THERAPEUTICS

Newer antidepressants for the treatment of depression in adults

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This is one of a series of occasional articles on therapeutics for common or serious conditions, covering new drugs and old drugs with important new indications or concerns. The series advisers are Robin Ferner, honorary professor of clinical pharmacology, University of Birmingham and Birmingham City Hospital, and Philip Routledge, professor of clinical pharmacology, Cardiff University. To suggest a topic for this series, please email us at practice@bmj.com.

Antidepressants are prescribed mainly for people with depression, although some are also used for anxiety disorders and other conditions, including chronic pain and enuresis. They are one of the most commonly prescribed medications (more than 43 million prescriptions were written for them between April 2010 and March 2011 in England[1]).

Antidepressants were developed in the 1950s, and their mechanism of action is thought to be by increasing the levels of extracellular synaptic neurotransmitters such as serotonin, noradrenaline, and dopamine; they also have other effects, including increasing hippocampal neurogenesis. The original antidepressants were known as tricyclics because of their chemical structure. Since the 1980s a new generation of antidepressants has been developed and marketed based on their mode of action. The nomenclature for referring to these newer drugs is confusing as they can be classified by several criteria, including the target molecule and the number of neurotransmitter sites involved.[2] Box 1 lists antidepressants grouped according to the current nomenclature used by the World Health Organization.

The focus of this article is on selective serotonin reuptake inhibitors (SSRIs) and other newer antidepressants (using the World Health Organization's nomenclature (box 1)) and their use in adults presenting with depressive disorders. We have excluded non-reversible monoamine oxidase inhibitors such as phenelzine as recent guidelines recommend these should usually be prescribed only by specialist mental health professionals.[3] Our article does not cover the use of antidepressants in children and adolescents or depression in bipolar disorder. See recent reviews for discussion of selective serotonin reuptake inhibitors in children and adolescents[4] and the long term treatment of depression with SSRIs.[5]

Box 1 | World Health Organization's current nomenclature for antidepressants, with examples of current drugs

Non-selective monoamine reuptake inhibitors
Tricyclic antidepressants: imipramine, amitriptyline*, clomipramine, lofepramine, amoxapine
Noradrenaline reuptake inhibitors: desipramine, nortriptyline, maprotiline

Selective serotonin reuptake inhibitors
Fluoxetine*, fluvoxamine, zimelidine, paroxetine, sertraline, citalopram, escitalopram

Monoamine oxidase inhibitors (non-selective)
Phenelzine, tranylcypromine, isocarboxazid

Monoamine oxidase A inhibitors
Moclobemide, toloxatone

Other antidepressants
Serotonin noradrenaline reuptake inhibitors: venlafaxine, duloxetine
Noradrenaline dopamine reuptake inhibitors: nomifensine, buproprion
Noradrenaline and selective serotonin antagonists: mirtazapine
Serotonin antagonist and reuptake inhibitor: trazadone
Melatonin receptor agonist with 5-HT2C receptor antagonist properties: agomelatine
Serotonin partial agonist: gepirone

*Listed in the WHO's list of essential medicines for use in depressive disorders

The use of antidepressants is increasing—for example, in the United Kingdom antidepressant prescribing doubled between 1993 and 2005; this has been explained by small changes in the proportion of patients receiving longer treatment.[6] However, evidence also exists of overuse: in one study about a quarter of those taking antidepressants had never had a depressive disorder.[7]

What are the indications for antidepressant use in depression?

In the UK the guideline from the National Institute for Health and Clinical Excellence (NICE) on managing depression recommends that doctors be alert for depression in patients with a history of depression or who have a chronic health problem with functional impairment.[3] Consider asking patients two screening questions for depression: "during the last month have you often been bothered by feeling down, depressed, or hopeless?" and "during the past month have you often been bothered by having little interest or pleasure in doing things"?[8] An answer of "yes" to one of these indicates possible depression. A "no" answer to both questions virtually rules out depression. A further assessment with a depression inventory such as the patient health questionnaire (PHQ-9)[9] (figure) or the hospital anxiety and depression scale (HADS)[12] is helpful for measuring the severity of the depression and for monitoring changes in response to treatment. This strategy is similar to measuring blood pressure when treating hypertension and is part of successful programmes to manage depression in primary care.[13] The initial assessment of a depressed patient includes the items listed in table 1.

