Learning points

Treatment pathways for managing depression

This second article by Stephen Bleakley reviewing the management of depression focuses on treatment pathways and treatment-resistant depression. To help readers reflect on their reading 10 multiple-choice questions are included at the end of the article.

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Introduction

Depression is a common, chronic illness with persistent and recurrent symptoms. Following a first episode of depression 22% will continue to have symptoms after one year and up to 85% of suffers will have two or more episodes despite active treatment. Having longer and more frequent depressive episodes, being single, having a low income and old age worsens the prognosis.[1,2]

The cost of depression to society makes impressive reading. In England alone the total cost of depression in 2000 was estimated to be more than £9 billion with £370 million attributed to direct treatment costs.[3]

Antidepressants remain an effective treatment choice for moderate, severe or recurrent depression and can reduce long-term suffering and prevent relapse.

Treatment guidelines

The choice of treatment in depression should always reflect the patient's preference, past experiences, previous response and any concurrent medical co-morbidity or drug therapy. The National Institute for Health and Clinical Excellence (NICE) depression guidelines advocate a stepped care model approach to treating depression with the majority of patients being treated in primary care as illustrated in Figure 1.[4]

Medication is recommended as first line treatment for those suffering with moderate or severe depression. Figure 2 shows the medication choices recommended by NICE.

Combining psychological interventions with medication is recommended at any time from step 1 to 4 in cases that do not respond to medication alone. All antidepressants should be titrated to an adequate therapeutic dose and given for at least for 4–6 weeks to assess response.

The evidence base for treatment-resistant depression has recently been improved by the publication of a series of effectiveness clinical trials (the sequenced treatment alternatives to relieve depression — STAR*D — trials). This

Who is responsible for care?	What is the focus?	What do they do?
Step 5: Inpatient care, crisis teams	Risk to life, severe self-neglect	Medication, combined treatments, electroconvulsive therapy
Step 4: Mental health specialists, including crisis teams	Treatment-resistant, recurrent, atypical and psychotic depression, and those at signficant risk	Medication, complex psychological interventions, combined treatments
Step 3: Primary care team, primary care mental health worker	Moderate or severe depression	Medication, psychological interventions, social support
Step 2: Primary care team, primary care mental health worker	Mild depression	Watchful waiting, guided self-help, computerised CBT, exercise, brief psychological interventions
Step 1: GP, practice nurse	Recognition	Assessment

CBT=cognitive behavioural therapy.

Figure 1: The stepped care model for treating depression proposed by NICE.[4]

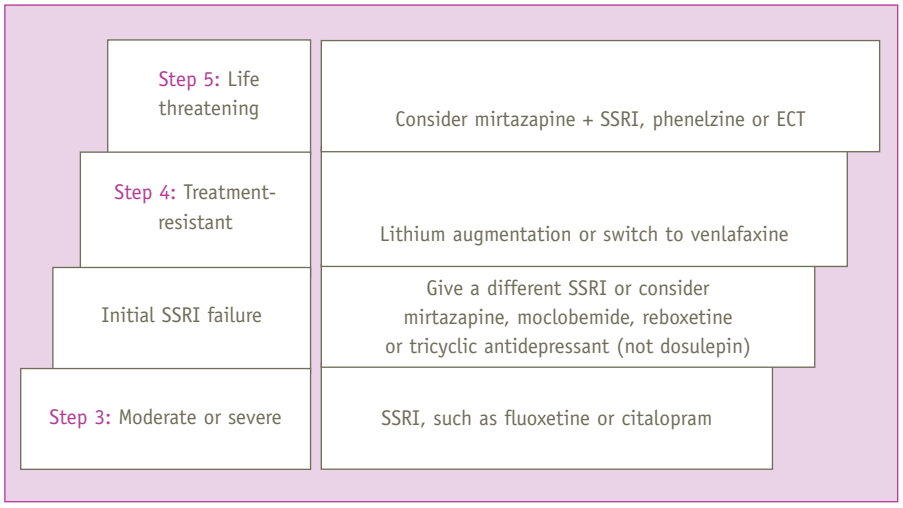

Figure 2. Medication choices recommended by NICE[4]

large pragmatic effectiveness study recruited almost 3000 outpatients suffering from major depression from 41 centres in the US. There were four steps to the study and remission of symptoms was the main outcome. Initially patients were randomised to flexible dosing of citalopram for up to 14 weeks.[5] Patients who were still symptomatic or failed to tolerate citalopram were then entered into the continued study of sequential treatments. Treatment could either be switched to an alternative antidepressant or a variety of medication added to augment the antidepressant. Very few significant differences between treatments were seen throughout the study. Of interest was that switching to sertraline after the failure of citalopram was as effective as switching to venlafaxine,[6] and that mirtazapine and venlafaxine in combination may have a role in treatment-resistant depression.[7]

