Learning points

How best to recognise and manage depression

This is the first part of two learning point articles reviewing the management of depression. This article focuses on the principles of recognising and managing depression with a review of current antidepressants. Part two, in the next issue of *Pharmacy in Practice*, will focus on treatment pathways and resistant depression. At the end of each article will be 10 multiple-choice questions taken from the text to enable you to reflect on your reading.

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Introduction

Depression is a common illness, which can affect people of all ages from childhood to old age. At any one time 5–10% of the adult population in the UK is affected.[1] The World Health Organization (WHO) classifies depression as the fourth leading contributor to the global burden of disease.[2]

The clinical presentation and severity of depression varies but typical symptoms include a lowering of mood, loss of interest and enjoyment, and a reduction of energy. The International Classification of Diseases 10th edition (ICD-10) from the WHO is the most widely used classification system and formalises the diagnosis of depression into mild, moderate, severe or recurrent (see Table 1).[3]

It is important to note that this simple symptom count does not take into account biological, psychological and social factors, which can affect treatment response. The lowered mood can vary from day to day, is unresponsive to circumstances and is typically present for most days for at least two weeks. A recurrent depressive disorder is characterised by repeated episodes of depression without separate episodes of mood elevation or increased energy. For other types of depression readers are referred to specialist texts.

There is no single cause of depression but an almost endless variety of factors that can precipitate the illness. For example, social stress and life events, family history, poor social background, early childhood experiences, abnormalities in endocrine function, chronic physical illness, substance misuse and some prescribed medications have all been implicated (Table 2).

Abnormalities in a variety of neurotransmitters has also been hypothesised as contributing to depression. This includes deficiencies in serotonin, noradrenaline, dopamine, gamma-aminobutyric acid (GABA) and peptide neurotransmitters.

Table 1. Symptoms needed to meet criteria for 'depressive episode' listed in ICD-10 Chapter 5, F32[3]

- ☐ Lowering of mood
- ☐ Reduction of energy and decreased activity
- ☐ Loss of interest and enjoyment
- ☐ Reduced concentration
- ☐ Disturbed sleep
- ☐ Disturbed appetite
- ☐ Reduced self-esteem and self-confidence
- ☐ Ideas of guilt and worthlessness

Mild depressive episode: Two to three of the above symptoms. Although the patient will be depressed they will generally be able to continue with ordinary activities.
Moderate depressive episode: Four or more of the above symptoms and the patient is unlikely to be able to carrying on with ordinary activities.
Severe depressive episode: Four or more of the above where symptoms are distressing typically with loss of self-esteem and ideas of worthlessness or guilt. Suicidal thoughts and acts are also common with severe depressive episodes.

Table 2. Drugs implicated with causing depression*[4]

- Propranolol
- Interferon alpha
- Interleukin-2
- Gonadrotrophin-releasing hormone agonists
- Mefloquine
- Corticosteriods
- Progestin-releasing implanted contraceptives

**This list is not exhaustive*

What causes these neurotransmitter abnormalities remains elusive. However, all current antidepressants are known to work by either increasing serotonin and/or noradrenaline neurotransmission.

Treatment options

In mild depression the National Institute for Health and Clinical Excellence (NICE) advocates a two-week period of watchful waiting to see if symptoms spontaneously improve. For those whose mild depression continues or who present with moderate depression psychological treatment is recommended. This includes cognitive behaviour therapy (CBT) which focuses on the 'here and now' and explores how the individual feels about themselves and others and how behaviour is related to these thoughts. For patients who present with enduring moderate, severe or recurrent depression antidepressants are recommended.[5]

The placebo effect

Recent concerns in the media have questioned the efficacy of antidepressants over placebo. This followed the publication of a meta-analysis by Kirsch and colleagues at the University of Hull.[6] Kirsch requested information from the Food and Drug Administration (FDA) on all efficacy studies conducted for six commonly used antidepressants. The disclosed studies included 31 randomised controlled trials and enabled the meta-analysis of four antidepressants: fluoxetine, paroxetine, nefazodone and venlafaxine. All studies were conducted pre-marketing, before 1999 and were of eight weeks or less in duration. Kirsch chose an effect size of 0.5 as a cut-off to determine efficacy of the four antidepressants, as did NICE. Effect size is a measure of the strength between two variables. In this case the size of the difference between antidepressants and placebo. The antidepressants reached an effect size of 0.32 so Kirsch concluded that the benefits of antidepressants were not clinically significant.

