preferred to SSRIs where sedation is required although this varies from one TCA to another (4).
- There is evidence that, if prescribed to patients with bipolar disorder to treat depression, TCAs may cause a 'switch' of symptoms to a manic phase, or into a mixed state. Hence it is important that proper diagnosis of the type of depression must be made before prescribing antidepressants (5).

Table 1: Tricyclic and tetracyclic antidepressants and their dose ranges (3)

	Examples	*Adult daily dose range for depression (mg)*
Tricyclic antidepressants	Amitriptyline	75 - 200
	Clomipramine	10 - 250
	Desipramine	25 - 300
	Dosulepine[a]	75 - 225
	Doxepin	75 - 300
	Imipramine	75 - 200
	Lofepramine[b]	140 - 210
	Nortriptyline	75 - 150
	Protriptyline	10 - 60
	Trimipramine	50 - 300

	Examples	*Adult daily dose range for depression (mg)*
Tetracyclic antidepressants	Amoxapine[c]	100 - 600
	Maprotiline	25 - 225
	Mianserin[c]	30 - 90

a. considered to be less suitable for prescribing due to its relatively high toxicity in overdose without therapeutic advantages over other tricyclics (6).

b. particular in that it is the only tricyclic which is not cardiotoxic in overdose, thus safer, albeit less potent than others within the same class (6).

c. often classed as tricyclic antidepressants and grouped with secondary amines.

Adverse effects

Table 2: Tricyclic antidepressant adverse effects (3)

Pathway	*Effect*
Adrenergic alpha-receptor antagonism	orthostatic hypotension
Direct membrane effects	arrhythmia, tachycardia
Histamine H1 receptor antagonism	sedation, weight gain
Muscarine M1 receptor antagonism	anti-cholinergic symptoms including dry mouth, dry eyes, blurred vision, constipation, confusion, drowsiness, sedation, urinary retention
Serotonin 5-HT_2 receptor antagonism	weight gain

Serotonin Syndrome involves excessive central and peripheral serotonergic activity caused by a sudden dose increase, the addition of another serotonergic drug, or the replacement of one for another without an appropriate wash-out period in between. Risk of occurrence is more common with SSRIs than with TCAs and the combination of SSRIs with MAOIs is contraindicated for this reason (3).

Selective Serotonin Reuptake Inhibitors (SSRIs)

Mechanism of action

SSRIs inhibit the neuronal reuptake of serotonin by specifically binding to 5-HT receptors within the synapses. Their effects on noradrenaline are minimal (3).

- Like the TCAs, onset of action of SSRIs is delayed by 7 - 14 days.
- In comparison with TCAs, SSRIs are better tolerated, safer in patients with cardiac defects, safe in overdose, and have low likelihood to cause seizures.
- SSRIs may be preferred to TCAs due to less frequent and less severe adverse effects (less weight gain, no anti-cholinergic adverse effects) (4).
- The risk of patients with bipolar depression switching to mania on treatment with antidepressants is much lower with SSRIs than with TCAs (5, 7).
- There is evidence that, if prescribed to patients with bipolar disorder to treat depression, SSRIs may be effective. Hence it is important that proper diagnosis must be made before prescribing antidepressants (8-10).
- Discontinuation syndrome is more common with SSRIs than with TCAs; the most common symp-

toms are headache, electric shock sensations in the head, neck and spine, influenza-like symptoms, sweating, tinnitus, paraesthesiae, fatigue, anxiety and dizziness. When stopping an SSRI, it is common practice to switch to a drug like fluoxetine that has a long half-life and is metabolised to an active metabolite, in order to reduce the risk of this happening (3).

Table 3: SSRIs and their dose ranges (3)

SSRI	*Adult daily dose range for depression (mg)*
Citalopram	20 - 40
Escitalopram	10 - 20
Fluoxetine	20 - 60
Fluvoxamine	50 - 300
Paroxetine	20 - 50
Sertraline	25 - 200

Adverse effects

Table 4: SSRI adverse effects (3)

Symptom group	*Effect*
Gastrointestinal symptoms	abdominal pain, constipation, diarrhoea, dyspepsia, nausea, vomiting, increased risk of bleeding[d]
Sexual dysfunction	anovulation, amenorrhoea, decreased libido and/or sexual arousal, galactorrhoea
Syndrome of inappropriate antidiuretic hormone secretion (SIADH)	hyponatraemia manifesting as confusion, drowsiness, dizziness, seizures

d. given that there is a risk of increased bleeding with the use of SSRIs it is presently suggested that if an SSRI is required in a patient at high risk of upper gastrointestinal bleeding, one should consider the use of a gastro-protective agent. Studies have shown the use of acid suppressing drugs, for example PPIs, are protective against upper gastrointestinal bleeds in patients receiving single-therapy SSRI or combination NSAID and SSRI treatment (11).