The NICE guideline, which is based on systematic reviews of the evidence and explicit consideration of cost effectiveness, recommends that antidepressants should not be used for persistent, subthreshold symptoms or mild depression as the risk to benefit ratio is poor unless the patient has a history of moderate to severe depression or persisting low level symptoms, or other interventions have not worked.[3] For people with moderate to severe depression NICE recommends antidepressants initially, as well as high intensity psychological interventions, combined treatments, collaborative care, consideration of referral, and further interventions.

How well do the newer antidepressants work?

How well the newer antidepressants work has become a controversial topic owing to concern about publication bias. A meta-analysis of 35 randomised controlled trials sourced from the Food and Drug Administration (which included unpublished data) found that antidepressants were clearly effective only in patients with severe levels of depression (Hamilton depression rating scale scores of ≥28).[15] However, this meta-analysis has been criticised for its statistical methods, and commentators have asserted that patients included in the trials were unlikely to be severely depressed and that the long term effects of antidepressants on preventing relapse were ignored.[16] A reasonable quality recalculation of the data from the original meta-analysis found that

Patient health questionnaire (PHQ-9)

Question 1

Over the past two weeks how often have you been bothered by any of the following problems?	Score			
	Not at all	Several days	More than half the days	Nearly every day
1 Little interest or pleasure in doing things	0	1	2	3
2 Feeling down, depressed, or hopeless	0	1	2	3
3 Trouble falling/staying asleep, sleeping too much	0	1	2	3
4 Feeling tired or having little energy	0	1	2	3
5 Poor appetite or overeating	0	1	2	3
6 Feeling bad about yourself or that you are a failure or have let yourself or family down	0	1	2	3
7 Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8 Moving or speaking so slowly that other people could have noticed. Or the opposite: being so fidgety or restless that you have been moving around more than usual	0	1	2	3
9 Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

Add the individual scores together to get a total score. Of those patients who score 10 or more in primary care, most (7.6% of all patients in primary care) will have a score 10 to 14, which indicates either subthreshold depression or moderate depression[10 11]; a smaller proportion (3.4% of all patients in primary care) will have a score of 15 to 19, indicating moderate to severe depression; and the smallest proportion (2% of all patients in primary care) will have a score of ≥20)

Question 2

If you indicated any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with people?

Not difficult at all	Very difficult
Somewhat difficult	Extremely difficult

Further information and copies of the PHQ-9 in various languages are available at www.phqscreeners.com/ and www.depression-primarycare.org/clinicians/toolkits/materials/forms/phq9/

Patient health questionnaire (PHQ-9)[9] and how to interpret the scores

Table 1 | Assessment of a patient with suspected depression

History item	Reason for item
Previous episodes	Depression is a recurrent disorder and it is important to know which treatments (drug and non-drug) have worked in the past and to consider long term antidepressant treatment to prevent relapse
Suicidality and suicide history	Taking a history will guide whether to use medication, which medication to use, and how closely to monitor
Severity and duration	Severity can be measured by symptom inventories—eg the patient health questionnaire, the hospital anxiety and depression scale, the Beck depression inventory, and the Center for Epidemiological Studies depression scale. The more severe and enduring the episode, the more likely the initial need for antidepressant medication
Evidence of psychosis	Patient may need antipsychotic medication in addition to antidepressants and advice from secondary care
Bipolarity	Evidence of past manic or hypomanic episodes would warrant advice from secondary care
Comorbid health conditions and other medication	To improve the accuracy of diagnosis in people with chronic physical problems consider asking about feelings of worthlessness, poor concentration, and thoughts of death
	Consider the role of medication in causing depression—eg steroids or interferon
	Be aware of the potential for drug interactions with antidepressants
Use of complementary therapies	In one US survey about half of depressed women had tried alternative therapies for depression.[14] Asking about complementary therapies is an opportunity for clinician and patient to collaborate in a management plan and to check for potential interactions
Adherence	Patients are likely to stop and start medication without clinician advice
Functional and social assessment	The assessment of social support, social networks, and social functioning is important in establishing the impact of the disorder and planning treatment. If the patient is not coping at home or work, increase the intensity of the treatment

antidepressants had some effect regardless of the severity of the depression, although the authors of this paper declared significant competing interests.[17]