Effect size, however, is a continuous marker and choosing 0.5 as a cut-off for clinical significance does not represent an accurate marker of efficacy. An effect size of 0.32 actually confirms that a small difference was shown and that antidepressants are effective above placebo.[7] Effectiveness, a different marker of clinical significance, will be discussed in part two of this article. Interestingly, alternative treatments for depression such as psychological therapy have a much poorer evidence base than pharmacological treatment and adverse effects have been reported.[8]

Selective serotonin reuptake inhibitors

The selective serotonin reuptake inhibitors (SSRIs; fluoxetine, paroxetine, sertraline, citalopram and escitalopram) are recommended as first-line antidepressants because of their improved safety profile compared to tricyclic antidepressants (TCAs).[5] Fluvoxamine is rarely used because it requires twice-daily dosing and has many problematic interactions. There is little efficacy or tolerability difference between the SSRIs, however, half-life and interaction profiles do differ.

Fluoxetine and norfluoxetine (the active metabolite) have a half-life of 4–6 days and 4–16 days respectively and thus are associated with a lower risk of discontinuation symptoms than other antidepressants. Paroxetine has the shortest half-life of 24 hours and is associated with a higher rate of discontinuation symptoms. Fluoxetine, paroxetine and sertraline (at higher doses) inhibit the P450 CYP2D6 liver enzyme so can increase the levels of some antipsychotics (notably haloperidol, clozapine, olanzapine, and risperidone), tricyclic antidepressants (TCAs) and some benzodiazepines. Citalopram and escitalopram are weak inhibitors of CYP2D6 so are unlikely to cause clinically significant interactions with the above medication.[9] Common adverse effects of SSRIs, which are worse in the first few weeks include nausea, vomiting, diarrhoea and insomnia. Reversible sexual dysfunction, such as decreased libido and delayed orgasm has been reported in up to 70% of patients receiving SSRIs.[10]

Recent reports have raised the concern about an increased risk of bleeding associated with the SSRIs.[11] This is particularly reported with, but not restricted to, upper gastrointestinal bleeding. The mechanism behind this is through inhibition of the uptake of serotonin into platelets, which reduces the ability of platelets to clot effectively. SSRI treated patients have a threefold increased risk of bleeding, which is slightly lower than the risk associated with non-steroidal drugs (NSAIDs) alone. Co-prescribing an SSRI with NSAIDs quadruples the risk of bleeding associated with SSRIs alone.[11] Caution should be used in any patient who has risk factors for any bleed or is undergoing invasive surgery. Although unproven, gastroprotection should be considered in patients receiving a combination of an SSRI and NSAID.[10,11]

Tricyclic antidepressants

Tricyclic antidepressants (TCA) are a common alternative to SSRIs and may be useful where sedation is required. They work by increasing both serotonin and noradrenaline in the synaptic cleft by inhibition of the re-uptake transporters. Affinity for serotonin and noradrenaline reuptake inhibition varies across the TCAs with clomipramine predominantly affecting serotonin signalling while lofepramine is specific to noradrenaline. Amitriptyline and dosulepin (previously called dothiepin) have equal receptor binding.[9] Doses above 125mg per day (75mg or less in the elderly) are effective in depression and must be achieved before assessing the response.

Adverse reactions such as sedation, postural hypotension, constipation, blurred vision and weight gain are

common with TCAs because of their effect on multiple neurotransmitter systems. Of concern is the relation between TCAs and increased risk of death following an overdose. This is caused by the multiple effects TCAs have on cardiac function. All patients taking TCAs should be considered for an ECG and they are best avoided in patients with any underlying cardiac disorder or at risk of an overdose.[10] Lofepramine appears to have a lower risk while dosulepin carries the greatest risk in overdose and should be prescribed by specialists only.[5] Tricyclic antidepressants are also associated with an increased risk of seizures and should be avoided in patients with epilepsy.[10]

Monoamine oxidase inhibitors (MAOIs) and reversible MAOI

Monoamine oxidase inhibitors (MAOIs; phenelzine, isocarboxazid and tranylcypromine) irreversibly block MAO-A and MAO-B isoenzymes and thus reduce the breakdown of serotonin and noradrenaline in the synaptic cleft. They are rarely prescribed for depression and restricted to third-line alternatives because of their problematic food and drug interactions. Patients prescribed MAOIs must adhere to a low-tryamine (a monoamine derived from the fermentation or decay of various proteins) diet to avoid a potentially life-threatening hypertensive crisis.[9] Moclobemide is a reversible MAO-A inhibitor so a restrictive diet is not necessary.

