Long term treatment of depression with selective serotonin reuptake inhibitors and newer antidepressants

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The introduction of fluoxetine in 1987 marked the arrival of the selective serotonin reuptake inhibitors (SSRIs) for the treatment for depression. In the United States antidepressant prescriptions accounted for 2.6% of primary care visits in 1989, rising to 7.1% in 2000.[1] This pattern was reflected across Europe, where SSRIs are now the most commonly prescribed antidepressants. Newer antidepressants, such as the serotonin norepinephrine reuptake inhibitors, including venlafaxine and duloxetine, also contributed to the remarkable increase in antidepressant prescribing.[2]

Several reasons were put forward for this trend: improved tolerability; reduced lethality in overdose; the aggressive marketing of newly patented drugs; the wider range of available antidepressants; and ease of prescription. An analysis of the UK general practice research database showed that prescriptions almost doubled from 1993 to 2005.[3] However, the increase in antidepressant prescribing was not accounted for by new diagnoses but rather a rise in the number of prescriptions given for long term treatment: although the proportion of patients receiving short term treatment declined, the proportion of patients receiving continuing prescriptions for over five years increased. Another primary care study found that the mean duration of antidepressant prescriptions for depression was 4.8 years and 48% of the sample received treatment for more than two years.[4]

The early optimism accompanying SSRIs has faded amid controversy over their effectiveness and safety.[5] Recent meta-analyses have concluded that antidepressants have only a modest advantage over placebo, with the magnitude of benefit increasing with severity of depression.[6 7] Debate has persisted about the association between SSRIs and suicidal behaviour,[8] considerable disquiet has been expressed about the perceived medicalisation of social problems that really require social solutions. In this review we examine the evidence for the benefits and harms of long term use of SSRIs and newer antidepressants in adults with major depression.

Do SSRIs reduce the risk of relapse or recurrence of depression?

Depression is commonly a recurrent illness: over half of people with a diagnosis of major depression will go on to have a further episode, and the risk of future relapse rises, with 80% of those having a second episode going on to have a third.[9] Most clinical guidelines recommend that treatment with antidepressants should be continued for four to six months after recovery to reduce the risk of relapse (re-emergence of original symptoms) and recurrence (new episode of depression).[10 11] However, the benefits of long term or maintenance treatment are considered, particularly by clinicians, to be less certain.[12]

A systematic review included 31 randomised trials (4410 participants) investigating whether continuing treatment with antidepressants (of all classes, although most included either a tricyclic antidepressant or an SSRI) reduced the risk of relapse.[13] These trials were mainly discontinuation studies in which participants with depressive disorders who had responded to acute treatment were randomly assigned to continue drug treatment or receive a placebo.

Pooled results found that, compared with placebo, continuing antidepressant treatment after recovery markedly reduced the proportion of patients who relapsed over one to three years (pooled odds ratio for

SOURCES AND SELECTION CRITERIA

To identify relevant articles, we searched the Cochrane Library, Clinical Evidence, the National Institute for Health and Clinical Excellence's website, and Medline. We combined the search terms "major depressive disorder" and "antidepressant" with terms for adverse events ("adverse events", "harms", "drug reactions", "toxicity") and benefit ("efficacy", "effectiveness"). We gave priority to systematic reviews, meta-analyses, and evidence based clinical guidelines published within the past 10 years. When no report of those types was available, we considered individual randomised controlled trials or observational studies.

