Chapter 5

Medications

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The essence of the theoretical background of antidepressant action is based on the monoamine hypothesis of depression. It the 1960s it was noted that reserpine, a catecholamine-depleting agent, induced depression and that this effect was reversed by antidepressants. The involvement of monoamines was also supported by the observations suggesting that dopamine (DA) and norepinephrine (NE; noradrenaline) were functionally deficient in depression and elevated in mania. Similarly, Ashcroft proposed that an indoleamine, now called serotonin (5HT), was deficient in depression, leading eventually to the development of selective serotonin reuptake inhibitors (SSRIs). It is widely believed that the chronic administration of SSRIs resulting in 5HT reuptake blockade is responsible for the downregulation of 5HT1A receptors present on the cell bodies of serotoninergic neurons. This effect reduces negative feedback, increasing 5HT neuronal firing and hence 5HT synaptic availability. This is a proposed mechanism to explain the delay between acute administration of an antidepressant and the therapeutic effect. It is unlikely to be the full explanation and does not generalize to drugs acting in different ways on the monoamine systems. It is also increasingly recognized that the onset of improvement with antidepressants is immediate, although significant clinical benefit takes some weeks to be evident. Current theories of the mechanism of action of antidepressants emphasize effects beyond the synapse such as neurotropic effects [1].

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This chapter describes antidepressants prescribed in clinical practice, with tables for pharmacology and clinical details of compounds commonly used in day-to-day practice. Newer drugs do not fit easily into the classical classification of antidepressants and for simplicity we have grouped them by their main pharmacology. For more detail, readers are referred to textbooks of pharmacotherapy [1–3]. Dosage may vary according to clinical presentation and age group. Many compounds have recommended twice or even three-times-daily administration based on the elimination half-life. However, in practice, antidepressants are often given once daily and there is no evidence of benefit in giving any antidepressant more than once daily, except to reduce side effects by influencing peak plasma effects. More than once-daily administration may impair adherence, and for many drugs single nighttime administration is acceptable and tolerable [4,5]. Average dose ranges are given, but these should be taken as guidelines only and reference to manufacturer's information and/or national formulary is advisable at the time of prescribing [6,7].

Selective serotonin reuptake inhibitors

Most guidelines support the use of SSRIs as first-line pharmacological treatment for depression on the basis of their safety and tolerability. The principal mechanism of action of SSRIs is to inhibit the reuptake of 5HT into the presynaptic nerve terminal. In terms of toxicity in overdose, SSRIs are generally considered at low risk, especially if taken alone, although citalopram (and possibly escitalopram) may carry a slightly increased risk compared with other SSRIs [8]. The smallest dose likely to cause death is not clearly defined but believed to be around 1 g or 2 g. Differences in SSRI tolerability probably result largely from pharmacokinetic considerations but there are also subtle pharmacodynamic differences, with fluoxetine being the least selective for 5HT over NE, and sertraline having some DA reuptake at higher doses. Fluvoxamine appears least well tolerated at least in doses >100 mg, but may be the least likely to cause sexual dysfunction, whereas paroxetine is the most likely. Paroxetine appears the most likely to cause discontinuation symptoms, and fluoxetine the least [9]. Recently maximum dose restrictions have been introduced for citalopram and escitalopram due to concern

Pharmacology of selective serotonin reuptake inhibitors

Drug	Active metabolite	$t_{1/2}$ ($t_{1/2}$ of metabolite)	Metabolism	Hepatic enzyme inhibition
Citalopram	Negligible	36	Hepatic	Negligible
Escitalopram (*S*-enantiomer of citalopram)	Negligible	36	Hepatic	Negligible
Fluoxetine	Norfluoxetine	72 (200)	Hepatic	CYP2D6, 3A4, 2C19
Fluvoxamine	Negligible	25	Hepatic	CYP1A2
Paroxetine	Negligible	20	Hepatic	CYP2D6, 2C9
Sertraline	Desmethylsertraline	25 (66)	Hepatic	CYP2D6 (weak)

Figure 5.1 Pharmacology of selective serotonin reuptake inhibitors. $t_{1/2}$, half-life (in hours); CYP, cytochrome P450; SSRI, selective serotonin reuptake inhibitor.