Other antidepressants

Venlafaxine and duloxetine selectively inhibit both serotonin and noradrenaline reuptake (Figure 1). Venlafaxine inhibits serotonin reuptake across the dose range, with noradrenaline reuptake inhibition occurring above 150mg/day.[9] Previous concerns regarding venlafaxine and adverse cardiac effects have proven unfounded but an increase in blood pressure has been reported at doses above 200mg/day.[10] Venlafaxine at a high dose is often used after the selective serotonin reuptake inhibitors (SSRIs) have proved ineffective. Duloxetine has been shown not to significantly affect blood pressure, and so may be useful if venlafaxine is considered inappropriate.

Mirtazapine has a rather unique mechanism of action — it blocks alpha-2-adrenergic autoreceptors, which indirectly increases noradrenaline and serotonin transmission. It also blocks 5-HT2A, 5-HT3 and H1 receptors, which reduce the risk of nausea, vomiting and sexual dysfunction seen with the SSRIs but often causes sedation and weight gain. Mirtazapine does not inhibit P450 CYP enzymes so pharmacokinetic interactions are unlikely. Mirtazapine is often used if the SSRI antidepressants have been poorly tolerated.

Reboxetine is a selective noradrenaline reuptake inhibitor (SNRI) with little affinity for other neurotransmitters. It may be a useful option where other serotinergic enhancing antidepressants have failed or been poorly tolerated. Insomnia, sweating, tachycardia and palpitations are commonly reported and caution is recommended when prescribing reboxetine in patients with cardiac disease.[10]

Trazodone's mechanism of action is yet to be fully understood but as seen with other antidepressants it appears to increase noradrenaline and serotonin turnover. It may be useful where sedation is required or where depression presents with anxiety symptoms. Nausea, vomiting, dizziness and headache are commonly reported as is postural hypotension and tachycardia.

Mianserin, flupenthixol and tryptophan are rarely used in clinical practice so readers are referred to specialist text.[9,10]

St John's Wort

St John's Wort (SJW) is the common name for *Hypericum perforatum* a widely available herbal product often used for depression. Current evidence in depression is