It is difficult to assess efficacy by comparing depression inventory scores as these scales focus on symptoms rather than function and are treated as ratio scales when in fact they are ordinal. It may be more helpful to consider the numbers needed to treat for significant improvement (rather than changes in rating scale scores) when comparing antidepressants with placebo using individual patient data in a meta-analysis (table 2).[18] Table 2 shows that for those with severe depression four people need to be treated with an antidepressant over two months for one extra person to get better compared with taking a placebo over the same period. This reinforces the need to add in psychological therapies or to try more than one antidepressant for patients with severe depression. For people with mild to moderate depression the initial choice of drug or non-drug treatment should be guided by patient preference and availability of resources.

The NICE guideline suggests that all newer antidepressants are equally effective. However, there is some debate about this. A meta-analysis of 117 head to head randomised controlled trials of 12 new generation antidepressants that included almost 26 000 patients showed a slightly better response rate with four of them: escitalopram, mirtazapine, sertraline, and venlafaxine.[20] The meta-analysis included patients from primary and secondary care and the differences were assessed at only eight weeks. Escitalopram and sertraline showed better acceptability (on the basis of overall withdrawal rates), which, if cost and patient history of drug response were not an issue, would make them potential first line SSRIs. However, a larger, updated meta-analysis of 234 studies failed to find any differences in efficacy among "second generation" antidepressants[21] A recent systematic review of reboxetine concluded that it was an ineffective and potentially harmful antidepressant.[22] Individual patients show large differences in response to antidepressants, and there is currently no reliable way to predict who will respond to which treatment.

How safe are the newer antidepressants?

The safety concerns for antidepressants range from adverse effects that make patients feel unwell or prone to stopping medication through to an increase in suicidal thoughts to death either from completed suicide or cardiac arrhythmias. Most adverse events are mild, although one in six patients treated with second generation antidepressants discontinue treatments in randomised controlled trials because of intolerable adverse effects.[23] However, as these data come from a meta-analysis of randomised controlled trials, the experience of adverse effects and withdrawal may be different in everyday patients.

Table 3 shows the common adverse effects and suggested management options. A systematic review of harms from second generation antidepressants found that sexual dysfunction was commonly reported, with between half and two thirds of patients experiencing some sexual dysfunction.[23] The highest incidence of sexual dysfunction was with citalopram, paroxetine, and venlafaxine; mirtazapine had the lowest rate. Sexual dysfunction is likely to be underreported in the clinical trials as they rely on spontaneous

Table 2 | Effectiveness using individual patient data based on six studies (718 outpatients) of paroxetene or imipramine versus placebo.[18] Values are scores except where stated otherwise

Severity (NICE criteria)	Hamilton depression rating scale-17	PHQ-9	HADS-D	BDI-II	Number needed to treat compared with placebo over six to eight weeks
Severe	≥23	≥20	≥15	≥29	4
Moderate	19 to 22	10 to19	11 to14	20-28	11
Mild	14 to 18	6 to 9	8 to 10	14-19	16

PHQ-9= the patient health questionnaire (9 item); HADS-D= the hospital anxiety and depression scale (German version); BDI-II= Beck depression inventory II.
The ranges are indicative only, and there is some evidence that they are not exactly equivalent.[19] Treatment decisions also need to consider other factors, such as patient preference, duration of depression, and impact on function.

reporting.[24] Nausea, vomiting, diarrhoea, dry mouth, sweating, headache, dizziness, and weight gain are other commonly reported adverse effects with SSRIs. Venlafaxine seems more likely than SSRIs to be associated with nausea and vomiting (numbers needed to harm 9); sertraline has higher rates of diarrhoea; mirtazapine and paroxetine cause more weight gain than other SSRIs.