Clinical use of selected serotonin reuptake inhibitors

Medication	Usual daily dose (mg)	Main adverse effects	Significant interactions
Citalopram	20–40	Nausea/vomiting, agitation, akathisia, insomnia/sedation, sexual dysfunction, dizziness, convulsions (rare), increased risk of suicidality (<30years), hyponatremia (especially in the elderly), increased risk of bleeding, discontinuation syndrome, prologation of QTc at high doses	MAOIs (serotonin syndrome) Lithium (therapeutic, serotonin syndrome) L-Tryptophan (therapeutic, serotonin syndrome) St John's wort (serotonin syndrome)
Escitalopram (*S*-enantiomer of citalopram)	10–20	As for citalopram*	As for citalopram*
Fluoxetine	20–40	As for citalopram* but insomnia and agitation more common, discontinuation syndrome less common	As for citalopram* plus: Antipsychotics (increased concentration) Opiates (increased concentration) TCAs (increased concentration)
Sertraline	50–200	As for citalopram*	As for citalopram*

Figure 5.2 Clinical use of selective serotonin reuptake inhibitors**(continues overleaf).**

Clinical use of selected serotonin reuptake inhibitors (continued)

Medication	Usual daily dose (mg)	Main adverse effects	Significant interactions
Paroxetine	20–40	As for citalopram* but discontinuation syndrome more common (slow discontinuation advisable)	As for fluoxetine
Fluvoxamine	100–200	As for citalopram* but nausea more common	As for citalopram* plus: Some TCAs (increased concentration) Olanzapine, clozapine (increased concentration) Warfarin (increased concentration) Propranolol (increased concentration)

Figure 5.2 Clinical use of selected serotonin reuptake inhibitors (continued). MAOI, monoamine oxidase inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA,tricyclic antidepressant.*no QTc prolongation.

about QTc prolongation and risk of cardiac arrhythmias at higher doses [10]. The pharmacology and clinical use of SSRIs are summarized in Figures 5.1 and 5.2.

Combined serotonin reuptake inhibition and 5HT receptor actions

Trazodone and nefazodone are only weak serotonin reuptake inhibitors (SRIs) and their main mechanism of action is believed to be due to 5-hydroxytryptamine (5HT)2 antagonism and possibly 5HT1A partial agonism. Vilazodone has been recently licensed in the USA and is a potent 5HT reuptake inhibitor and 5HT1A partial agonist. Vortioxetine has also recently been licensed in the USA and Europe and combines 5HT reuptake inhibition and multiple actions at 5HT receptors. The pharmacology and clinical use of combined SRI-5HT receptor active drugs are summarized in Figures 5.3 and 5.4.

Trazodone and nefazodone

Trazodone is a potent 5HT2 antagonist with less strong 5HT1A partial agonism and weak 5HT reuptake inhibition. Other pharmacological

Pharmacology of combined serotonin reuptake inhibitor-5-hydroxytryptamine receptor-active drugs

Drug	Active metabolite	$t_{1/2}$ ($t_{1/2}$ of metabolite)	Metabolism	Hepatic enzyme inhibition
Trazodone	m-Chlorophenylpiperazine	3–9 (up to 72)	Hepatic	Negligible
Nefazodone	Negligible	2–4	Hepatic	CYP3A4
Vilazodone	Negligible	25	Negligible	CYP2C8, CYP3A4/5
Vortioxetine	Negligible	66	Hepatic	Negligible

Figure 5.3 Pharmacology of combined serotonin reuptake inhibitor 5-hydroxytryptamine receptor-active drugs. $t_{1/2}$, half-life (in hours); CYP, cytochrome P450.