SUMMARY POINTS

- The rise in the prescribing of antidepressants is largely accounted for by an increase in long term treatment
- Half of people with a diagnosis of major depression will go on to have a further episode, and risk of recurrence increases with each episode
- Evidence for the benefits of long term prescribing of antidepressants comes almost exclusively from secondary care settings
- Continuing antidepressant treatment roughly halves the absolute risk of relapse
- The increased risk of suicidal behaviour associated with selective serotonin reuptake inhibitors (SSRIs) is restricted to people aged under 25
- People with risk factors for relapse of depression should be advised to continue with SSRIs for at least 12 months and consider long term treatment

Table 1 | Antidepressant drugs compared with placebo for preventing relapse in depression: summary measures by length of follow-up*

Follow-up (months)	Relapse rate in participants (%)		Relative risk reduction (%) (95% CI)	Absolute risk reduction (%) (95% CI)	Number needed to treat (95% CI)	No of studies (participants: antidepressant/placebo)
	Antidepressant	Placebo				
6	14.7	36.8	60 (48 to 70)	22 (16 to 29)	4.5 (3.5 to 6.4)	9 (442/296)
12	17.1	37.0	54 (47 to 59)	20 (17 to 23)	5.0 (4.3 to 6.0)	12 (1604/1122)
18	16.2	47.9	66 (47 to 78)	32 (21 to 43)	3.1 (2.3 to 4.8)	3 (117/123)
24	28.4	60.8	53 (40 to 64)	32 (23 to 42)	3.1 (2.4 to 4.4)	6 (190/166)
36	29.8	71.5	58 (47 to 67)	42 (32 to 51)	2.4 (1.9 to 3.1)	5 (174/176)
Overall	19.1	43.0	55 (51 to 59)	24 (21 to 27)	4.2 (3.8 to 4.7)	35 (2525/1883)

95% CI= 95% confidence interval.

Absolute numbers were extracted from figure 1 of Furukawa et al.[14] Recalculations were performed using the spreadsheet available at www.ebpcenter.com/spreadsheets/index.html.

relapse 0.30; 95% confidence interval 0.22 to 0.38). A re-analysis of these data (shown in table 1), summarises the rates of relapse by length of follow-up.[14] While the absolute risk reduction progressively increased from six to 36 months of follow-up, the relative risk reduction was stable (from 60% at six months to 58% at 36 months), suggesting that continuing antidepressant treatment more than halved the average relapse rate regardless of the duration of treatment. The absolute risk reduction was similar at six and 12 months, although the larger sample size at 12 months provides a more precise estimate. On average four patients required antidepressant treatment to prevent one additional relapse. Further systematic reviews, restricted to data on SSRIs and newer antidepressants (bupropion, mirtazapine, nefazodone, and venlafaxine), produced similar findings: a risk reduction in the proportion of patients relapsing of about 50%.[15] These trials also indicate that the reduction in relapse rates with prophylactic antidepressants is greater for patients with single episodes (odds ratio for relapse 0.12; 0.06 to 0.26) than for those with recurrent episodes (0.37; 0.31 to 0.44).[16]

Discontinuation trials have been criticised as their results apply only to patients responding to treatment and not to those who experience spontaneous recovery.[17] In addition, discontinuation of treatment may result in withdrawal symptoms that mimic depression itself, leading to an overestimate of the true effect of the medication. A systematic review comprising continuation trials only—that is, trials in which participants with depression were randomly assigned to SSRIs or placebo, with longer term follow-up of those that responded—pooled results from six trials that comprised 1299 participants and found that SSRIs were significantly superior to placebo at six to eight months (odds ratio 1.66, 1.12 to 2.48), though a less dramatic effect than that observed in discontinuation trials.[18]

What are the potential harms of long term treatment with SSRIs?

Self harm and suicide

Systematic reviews of randomised trials suggest an increased risk of self harm in people prescribed SSRIs, particularly those aged under 25 years, but no clear relation with completed suicide.[8] The evidence from trials is limited, however, by short duration of follow-up, and as suicide is a rare outcome most trials lack sufficient power to measure an effect.