In patients aged over 65 years a cohort study of more than 60 000 patients in UK primary care with a new diagnosis of depression found that SSRIs increased the risk of falls (hazard ratio 1.66, 95% confidence interval 1.58 to 1.73) and that citalopram, escitalopram, and fluoxetine were associated with hyponatraemia (hazard ratio 1.52, 1.33 to 1.75).[25] Trazadone, mirtazapine, and venlafaxine were associated with an increase in all cause mortality. Most adverse effects occurred in the first month after starting the antidepressants.

Box 2 outlines the main concerns about interactions and contraindications for different drug classes.

How cost effective are the newer antidepressants?

A trial of SSRIs and supportive psychotherapy versus supportive therapy alone in the treatment of mild to moderate depression in UK general practice found that adding SSRIs to supportive therapy was cost effective, with mean costs of £90 (€108; $140) per point improvement in the Hamilton depression rating scale and £14 854 per quality adjusted life year gained.[31] The NICE guideline found that there was weak evidence that escitalopram was more cost effective than three other antidepressants. It also reported a weak trend showing that SSRIs may be more cost effective than tricyclic antidepressants.[3]

How do the newer antidepressants compare with older pharmacological treatments for depression?

The second generation antidepressants seem to be as effective as the tricyclics and monoamine oxidase inhibitors. The major differences are in the frequency and type of adverse effects, ease of dosing, and lethality in overdose. A Cochrane review of antidepressants versus placebo for treating depression in primary care found that the number needed to harm (NNH for withdrawal owing to adverse effects over six to eight weeks) ranged from 4 to 30 (median 17) for tricyclic antidepressants and from 20 to 90 (median 23) for SSRIs.[32] For tricyclics the most common side effects are related to their anticholinergic action and include dry mouth, constipation, and urinary retention. A major consideration in prescribing antidepressants is the risk of their being taken in overdose and the consequences of such an act. Tricyclic antidepressants are associated with a higher case fatality

Table 3 | Adverse effects and suggested management

Adverse effect	Comment	Management
Dizziness	Occurs in about one in 10 people who take second generation antidepressants and is more common with venlafaxine and less common with sertraline or fluoxetine	Check blood pressure standing and lying; symptoms may improve over time; decrease dose or change treatment. Ensure adequate fluid intake
Sedation	More common with trazadone but can occur with all second generation antidepressants	Sedation may be desirable; it may improve over time. Change time of dosing and treatment
Dry mouth	Probably dose related	Tolerance may develop; change treatment; suggest sugarless gum or saliva substitutes
Sexual dysfunction	Common but often not asked about	Consider reducing dose, waiting for the effects to improve, switching to a different antidepressant (some evidence exists for lower rates of sexual dysfunction with mirtazapine, moclobemide, duloxetine and buproprion), or consider sildenafil
Insomnia	Common problem but hard to distinguish from insomnia caused by depression	Change time of dosing (earlier or later may help), pay attention to sleep hygiene, try a different antidepressant, or possibly try short course of benzodiazepine, zopiclone, or low dose trazadone
Suicidal thoughts	Antidepressants may paradoxically increase suicidal thoughts in those aged under 30	Review often (within a week of starting antidepressants and continue until no longer clinically needed). No evidence exists that asking about suicide makes people more likely to harm themselves. Prescribe small amounts of medication. Prescribe antidepressants that are less lethal in overdose (such as SSRIs). Venlafaxine has a greater risk of death from overdose than other newer antidepressants, although the greatest risk is with the tricyclics (except for lofepramine)[3]
Anxiety	Often occurs when starting SSRIs	Consider using a benzodiazepine for no longer than two weeks
Hyponatraemia	Particularly a problem in the elderly and more common with SSRIs	Check sodium before and after starting treatment, and consider changing to mirtazapine if it becomes problematic
Serotonin syndrome	Characterised by changes in mental state (eg confusion or agitation), autonomic instability (eg high temperature, shivering, sweating, changes in blood pressure), and neuromuscular hyperactivity (eg clonus or hyper-reflexia). Seen particularly with SSRIs and other drugs that effect serotonin	Stop the antidepressant. Use supportive measures such as hydration, management of hyperthermia, and benzodiazepines. Consider cyproheptadine or chlorpromazine in severe cases
Discontinuation syndrome	More common with SSRIs that have a short half life (eg paroxetine or venlafaxine)	Decrease dose over four weeks. Warn the patient