Clinical use of combined serotonin reuptake inhibitor-5-hydroxytryptamine receptor-active drugs

Medication	Usual daily dose (mg)	Main adverse effects	Significant interactions
Trazodone	150–300	Sedation, dizziness, headache, nausea/ vomiting, tremor, postural hypotension, tachycardia, rarely priapism	Negligible
Nefazodone	300–600	As trazodone apart from priapism; less sedative	TCAs (increased concentration) Alprazolam (increased concentration) Potential hepatoxicity; its use is subject to monitoring of hepatic function in North America
Vilazodone	40	Diarrhea, nausea, vomiting, insomnia. Sexual dysfunction comparable to placebo	MAOIs (serotonin syndrome) Lithium (therapeutic, serotonin syndrome), l-Tryptophan (therapeutic, serotonin syndrome), St John's wort (serotonin syndrome)
Vortioxetine	10-20	Nausea, dizziness, sexual dysfunction at higher doses	As vilazodone

Figure 5.4 Clinical use of combined serotonin reuptake inhibitor 5-hydroxytryptamine receptor-active drugs. MAOI, monoamine oxidase inhibitor ; TCA, tricyclic antidepressant.

actions include α1 antagonism and weak antihistaminergic properties. Its metabolite m-chlorophenylpiperazine has 5HT agonist properties and

releases 5HT. Nefazodone has similar pharmacology to trazodone but lacks antihistaminergic properties. Both lack the typical effects of SSRIs and a major advantage is that they do not interfere with sexual function significantly. Nefazodone was withdrawn from the European market in 2003 due to hepatotoxicity. The use of nefazodone is subject to monitoring of hepatic function in North America and it is rarely prescribed.

Vilazodone

Vilazodone is a high affinity SSRI and a partial antagonist at 5HT1A receptors. The reduced negative feedback mediated by presynaptic 5HT1A autoreceptors could potentially speed antidepressant response but this has yet to be established in practice. There is little experience of its use in antidepressant combination therapy and serotonin syndrome a potential concern given the 5HT enhancement. Treatment should start at 10 mg daily and be titrated to 40 mg over two weeks. The dose should be limited to 20 mg if used with strong inhibitors of CYP3A4 which may increase vilazodone plasma concentration.

Vortioxetine

Vortioxetine is an SRI with multiple actions at 5HT receptors; 5HT1A agonism, 5HT1B partial agonism, 5HT1D, 5HT3 and 5HT7 antagonism. It also binds to β1-receptors. It elevates levels of 5HT, NE, DA, acetylcholine and histamine in specific brain regions and has been called a multimodal antidepressant. The recommended starting dose is 10 mg, increasing to a treatment dose of 20 mg as efficacy is dose-related. The dose can be reduced to 5 mg if higher doses are not tolerated; a maximum of 10 mg is recommended if administered with drugs that inhibit CYP2D6. It is better tolerated than selective norepinephrine reuptake inhibitors (SNRIs) and the most common side effects are nausea, diarrhea and dizziness. Sexual adverse effects are more common than with placebo and dose-related, but seem less common than with SSRIs.

Serotonin and norepinephrine reuptake inhibitors

Venlafaxine, desvenlafaxine (licensed in North America), duloxetine, and milnacipran (licensed in France and Japan) are known as ‘dual

action' reuptake inhibitors because of their action as selective 5HT and NE reuptake inhibitors. The pharmacology and clinical use of SNRIs are summarized in Figures 5.5 and 5.6.

Pharmacology of selected norepinepherine reuptake inhibitors

Drug	Active metabolite	$t_{1/2}$ ($t_{1/2}$ of metabolite)	Metabolism	Hepatic enzyme inhibition
Venlafaxine	Desvenlafaxine (*O*-desmethylvenlafaxine)	5 (11)	Hepatic	Negligible
Duloxetine	Negligible	12	Hepatic	CYP2D6, CYP1A2
Milnacipran	Negligible	8	Negligible	Negligible

Figure 5.5 Pharmacology of selected norepinephrine reuptake inhibitors. $t_{1/2}$, half-life (in hours); CYP, cytochrome P450.