Switching antidepressants

Switching between antidepressants can be problematic and should be done with due caution. Risks when switching antidepressants include discontinuation symptoms, serotonin syndrome and pharmacokinetic or pharmacodynamic interactions. In some cases a gap or 'wash-out period' between antidepressants is essential to prevent problems. For example, when switching from a monoamine oxidase inhibitor to any other antidepressant a two-week gap is recommended. In other cases a cautious cross-taper may be appropriate, for example, when switching from a selective serotonin reuptake inhibitor (SSRI) to mirtazapine. For complete listings and recommendations readers are referred to specialist texts.[8]

Serotonin syndrome

Serotonin syndrome is a potentially life-threatening adverse reaction that may result from the therapeutic use of antidepressants, after an interaction between two or more serotonin enhancing drugs or following an overdose. All antidepressants that enhance serotonin have been associated with serotonin syndrome — as have many non-antidepressant drugs (see Table 1).

> The choice of treatment in depression should always reflect the patient's preference, past experiences, previous response and any concurrent medical co-morbidity or drug therapy.

Signs and symptoms of serotonin syndrome range from mild diarrhoea and tremor to ataxia and convulsions (see Figure 3). Treatment is to immediately remove the offending agent and give supportive care. Moderate-to-severe cases should receive immediate medical attention and may need care in a high dependency unit. Onset of symptoms is usually rapid with 60% of patients presenting within six hours of the initial precipitating factor. Any drug that inhibits the metabolism of a serotonergic drug may also worsen or precipitate serotonin syndrome.[9,10]

Augmentation strategies

Lithium augmentation of an antidepressant is well established and recommended by NICE in treatment-resistant depression (see Figure 2).[4] Lithium may enhance seroton-

Table 1. Drugs* that are associated with serotonin syndrome[9,10]

Antidepressants	**Antimigraine drugs**
Selective serotonin reuptake inhibitors	Triptans
Tricyclic antidepressants	
Monoamine oxidase inhibitors	**Drugs of abuse**
Moclobemide	MDMA (ecstasy)
Trazodone	LSD
Venlafaxine	
Duloxetine	
Mirtazapine	
Herbal products	**Others**
St John's Wort	Lithium
Tryptophan	Buspirone
	Linezolid
Analgesics	Sibutramine
Tramadol	Amphetamines
Fentanyl	
Pethidine	

**These drugs, when given alone — and potentially when given in various combinations — could cause serotonin syndrome*

Learning points

Serotonin syndrome is a potentially life-threatening adverse reaction that may result from the therapeutic use of antidepressants, after an interaction between two or more serotonin enhancing drugs or following an overdose.

ergic transmission above that found with the antidepressants alone and may treat an undiagnosed bipolar depression. Lithium has a narrow therapeutic ratio and so regular monitoring of lithium blood levels is essential (every week until they are therapeutic and stable). Blood for lithium sampling should be taken 12 hours after the last dose aiming for levels between 0.6–1.0mmol/L.[8]

Many commonly prescribed and over-the-counter medications can increase lithium levels and cause toxicity, for example angiotensin-converting enzyme inhibitors, diuretics (especially thiazide diuretics) and non-steroidal anti-inflammatory drugs (excluding aspirin). A diet very low in salt or dehydration can also lead to lithium toxicity. In the longer term lithium could cause hypothyroidism and can reduce the glomerular filtration rate so baseline and six-monthly monitoring of thyroid and renal function is also necessary.[8]

Liothyronine sodium (tri-iodothyronine) augmentation with antidepressants seems to be useful even when thyroid function tests are within the normal range. A dose between 25 to 50 mcgs per day is usually recommended. Augmentation with liothyronine sodium has been shown to be as effective but better tolerated than lithium.[11]

A variety of other medications have been added to antidepressants in an attempt to enhance the antidepressant effect. For example olanzapine, quetiapine, lamotrigine, buspirone, pindolol and tryptophan have all been used. Supporting evidence for such augmentation strategies varies and readers are referred to specialist texts for an in depth discussion.[8]