SSRIs=selective serotonin reuptake inhibitors.

Box 2 | Precautions when prescribing for depression

Interactions with SSRIs

Tramadol or oxycodone

In older people interactions between antidepressants (usually SSRIs) and tramadol or oxycodone form about a third of reported drug interactions.[26] This interaction can result in a serotonin syndrome at any age.

St John's wort

This induces liver CYP450 enzymes so may decrease levels of SSRIs; also, using St John's wort with SSRIs may precipitate a serotonin syndrome.

Tricyclic antidepressants

SSRIs may prevent the metabolism of tricyclics through the CYP450 enzyme system, resulting in toxic levels of the tricyclic.

Hepatic disease

Hepatic disease increases the half life of antidepressants, so a decrease in the usual dose is needed.

Pregnancy and breastfeeding

If psychotherapies are unavailable or ineffective in depressed women who are pregnant, balance the risks of any potential damage to the fetus from antidepressants with the benefits of antidepressant treatment. A recent systematic review found that 10 of the 12 small studies showed little evidence of effect on the neurodevelopmental outcome of infants exposed to antidepressants.[27] NICE states that in pregnancy amitriptyline, imipramine, nortriptyline, and fluoxetine have lower risks than other antidepressants and that imipramine, nortriptyline, and sertraline are present in breast milk at relatively low levels.[28]

Heart disease

About one in five people with coronary heart disease have major depression, which is associated with a worse prognosis. In patients with heart disease, tricyclic antidepressants are best avoided because of their risk of causing arrhythmias and postural hypotension; SSRIs should be tried first, with baseline electrocardiography.[29] Concerns have been expressed about venlafaxine, as in high doses it can exacerbate hypertension.

Bleeding

Selective serotonin reuptake inhibitors and serotonin noradrenaline reuptake inhibitors are associated with an increased risk of gastrointestinal bleeding as they reduce platelet aggregation (although the absolute increase risk is low, the number needed to harm is 411 people prescribed an SSRI for a year).[30] Patients at increased risk include those with peptic or liver disease and those receiving anticoagulant, antiplatelet, or non-steroidal anti-inflammatory drugs. Proton pump inhibitors may reduce the risk of gastrointestinal bleeds from SSRIs.

TIPS FOR PATIENTS

Antidepressants work by their effect on neurotransmitters in the brain. They are effective treatments for moderate to severe depression. There are many non-drug treatments that are effective either alone (especially for mild to moderate depression) or used with antidepressants. Non-drug treatments include behavioural activation, which can include regular exercise; cognitive behavioural therapy either individually or through guided self help, group therapy, or by computer; interpersonal therapy; and problem solving therapy.

Antidepressants may not work instantly and can take a week or two to take effect. Report side effects to your doctor. Side effects are often worse when first starting the medication but can improve with time. Doses and medications can also be changed if side effects persist.

Antidepressants are not addictive or habit forming. They are not stimulants ("uppers"), not tranquilisers.

People who have had two or more recent episodes of depression may need to continue to take their medication for up to two years or longer to prevent recurrence of the depression.

Don't stop taking antidepressants without discussion with your doctor. Taking antidepressants is a bit like taking antibiotics—you take a course of tablets regularly for a certain amount of time and then stop.