Clinical use of selected norepinepherine reuptake inhibitors

Medication	Usual daily dose (mg)	Main adverse effects	Significant interactions
Venlafaxine	75–225 XL 75– 375	Nausea, insomnia, dry mouth, sedation, dizziness, sweating nervousness, headache, sexual dysfunction, hypertension at higher doses, discontinuation syndrome	MAOIs (serotonin syndrome) Lithium (therapeutic, serotonin syndrome) l-Tryptophan (therapeutic, serotonin syndrome) St John's wort (serotonin syndrome)
Desvenlafaxine	50	As venlafaxine, but better tolerated at recommended dose	As venlafaxine
Duloxetine	60–120	Nausea, insomnia, dizziness, dry mouth, constipation, anorexia, and increased blood pressure and heart rate	As venlafaxine plus TCAs (increased concentration) Antipsychotics (increased concentration) May cause liver damage or exacerbate pre-existing liver damage (avoid alcohol)
Milnacipran	100	Nausea, vertigo, increased anxiety, sweats, shivering, dysuria, itching, and testicle pain	As venlafaxine

Figure 5.6 Clinical use of selected norepinephrine reuptake inhibitors. MAOI, monoamine oxidase inhibitor; TCA, tricyclic antidepressant.

Venlafaxine

The efficacy of venlafaxine is similar to TCAs (eg, amitriptyline, clomipramine, and imipramine), but better tolerated. There is some evidence that its dual mechanism of action makes venlafaxine more efficacious in the treatment of more severe depressive disorders, and guidelines tend to favor its use in cases of lack of, or insufficient, response to, SSRIs. However, dual action is believed to occur only at higher doses. Reuptake of 5HT occurs at a dose of 75 mg, whereas for blockade of NE, reuptake dose is 150 mg/day and greater. At the highest doses venlafaxine may also be a DA reuptake inhibitor. Venlafaxine has typical SSRI-like side effects, including sexual dysfunction and discontinuation syndrome, as well as those attributable to effects on NE. It is contraindicated in patients at high risk of serious cardiac ventricular arrhythmia and uncontrolled hypertension. It is considered good practice to ensure that the patient is normotensive at the time of prescribing and to monitor blood pressure at doses of 300 mg/day or above. It is advisable to seek specialist supervision in case of doses reaching 300 mg/day and above. It is more toxic in overdose than SSRIs but much less than TCAs.

Desvenlafaxine

Desvenlafaxine (O-desmethylvenlafaxine) is the major metabolite of venlafaxine and has a relatively higher NE:5HT transporter inhibition ratio than its parent compound, and more similar to that of duloxetine. Unlike venlafaxine, little metabolism occurs through hepatic CYP450 pathways, reducing the risk of pharmacokinetic drug interactions; dose adjustments are not required in hepatic disease. It is well tolerated at its recommended dose of 50 mg and does not require dose titration. Doses higher than 50 mg are less well tolerated without increased efficacy.

Duloxetine

Duloxetine is a 5HT and NE reuptake inhibitor with weaker inhibition of DA than 5HT reuptake. It has been proposed to be particularly effective compared with other antidepressants for painful physical symptoms occurring in depression, but direct evidence of this is lacking. Its license includes treatment of pain syndromes such as diabetic peripheral

neuropathic pain, fibromyalgia and chronic musculoskeletal pain (the last two in the USA but not Europe). Usual dosage is in the range of 60–120 mg/day. Although the starting dose is recommended as 60 mg, it is better to titrate up from 30 mg in antidepressant-naïve patients to improve tolerability.

Milnacipran

Milnacipran is a dual reuptake inhibitor with slightly more action on NE than 5HT reuptake. Metabolism does not involve the CYP450 system, and it is excreted as a mixture of active and inactivated compound. Renal, but not hepatic, disease delays excretion. Levomilnacipran is an active enantiomer of milnacipran in clinical development.

Monoamine receptor-active drugs

The pharmacology and clinical use of monoamine receptor-active drugs are summarized in Figures 5.7 and 5.8.

Pharmacology of monoamine receptor-active drugs

Drug	Active metabolites	$t_{1/2}$ ($t_{1/2}$ of metabolite)	Metabolism	Hepatic enzyme inhibition
Mirtazapine	Negligible	26-37	Hepatic	Negligible
Agomelatine	Negligible	1-2	Hepatic	Negligible

Figure 5.7 Pharmacology of monoamine receptor-active drugs. CYP, cytochrome P450; $t_{1/2}$, half-life (in hours).