Noradrenaline reuptake inhibitors (NRIs or NERIs)

Mechanism of action

NRIs inhibit the reuptake of the neurotransmitters norepinephrine (noradrenaline) and epinephrine (adrenaline) by blocking the action of the norepinephrine transporter, which leads to increased extracellular concentrations of the two neurotransmitters (3).

Table 5: NRIs and their dose ranges

NRI	*Adult daily dose range for depression (mg)*
Atomoxetine[e]	-
Reboxetine	8 - 12

e. licensed for use in attention deficit hyperactivity disorder (ADHD). Not effective in clinically significant depression, however may improve global cognitive performance and daytime sleepiness (12).

Adverse effects

Table 6: NRI adverse effects (3)

NRI	*Effect*
Atomoxetine	abdominal pain, anorexia, dry mouth, dyspepsia, constipation, flatulence, nausea, taste disturbances, vomiting, increased blood pressure, palpitations, tachycardia
Reboxetine	constipation, dizziness, dry mouth, impaired visual accommodation, urinary retention, tachycardia, postural hypotension, vasodilation

Serotonin-noradrenaline reuptake inhibitors (SNRIs)

Mechanism of action

SNRIs inhibit the neuronal reuptake of serotonin and noradrenaline at neuronal ends, thereby increasing both levels within the synapse.

There is evidence that, if prescribed to patients with bipolar disorder to treat depression, SNRIs may cause a 'switch' of symptoms to a manic phase, or into a mixed state. Hence it is important that proper diagnosis of the type of depression must be made before prescribing antidepressants (13).

Table 7: SNRIs and their dose ranges (3)

SNRI	*Adult daily dose range for depression (mg)*
Duloxetine	30 - 120
Venflaxine	75 - 375

Adverse effects

Table 8: SNRI adverse effects (3)

SNRI	*Effect*
Duloxetine[f]	constipation, decreased appetite, diarrhoea, dry mouth, nausea, vomiting, somnolence, headache, dizziness, insomnia, fatigue, sweating, erectile dysfunction
Venflaxine[g]	hypertension, headache, dizziness, nausea, dry mouth, constipation, abnormal ejaculation, impotence, insomnia, somnolence, nervousness, sweating

f. also commonly used to control diabetic neuropathy and stress urinary incontinence.

g. due to higher noradrenaline activity, hypertension is more common than with TCAs and SSRIs

Venflaxine effects are initiated more quickly than other antidepressants. This may be due to its acute onset of down-regulation of beta-adrenergic receptors (4).

Noradrenaline-dopamine reuptake inhibitors (NDRIs)

Mechanism of action

NDRIs inhibit the reuptake of the neurotransmitters noradrenaline and dopamine by blocking the action of the noradrenaline and the dopamine transporters, respectively (3).

Table 9: NDRIs and their dose ranges

NDRI	*Adult daily dose range for depression (mg)*
Bupropion[h]	-

h. marketed as an aid to smoking cessation, however use in depression may be considered instead of SSRIs where SIADH is a problem (3).

Adverse effects

Table 10: NDRI adverse effects (3)

NDRI	*Effect*
Bupropion	agitation, anxiety, dizziness, dry mouth, gastrointestinal disturbances, insomnia, sweating, taste disturbances, tremor

Monoamine oxidase inhibitors (MAOIs)

Mechanism of action

MAOIs inhibit the enzyme monamine oxidase from removing the neurotransmitters noradrenaline, serotonin and dopamine from the brain, resulting in their accumulation. They are in turn divided into selective and non-selective MAOIs.