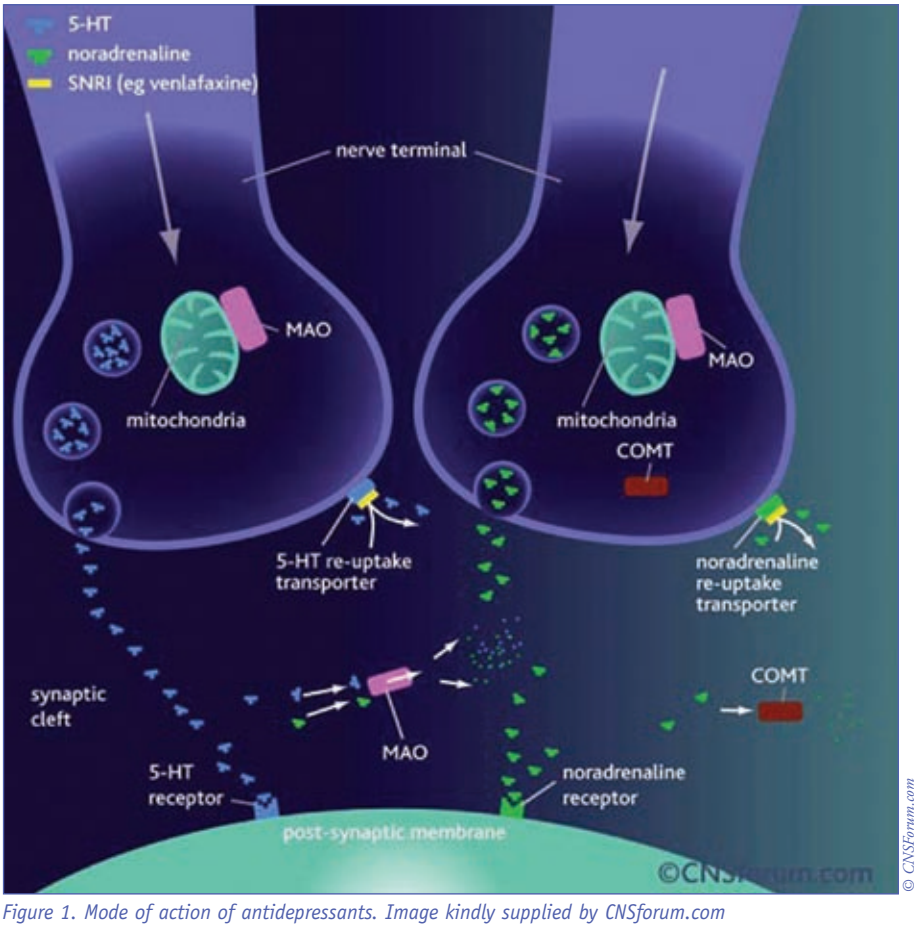

Figure 1. Mode of action of antidepressants. Image kindly supplied by CNSforum.com

inconsistent but a pooled meta-analysis in 2005 concluded that SJW extracts improved symptoms more than placebo and similar to standard antidepressants in mild-to-moderate depression. Only minor benefits were seen in major depression and no benefit was seen in patients with a prolonged duration of depression.[12] Although generally well tolerated SJW is a potent inducer of many liver cytochrome P450 enzymes (3A4, 1A2 and 2C9) thus can increase the breakdown of some drugs and cause treatment failure. If SJW is stopped while taking the affected drug an increase in levels leading to toxicity may occur. Drug levels that are reduced by SJW include many antiretrovirals, anticonvulsants, antidepressants, ciclosporin, digoxin, oral contraceptives, methadone, theophylline/aminophyline and warfarin. Because of the multiple interaction problems and lack of standard preparation in the UK SJW should not be routinely recommended for prescribing.[10]

Depression in children and adolescents

Psychological treatments should always be considered first line when treating depression in children. If they are inappropriate or have failed then fluoxetine is the antidepressant of choice. Other SSRIs have dubious efficacy in children and may increase the risk of suicidal acts or thoughts.[13]

Discontinuation symptoms

All antidepressants can cause discontinuation symptoms, which are usually mild and self-limiting. Paroxetine, venlafaxine and MAOIs are associated with the most reports.[14] Symptoms reported when discontinuing SSRIs include flu-like symptoms, dizziness and electric shock sensations.[10] These typically peak within the first week of withdrawal and taper off after two-to-three weeks. Unless there is a medical emergency antidepressants should be discontinued slowly over four or more weeks. This can be done by reducing the dose by 20-25% every week. Fluoxetine is unlikely to cause discontinuation symptoms and can be stopped at 20mg/day. Although antidepressants can cause discontinuation symptoms, they are not associated with tolerance or cravings so are not addictive.

Hyponatraemia

All antidepressants have been rarely shown to cause hyponatraemia. Any patient prescribed antidepressants showing signs of hyponatraemia, for example dizziness, nausea, confusion, cramps and seizures should have sodium levels checked urgently. Older people, females and those underweight are more at risk. Stopping the antidepressant and switching to a different class is recommended.[10]

Conclusion

Depression is a common and chronic illness accounting for significant mortality and morbidity worldwide. Effective treatment and management is a challenge for all health care professionals. Pharmacists can play a unique role in ensuring effective, appropriate and safe use of antidepressants.

Declaration of competing interests

The author declares that he has no competing interests.

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Questions

1.	A deficiency in peptide neurotransmitters may contribute to depression?	True	False
2.	Corticosteriods can cause depression?	True	False
3.	Antidepressants are recommended first in mild depression?	True	False
4.	Effect size is a continuous marker?	True	False
5.	Sertraline induces CYP 2D6 liver enzyme?	True	False
6.	SSRIs have a higher risk of bleeding than NSAIDs?	True	False
7.	Tricyclic antidepressants are recommended in epilepsy?	True	False
8.	SJW can reduce drug levels of digoxin?	True	False
9.	Psychological treatments are considered first in childhood depression?	True	False
10.	All antidepressants can cause hyponatraemia?	True	False

Quiz

Now try your hand at answering these questions. Just answer true or false to each of the questions. We have given you the answers upside down below — but no peeking!

Answers: 1. True. 2. True. 3. False. 4. True. 5. False. 6. False. 7. False. 8. True. 9. True. 10. True.