Clinical use of monoamine receptor-active drugs

Medication	Usual daily dose (mg)	Main adverse effects	Significant interactions
Mirtazapine	15–45	Increased appetite, weight gain, drowsiness, edema, dizziness, headache	Potentiation of benzodiazepine effect (↓ excretion)
Agomelatine	25–50	Headache, nausea, fatigue, dizziness, raised liver enzymes and hepatotoxicity. Monitoring of liver enzymes required. Caution in liver disease	Negligible

Figure 5.8 Clinical use of monoamine receptor-active drugs.

Mirtazapine and mianserin

Mirtazapine's mechanisms of action include antagonism of α2-presynaptic receptors, which ultimately increases both NE and 5HT neurotransmission by increased cell firing and synaptic release; antagonism of postsynaptic 5HT2 and 5HT3 receptors, which may also improve the tolerability of mirtazapine but contribute to weight gain; and a potent antihistaminergic effect contributing to its side effects of weight gain, sedation, and anxiolytic properties. It has a low incidence of sexual side effects. It may be a little more toxic in overdose than SSRIs but much less that TCAs.

Mianserin is an older drug which has been largely superseded by mirtazapine with which it shares most of its pharmacology. However, it also antagonizes α1-presynaptic receptors which results in decreased presynaptic stimulation of 5HT neurons compared with mirtazapine, and hence less enhancement of 5HT release. It has similar side effects to mirtazapine but is also associated with blood dyscrasias and so complete blood count monitoring is required.

Agomelatine

Agomelatine is a melatonin agonist and 5HT2 antagonist licensed in Europe. A proposed mechanism of action is through beneficial effects on circadian rhythms and sleep but this has yet to be definitively demonstrated. It is well tolerated with a low incidence of side effects including sexual side effects. There is an increased rate of elevated hepatic transaminases and hepatotoxicity has been reported; monitoring of liver enzymes is required.

Norepinephrine reuptake inhibitors

Reboxetine

Reboxetine is a specific reuptake inhibitor of NE licensed widely worldwide but not in the USA. There is debate about its efficacy over placebo in treating depression. Dosage is usually between 8 and 12 mg/day in twice-daily administration. Side effects include insomnia, sweating, dizziness, dry mouth, constipation, tachycardia, urinary retention, and sexual dysfunction. Dose titration may improve its tolerability. The pharmacology and clinical use of reboxetine is summarized in Figures 5.9 and 5.10.

Pharmacology of reboxetine

Drug	Active metabolites	$t_{1/2}$ ($t_{1/2}$ of metabolite)	Metabolism	Hepatic enzyme inhibition
Reboxetine	Negligible	13	Hepatic	CYP3A4 inhibitor (eg, erythromycin, ketoconazole) may increase its plasma concentration

Figure 5.9 Pharmacology of reboxetine. $t_{1/2}$, half-life (in hours); CYP, cytochrome P450.

Clinical use of reboxetine

Medication	Usual daily dose (mg)	Main adverse effects	Significant interactions
Reboxetine	8–12	Insomnia, sweating, dizziness, dry mouth, constipation, tachycardia, urinary retention, sexual dysfunction	Potentiation of benzodiazepine effect (↓ excretion)

Figure 5.10 Clinical use of reboxetine.

Dopamine reuptake inhibitors

Bupropion (amfebutamone)

The mechanism of action of bupropion is not fully understood but the main action is thought to be the inhibition of DA reuptake, although it is also a weak NE reuptake inhibitor. Bupropion is licensed in the USA for the treatment of depression in immediate-release and delayed-release forms. Its use includes augmentation with SSRIs for treatment-resistant depression. At high doses, it may cause seizures and it is contraindicated in cases with a history of, or susceptibility to, developing seizures. Its metabolism mainly involves CYP2D6. The pharmacology and clinical use of buproprion is summarized in Figure 5.11.