- MAOIs are used much less frequently than SSRIs and TCAs due to their significant effect on the digestive system and their tendency to interact with other drugs.
- In inhibiting the enzyme monoamine oxidase, the non-selective MAOIs inhibit the breakdown of tyramine, which is an amino acid responsible for the regulation of blood pressure: the higher the levels, the greater the blood pressure. The consumption of tyramine-containing foods, like yeast, red wine, and aged cheese thus results in its accumulation and a possible dangerous rise in blood pressure. Monamine oxidase takes several weeks to be replaced, therefore the danger of such an interaction persists for up to two weeks following discontinuation of the MAOI.
- Contra-indicated for use alongside SSRIs due to the risk of triggering the serotonin syndrome.
- Phobic patients, and depressed patients with atypical, hypochondriacal, or hysterical features are said to respond best to MAOIs. MAOIs may also be used in the treatment of panic disorder with agoraphobia, social phobia, post-traumatic stress disorder, borderline personality disorder, and bipolar depression.

Table 11: MAOIs and their dose ranges (3)

	Examples	*Adult daily dose range for depression (mg)*
Non-selective irreversible MAOIs	Phenelezine	15 - 90
	Tranylcypromine	10 - 30
	Isocarboxazid	30 - 60
Selective reversible MAOIs (type A)	Moclobemide	150 - 600
Selective MAOIs (type B)	Rasagaline[i]	-
	Selegiline[i]	-

i. used for the treatment of Parkinson disease rather than depression, due to selective effect on dopaminergic neurotransmission

Adverse effects

Table 12: MAOI adverse effects (3)

MAOI	*Effect*
Phenelezine Tranylcypromine Isocarboxazid Moclobemide Rasagaline Selegiline	dizziness, headache, postural hypotension, weight gain, sleep disturbance, sexual dysfunction

Atypical antidepressants and other classes

Table 13: Atypical antidepressants and other classes

Drug	*Classification*	*Mechanism of action*	*Dose (mg)*	*Common adverse effects*	*Notes*
Mirtazapine (3, 4)	Noradrenergic and specific serotonergic antidepressant (NaSSA)	Antagonises the pre-synaptic alpha$_2$ adrenoreceptor and serotonin receptor subtypes 5-HT$_{2A}$, 5-HT$_{2C}$, and 5-HT$_3$ to increase central noradrenergic and serotonergic neurotransmission	15 - 45	constipation, dizziness, drowsiness, dry mouth, increased appetite, somnolence, weight gain	May act more rapidly than other antidepressants and causes less of the adverse effects that are common to TCAs and SSRIs. However, has a significant anti-histermine effect
Trazodone (3, 4, 14)	Serotonin antagonist and reuptake inhibitor (SARI)	Antagonises all 5-HT receptor sites except 5-HT$_{1A}$, where it acts as a partial agonist. Also simultaneously (weakly) inhibits serotonin transporters (SERT)	150 - 600	blurred vision, drowsiness, dizziness, dry mouth, fatigue, headache, nausea, nervousness, priapism	Used particularly where sedation is required due to its hypnotic and anxiolytic effects
Nefazodone (3, 4)	SARI		-	sedation, impaired concentration, lethargy	Lack of anti-histaminic and anti-cholinergic activity improves tolerance and safety
Tianeptine (3)	Selective serotonin reuptake enhancer (SSRE)	Increases the uptake of serotonin within synapses. It is not known how this results in relieving depression but theories include modulation of glutamatergic transmission and its agonist effects on mu-opiate receptors	12 - 36	dizziness, drowsiness, dry mouth, constipation, headache, insomnia	Lacks cardiovascular, anti-cholinergic and sedative adverse effects and has a quicker onset of action to traditional antidepressants
Tryptophan (3)	Essential amino acid	Converted into serotonin itself following reactions of condensation, reductive decarboxylation and catalysis	6,000 - 12,000	dizziness, drowsiness, dry mouth, headache, loss of appetite, nausea	May be obtained from protein-based dietary sources or as a supplement

Drug	*Classification*	*Mechanism of action*	*Dose (mg)*	*Common adverse effects*	*Notes*
Agomelatine (3, 15)	Melatonergic antidepressant	Agonist for melatonergic MT_1 and MT_2 receptors and antagonist for the serotonin 5-HT_{2C} receptor	25 - 50	abdominal pain, constipation, diarrhoea, nausea, vomiting, raised liver enzymes	No dosage tapering required on treatment discontinuation

Conclusion

The efficacy of antidepressants in treating unipolar depression is similar between classes, despite their different mechanisms of action. The choice is therefore based on the adverse effects to be avoided. There is no one ideal drug capable of exerting its therapeutic effects without any adverse effects. Increasing knowledge of what exactly causes depression should enable researchers not only to create more effective antidepressants rationally, but also to understand the limitations of existing drugs (4).