Useful resources

Royal College of Psychiatrists (www.rcpsych.ac.uk/mentalhealthinformation/mentalhealthproblems/depression/depression.aspx)

NHS Choices (www.nhs.uk/conditions/Depression/Pages/Introduction.aspx)

MIND (www.mind.org.uk/help/medical_and_alternative_care/making_sense_of_antidepressants)

Rethink Mental Illness (www.rethink.org/about_mental_illness/mental_illnesses_and_disorders/depression/index.html)

Northumberland, Tyne and Wear NHS Foundation Trust (www.ntw.nhs.uk/pic/selfhelp)

ratio (the ratio of the number of deaths caused by self poisoning to non-fatal self poisoning episodes for a particular drug), with case fatality ratios of 13.8 compared with 2.5 for venlafaxine, 1.9 for mirtazapine, and 0.5 for SSRIs.[33]

In general, the newer antidepressants can be started at their therapeutic dose and given once a day whereas the older antidepressants need to be started at a low dose and gradually increased to their therapeutic levels, sometimes splitting the dose over the day.

How are the newer antidepressants taken and monitored?

Which antidepressant to use first

The NICE guidelines on depression recommend an SSRI as the first choice of antidepressant.[3] Measurement of change in symptoms should be monitored with depression rating scales.

How soon they will work and what to do if they don't work

The usual advice is that antidepressants should start working after one to two weeks, although a meta-analysis of placebo controlled trials of SSRIs found that the therapeutic response is greatest in the first week.[34] The advice on when to see the patient after the first visit differs by guideline and varies from one to two weeks, more often if there are suicidal thoughts at the baseline assessment. The guidelines also differ on when to change management if the patient is not showing signs of improvement. Canadian guidelines suggest that if there is less than a 20% reduction in scores at six weeks then a change in treatment (such as an increase in dose) should be considered.[24] The NICE guidance recommends that if there is no improvement after three to four weeks the treatment should change.[3] The Macarthur Foundation on Depression in Primary Care suggests that a five point drop in the PHQ-9 score from baseline is a sign of adequate treatment and a two to four point drop warrants an increase in medication dose.[11] For those with insomnia, agitation, or anxiety (other than those with chronic anxiety) the NICE guidelines advise treatment with a benzodiazepine for no longer than two weeks to avoid dependence.[3]

If a patient shows no response to the initial antidepressant, the first steps are to check adherence, increase the frequency of appointments, consider the addition of psychotherapy, increase the dose of antidepressant, and consider changing to another antidepressant. The evidence for the effectiveness of an increase in dose or a switch to another antidepressant is not strong. If choosing to change medications, consider a different SSRI and then an antidepressant of a different pharmacological class. After this step, other strategies are best considered after consultation with specialist services and may include augmentation with other drugs (such as lithium, triiodothyronine or second generation antipsychotics) or combination antidepressant

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treatment.[35] For all these strategies the effect size is modest and the number of side effects is significantly increased.

Switching antidepressants

Switching from SSRIs to tricyclics generally means reducing the dose of the SSRI and slowly increasing the dose of the tricyclic from low doses. Fluoxetine, because of its longer half life, should be stopped four to seven days before starting the tricyclic at a low dose. Monoamine oxidase inhibitors should generally be stopped for two weeks before starting other antidepressants. When switching from a tricyclic to an SSRI the dose of the tricyclic should be halved and the SSRI added before further reducing the dose of the tricyclic. It is wise to consult local prescribing guidelines, seek specialist advice, and read the specific product details of the antidepressant before switching antidepressants.

Stopping antidepressants

There is no evidence that antidepressants cause psychological dependence, are "addictive," or that people develop tolerance to their actions. However, about a third of patients report discontinuation symptoms when stopping antidepressants, with the greatest risk occurring with paroxetine, venlafaxine, and amitriptyline. The symptoms include affective, gastrointestinal, neuromotor, vasomotor, neurosensory, and other neurological symptoms, which usually occur within five days of stopping treatment. They are best managed by avoiding abrupt withdrawal so that the dose is reduced over four weeks and by reassuring the patient that the symptoms usually disappear after a few days. If the symptoms are severe then the original antidepressant may need to be reintroduced and the dose tapered more gradually.

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