Tricyclic antidepressants

Tricyclic antidepressants (TCAs) are amines that inhibit the reuptake of 5HT and NE. Tertiary amines (amitriptyline, imipramine, and clomipramine) are more potent 5HT blockers, whereas secondary amines (nortriptyline, desipramine, protriptyline) are more effective on NE. Other effects are anticholinergic and antihistaminergic. Tertiary amines are metabolized to secondary amines; for example, amitriptyline to nortriptyline, imipramine to desmethylimipramine (desipramine). Desipramine has been largely

Pharmacology and clinical use of bupropion

Drug	Active metabolites	$t_{1/2}$ ($t_{1/2}$ of metabolite)	Metabolism	Hepatic enzyme inhibition
Bupropion (amfebutamone)	*R*,*R*-Hydroxybupropion, *S*,*S*-Hydroxybupropion threo-Hydrobupropion erythro-Hydrobupropion	10 (up to 26)	Hepatic	Hydroxy-bupropion CYP2D6 inhibitor

Medication and dose (mg)	Main adverse effects	Significant interactions
Bupropion (amfebutamone) 300–450	MAOIs (serotonin syndrome) Carbamazepine/phenytoin (reduced concentration of bupropion) Valproate (increased concentration bupropion) Citalopram (increased concentration of citalopram)	Dry mouth, insomnia, anxiety, gastro-intesinal disturbance, sweating, hypertension

Figure 5.11 Pharmacology and clinical use of bupropion. $t_{1/2}$, half-life (in hours); CYP, cytochrome P450; MAOI, monoamine oxidase inhibitor.

superseded by more modern compounds but is still available in the USA. TCAs have high toxicity and fatality in overdose, particularly dosulepin, amitriptyline, and desipramine. Amitriptyline and desipramine should be prescribed with caution in cases of high suicide risk (eg, limited prescription, supervised administration) and dosulepin avoided. Lofepramine is the least toxic of all TCAs and clomipramine intermediate. The pharmacology and clinical use of TCAs are summarized in Figures 5.12 and 5.13.

Monoamine oxidase inhibitors

Monoamine oxidase inhibitors (MAOIs) are inhibitors of MAO enzymes A and B. These enzymes are widely distributed in the CNS, but also peripherally, especially in the gastrointestinal system. MAO-A metabolizes NE, 5HT, DA, and tyramine, whereas the substrates of MAO-B are DA, tyramine, and phenylethylamine.

The inhibitory action of MAOIs results in an increased availability (storage and release) of 5HT and NE. Lack of selectivity for the CNS and irreversibility of the inhibition (for older compounds) are responsible for the most significant side effects. The most dangerous phenomenon associated with MAOIs is a hypertensive "cheese reaction" attributable to tyramine-containing foods (eg, cheese, yeast extracts, hung game, some

Pharmacology of tricyclic antidepressants

Drug (active metabolite)	$t_{1/2}$ ($t_{1/2}$ of metabolite)	Metabolism	Comparative pharmacology			
			NE reptake inhibition	5HT reuptake inhibition	Anticho-linergic effects	Sedation
Amitriptyline (nortriptyline)	16 (36)	Hepatic	++	+++	+++	+++
Imipramine (desipramine)	16 (24)	Hepatic	++	+++	++	++
Clomipramine (desmethyl-clomipramine)	18 (36)	Hepatic	+	+++	+++	+
Nortriptyline	36	Hepatic	+++	+	++	+
Dosulepin* (northiaden)	20 (40)	Hepatic	+	+	++	++
Lofepramine (desipramine)	5 (24)	Hepatic	+++	+	+	+

Figure 5.12 Pharmacology of tricyclic antidepressants. 5HT, 5-hydroxytryptamine; CYP, cytochrome P450; NE, noradrenaline; TCA, tricyclic antidepressant; $t_{1/2}$, half-life (in hours).*Previously called dothlepin.

alcoholic drinks, broad bean pods, pickled herring), normally inactivated in the gut by MAO. Another cause is related to indirect sympathomimetic drugs such as phenylephrine (eg, nonprescription cold remedies).

Symptoms include flushing, headache, increased blood pressure, cerebral vascular accident. The most effective treatment of this condition is α-adrenergic blockade with phentolamine or chlorpromazine. MAOIs are generally contraindicated in cardio- and cerebrovascular disease, children, epilepsy, hepatic disease, pheocromocytoma, and hyperthyroidism. Irreversible MAOIs include traditional molecules (phenelzine, isocarboxazid, tranylcypromine) and selective MAO-B inhibitors (eg, selegiline). Selegiline transdermal patches have been licensed in the USA for the treatment of depression. This reduces first-pass metabolism and the risk of hypertensive reactions and food restrictions. The only available reversible MAOI is moclobemide, an MAO-A inhibitor, also called a RIMA (reversible inhibitor of MAO-A). At usual doses moclobemide does not necessitate dietary restrictions as competitive antagonism allows tyramine to displace moclobemide from MAO.