It is important that antidepressants should be used to treat depression only after a proper assessment and diagnosis of the type of depression, whether unipolar or bipolar, situational or endogenous, has been made, since this will affect the efficacy and appropriateness of the antidepressant treatment choice.

References

1. Azzopardi LM. Lecture notes in pharmacy practice: Pharmaceutical Press; 2009
2. Fekadu N, Shibeshi W, Engidawick E. Major depressive disorder: pathophysiology and clinical management. Journal of Depression and Anxiety 2016;6:255
3. Joint Formulary Committee. British National Formulary. 75th ed. London: BMJ Group and Pharmaceutical Press; 2018
4. Feighner JP. Mechanism of action of antidepressant medications. The Journal of Clinical Psychiatry. 1999;60:4-11
5. Peet M. Induction of mania with selective serotonin re-uptake inhibitors and tricyclic antidepressants. The British Journal of Psychiatry. 1994 Apr;164(4):549-50
6. Safety bulletin: dosulepin prescribing [Internet]. NHS Dorset Clinical Commissioning Group; 2016 [cited 17 December 2018]. Available from: https://www.dorsetccg.nhs.uk/Downloads/aboutus/medicines-management/Other%20Guidelines/2016_17%20-%20Safety%20bulletin%20Dosulepin.pdf
7. Rihmer Z, Gonda X. The effect of pharmacotherapy on suicide rates in bipolar patients. CNS Neuroscience & Therapeutics. 2012 Mar;18(3):238-42
8. El-Mallakh RS, Vöhringer PA, Ostacher MM, Baldassano CF, Holtzman NS, Whitham EA, Thommi SB, Goodwin FK, Ghaemi SN. Antidepressants worsen rapid-cycling course in bipolar depression: a STEP-BD randomized clinical trial. Journal of Affective Disorders. 2015 Sep 15;184:318-21
9. Rihmer Z, Rihmer A, Döme P. Suicidal behaviour in patients with mood disorders. Evidence-Based Psychiatric Care. 2015;1:19-26
10. Rihmer Z, Gonda X. Pharmacological prevention of suicide in patients with major mood disorders. Neuroscience & Biobehavioral Reviews. 2013 Dec 1;37(10):2398-403
11. Woodland G. What is the risk of gastrointestinal bleeding associated with selective serotonin reuptake inhibitors (SSRIs)? SPS - Specialist Pharmacy Service. The first stop for professional medicines advice [Internet]. Sps.nhs.uk. 2015 [cited 14 January 2019]. Available from: https://www.sps.nhs.uk/articles/what-is-the-risk-of-gastrointestinal-bleeding-associated-with-selective-serotonin-reuptake-inhibitors-ssris/
12. Weintraub D, Mavandadi S, Mamikonyan E, Siderowf AD, Duda JE, Hurtig HI, Colcher A, Horn SS, Nazem S, Ten Have TR, Stern MB. Atomoxetine for depression and other neuropsychiatric symptoms of Parkinson disease. Neurology. 2010 Aug 3;75(5):448-55

13. Patel R, Reiss P, Shetty H, Broadbent M, Stewart R, McGuire P, Taylor M. Do antidepressants increase the risk of mania and bipolar disorder in people with depression? A retrospective electronic case register cohort study. BMJ Open. 2015 Dec 1;5(12):e008341

14. Fagiolini A, Comandini A, Dell'Osso MC, Kasper S. Rediscovering trazodone for the treatment of major depressive disorder. CNS Drugs. 2012 Dec 1;26(12)1033-49

15. Manikandan S. Agomelatine: A novel melatonergic antidepressant. Journal of Pharmacology & Pharmacotherapeutics. 2010 Jul;1(2):122