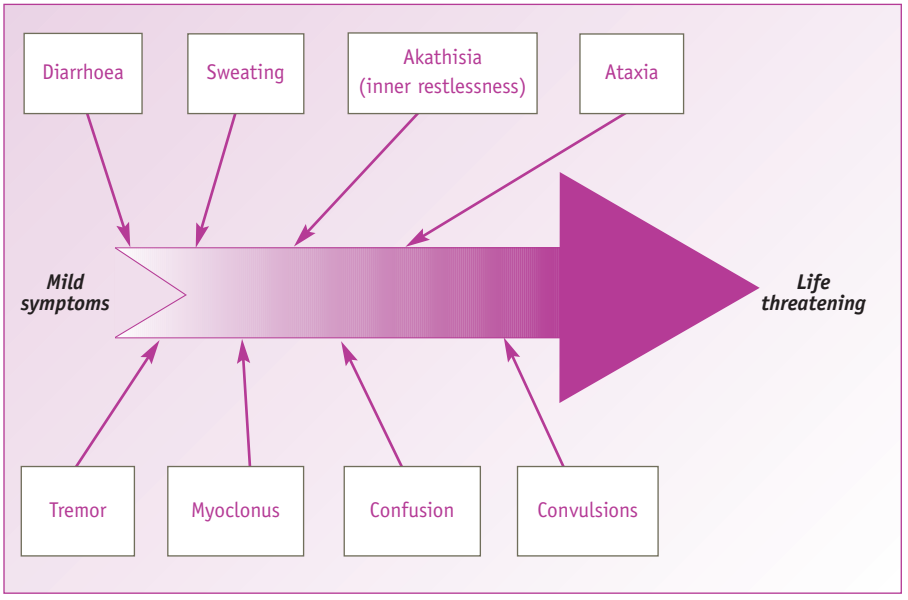

Figure 3: The spectrum of symptoms associated with serotonin syndrome[9,10]

Combining antidepressants

Combining mirtazapine with either a SSRI or venlafaxine is becoming more common for patients where other treatments have failed to work. Despite recent advances the evidence base supporting such a combination remains limited and not all patients will tolerate such a combination.[7] Doses should be increased slowly with close monitoring for serotonin syndrome.

Electroconvulsive therapy

Electroconvulsive therapy (ECT) is an effective and appropriate treatment for severe depression. There is substantial evidence supporting the short-term efficacy of ECT and it is probably superior to drug treatment. Modern ECT involves giving the patient a short-acting general anaesthetic (usually propofol) and the muscle relaxant, suxamethonium. Treatment is given under the care of an experienced anaesthetist, psychiatrist and psychiatric nurse.

During ECT an electric current is passed through the brain via electrodes applied to the scalp with the aim to induce a seizure. Up to one third of patients suffer from significant memory loss, which can be reduced by placing both electrodes on the non-dominant hemisphere of the scalp (unilateral electrode placement) and having no more than two treatments per week.[12] NICE recommends ECT in severe or life-threatening symptoms after the failure of other treatment options.[13]

Relapse prevention

Antidepressants reduce the risk of a relapse of depression by up to two-thirds. Continuing an antidepressant for one year may provide additional protection from a relapse for a further two years.[14] NICE recommends that antidepressants are continued for at least six months after remission to prevent a relapse of symptoms.[4]

Conclusions

Antidepressants remain effective treatment choices in depression, which can reduce long-term suffering and prevent relapse.

Declaration of competing interests

The author declares that he has no competing interests.

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Summary

The SSRIs are recommended for first line treatment in moderate to severe depression

If the first SSRI is not effective another SSRI should be tried

If the first SSRI is poorly tolerated consider mirtazapine, moclobemide, reboxetine or tricyclic antidepressants (not dosulepin)

Serotonin syndrome is a potentially life-threatening adverse reaction associated with all drugs that enhance serotonin transmission

Antidepressant therapy should be continued for at least six months after the remission of symptoms to reduce the risk of a relapse

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Questions

1.	When switching between MAOIs and TCAs a cross-taper is appropriate	True	False
2.	Tramadol has been associated with serotonin syndrome	True	False
3	The combination of mirtazapine and venlafaxine may cause serotoin syndrome	True	False
4.	Aspirin increases lithium levels	True	False
5.	Lithium is better tolerated than liothyronine sodium in antidepressant augmentation	True	False
6.	Lithium levels should be measured 12 hours after the last dose	True	False
7.	Liothyronine augmentation is only tried if thyroid function test are abnormal	True	False
8.	ECT is recommended in life-threatening depression	True	False
9.	Unilateral electrode placement during ECT reduces memory loss	True	False
10.	Antidepressants should be discontinued three months after remission	True	False

Quiz

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

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

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