Clinical use of tricyclic antidepressants

Medication	Usual daily dose (mg)	Main adverse effects	Significant interactions
Amitriptyline	75–150*	Dry mouth, blurred vision, constipation, urinary retention, sedation, postural hypotension, tachycardia/ arrhythmia, weight gain	MAOIs (toxicity) Paroxetine, fluoxetine (↑ levels of TCAs) Phenothiazines (↑ levels of TCAs) Cimetidine (↑ levels of TCAs) Antimuscarinics (enhanced effect) Alcohol
Imipramine	75–150*	As for amitriptyline but less sedative	As for amitriptyline MAOIs (toxicity, serotonin syndrome)
Clomipramine	75–150*	As for amitriptyline but less sedative	As for amitriptyline MAOIs (toxicity marked)
Nortriptyline	50–150	As for amitriptyline but less sedative, anticholinergic, and hypotensive. Constipation is common	As for amitriptyline
Dosulepin (dothiepin)†	75–225	As for amitriptyline	As for amitriptyline
Lofepramine†	140–210	As for amitriptyline but less sedative, anticholinergic, hypotensive, and low cardiotoxicity. Sweating	As for amitriptyline

Figure 5.13 Clinical use of tricyclic antidepressants. *Higher doses (eg, up to 200–300 mg are commonly used in the USA). †Not available in the USA. MAOI, monoamine oxidase inhibitor; TCA, tricyclic antidepressant.

As a result of the risk of adverse reactions, the traditional MAOIs should be reserved for patients failing other antidepressants and prescribed under specialist supervision. The pharmacology and clinical use of MAOIs are summarized in Figures 5.14 and 5.15.

Other drugs

Investigational compounds

Drugs targeting glutamate receptors are currently in clinical trials based on evidence that the glutamatergic dissociative anaesthetic, ketamine, has rapid antidepressant effects.

Pharmacology of monoamine oxidase inhibitors

Drug	$t_{1/2}$ ($t_{1/2}$ of metabolite)*	Metabolism	Comparative pharmacology
Moclobemide	2–4	Hepatic	Reversible inhibitor of MAO-A
Selegiline† (desmethylselegiline, L-amphetamine, L-methylamphetamine)	3.5 (up to 14)	Hepatic	Irreversible inhibitor of MAO-B
Phenelzine	1.5	Hepatic	Irreversible, nonselective MAO-A and -B inhibitor
Tranylcypromine	2.5	Hepatic	Irreversible, nonselective MAO-A and -B inhibitor
Isocarboxazid	36	Hepatic	Irreversible, nonselective MAO-A and -B inhibitor

Figure 5.14 Pharmacology of monoamine oxidase inhibitors. *Note that for irreversible inhibitors, the half-life does not reflect the duration of pharmacological effect. †Transdermal administration reduces first pass metabolism with lower concentration of metabolities. $t_{1/2}$, half-life (in hours); CYP, cytochrome P450; MAOI, monoamine oxidase inhibitor.

Clinical use of monoamine oxidase inhibitors

Medication	Usual daily dose (mg)	Main adverse effects	Significant interactions
Moclobemide	150–600	Sleep disturbance, headache, nausea, agitation	Other antidepressants, pethidine, alcohol, barbiturates, insulin
Selegiline* (transdermal)	6-12 every 24h	Application site reaction, insomnia, diarrhea, pharyngitis (after oral administration similar to phenelzine)	No dietary restrictions at lowest dose. Low risk transdermally. As for phenelzine with oral administration
Phenelzine	45–60	Postural hypotension, dizziness, drowsiness, insomnia, headaches, edema, anticholinergic effects, weight gain, restlessness, sexual difficulties, sweating, tremor	Tyramine in food, sympathomimetics, alcohol, opioids, antidepressants, L-dopa
Tranylcypromine	20–30	As for phenelzine. More stimulating than phenelzine	As for phenelzine but interactions more severe and it is not advisable to use in combination
Isocarboxazid	10–40	As for phenelzine	Tyramine in food, sympathomimetics, alcohol, opioids, antidepressants, L-dopa

Figure 5.15 Clinical use of monoamine oxidase inhibitors. MAOI, monoamine oxidase inhibitor. *Transdermal selegiline is not currently licensed in Europe.

Augmentation strategies

Augmentation strategies include synergistic prescribing of antidepressants and/or other compounds including lithium, T_3, and atypical antipsychotics. Chapter 6 describes the use of augmentation strategies as next-step treatments. Their use should be supervised by mental health specialists. The clinical use of lithium is further described but for other drugs the reader is referred to the appropriate reference book, such as the *British National Formulary* [6].

Lithium (usually given as lithium carbonate) is the best-established augmentation treatment, but its popularity has decreased with the availability of new drugs and the complexities of its use. It has multiple potential actions including enhancing 5HT function. It has a narrow therapeutic range and needs regular blood tests to maintain a serum concentration in the range of 0.5–1.0 mmol/L (preferably <0.8 mmol/L to minimize side effects). Lithium is excreted by the kidneys and can interfere with thyroid hormone release and affect cardiac conduction. Pretreatment assessment of renal and thyroid function is required and, if indicated, cardiovascular status including an electrocardiography. Monitoring of renal and thyroid function is required approximately every 6 months. Adverse effects include polyuria and polydipsia, tremor, gastrointestinal symptoms, and a metallic taste in the mouth. Dehydration, sodium depletion (diarrhea, sweating), hypovolemia, and renal failure can increase serum lithium concentrations leading to lithium toxicity, which requires immediately stopping lithium, and medical assessment and intervention, including dialysis, if levels are very high.

Specific adverse effects of antidepressants

Serotonin syndrome

The serotonin syndrome is an acute neuropsychiatric condition due to increased CNS 5HT activity. Rarely, it can be an idiosyncratic reaction to a serotoninergic drug but usually it results from a pharmacodynamic interaction between drugs that enhance 5HT function (eg, SSRI + MAOI). Symptoms include confusion, myoclonic jerks, hyperreflexia, pyrexia, sweating, autonomic instability, gastrointestinal symptoms, mood change,

and mania. Management is based on stopping the offending drug(s) and supportive measures [11].

Antidepressant discontinuation syndrome

The discontinuation syndrome usually occurs only after antidepressant treatment has been established for some weeks and occurs on stopping the drug, especially if it is done abruptly, with symptoms starting in the first few days. The symptoms are variable and differ between classes of antidepressants but include sleep disturbance, gastrointestinal symptoms, affective symptoms, and general somatic symptoms such as lethargy and headache. In addition, SSRIs are associated with sensory symptoms, such as electric shock feelings and paraesthesia, and disequilibrium symptoms. MAOIs may cause more severe symptoms, including worsening depression and anxiety, confusion, and psychotic symptoms. With most antidepressants, psychotic symptoms, mania, and extrapyramidal symptoms have rarely been reported. Paroxetine and venlafaxine have been associated with high rates of discontinuation symptoms, whereas fluoxetine appears to have low rates, presumably due to its long half-life.

Management is based on education and reassurance, which suffice in most cases because the course tends to be mild and self-limiting (1 or 2 weeks). In more severe cases the implicated medication can be restarted and tapered more slowly. For SSRIs and SNRIs, fluoxetine can be prescribed and then stopped because its long half-life produces a natural taper. Prevention of the discontinuation syndrome can usually be achieved by tapering down the antidepressant dose over a few weeks.

Suicidality

There has been recent concern that some antidepressants, particularly SSRIs, might cause increased suicidality in some patients. However, the evidence considered overall does not support an increased risk of completed suicide or clinically significant increased risk of suicidal behavior in adults with antidepressant use, and population studies have tended to find that antidepressants are associated with decreased suicide rates. However, individual sensitivity cannot be ruled out and

SSRIs may be associated with a very small increase in nonfatal suicidal ideation/behavior in adolescents. More important is the recognition that all patients can experience an increase in suicidality during treatment and that this needs appropriate management (see Chapter 4) [12].

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