Observational studies with large populations offer an additional perspective and, importantly, include completed suicide as an outcome. A recent systematic review combined data from eight observational studies (over 200 000 patients) that reported data on completed or attempted suicide in depressed individuals who had taken SSRIs for depression and in individuals who had received no antidepressant treatment.[19] SSRIs increased the risk of completed or attempted suicide when prescribed for adolescents (odds ratio 1.92; 95% confidence interval 1.51 to 2.44) but reduced the risk when prescribed for adults (0.57; 0.47 to 0.70). In individuals aged 65 or above, exposure to SSRIs also had a protective effect (0.46; 0.27 to 0.79). These results are in line with the conclusions of the recent US Food and Drug Administration's re-analysis of clinical trial data, which showed that the risk of suicidal behaviour was raised in people aged under 25, not affected in those aged 25-64, and reduced in those aged 65 and older,[20] suggesting that prescribing SSRIs in adults with major depression may be considered a strategy for reducing suicide risk.

Discontinuation effects

Missed doses are common with any long term drug treatment, but with SSRIs and newer antidepressants abrupt interruption of treatment may lead to discontinuation symptoms.[21] These symptoms develop 24-72 hours after interruption and include dizziness, vertigo, nausea, fatigue, headache, anxiety, agitation, insomnia, irritability, akathisia, electric shock-like sensations, and, possibly, aggressive and impulsive behaviour. For most, discontinuation symptoms are mild and short lived,

QUESTIONS FOR FUTURE RESEARCH

- Do selective serotonin reuptake inhibitors (SSRIs) continue to reduce the risk of relapse after three years?
- Do antidepressants differ in their effectiveness for preventing relapse?
- Are some subtypes of depression more responsive than others to treatment with selective serotonin reuptake inhibitors?
- How do psychological treatments compare with selective serotonin reuptake inhibitors in the prevention of relapse?

but they can sometimes be severe and prolonged. They may be mistaken for signs of physical illness, or as they include psychological and behavioural symptoms they may be misinterpreted as early signs of relapse.

Data on SSRI discontinuation symptoms are mainly drawn from spontaneous reports of adverse drug reactions, but evidence from prospective studies shows that duration of treatment increases the risk of occurrence and that they are more likely after treatment with antidepressants that have a short half life, such as paroxetine and venlafaxine.[21 22] Consequently, clinical guidelines recommend warning patients about the possibility of discontinuation symptoms and advising that antidepressants should not be stopped abruptly. Dose of treatment should be gradually reduced over at least four weeks.[21 23]

Sexual dysfunction

Sexual dysfunction is a common though often neglected adverse effect of antidepressants. All three phases of the sexual response cycle may be affected: reduced interest and desire for sex; erectile dysfunction in men and diminished arousal in women; and difficulty in attaining orgasm in both sexes. A systematic review quantifying prevalence of sexual adverse effects emerging with use of antidepressants found rates of 4% to 80% after four to 12 weeks of treatment (table 2) compared with 14% associated with placebo.[24] Newer antidepressants were associated with the highest rates of sexual dysfunction,[24] a finding confirmed in a meta-analysis of 104 experimental and observational studies: citalopram (73%), paroxetine (71%), and venlafaxine (67%) had the highest incidence of sexual dysfunction, while mirtazapine (24%) and nefazodone (8%) had the lowest.[25] Evidence is lacking to support any strategy to manage sexual dysfunction caused by antidepressants. Spontaneous remission may occur, but for most patients sexual dysfunction persists during treatment.[26] Switching drugs is an option, but another drug may not be equally effective.

Pregnancy

The safety of antidepressants in pregnancy is an important consideration for women treated with SSRIs. A review of antenatal mental health care is beyond the scope of this article, but substantial literature is now available to support decision making.[27] SSRIs do not seem to increase the risk of birth defects after exposure during the first trimester; the exception is paroxetine, which is associated with a 1.5-fold increased risk for congenital heart defects. As a class, SSRIs taken after 20 weeks' gestation may be associated with an increased risk of persistent pulmonary hypertension in the neonate, and all antidepressants prescribed in the third trimester may cause discontinuation effects, notably irritability, in the newborn, although these are usually mild and self limiting. Clinical guidelines recommend therefore that paroxetine should be stopped during pregnancy, and although SSRIs are not contraindicated, consideration should be given to use of tricyclic antidepressants, which have lower known risks in pregnancy.[28]

Bleeding disorders

Observational studies have shown that SSRIs and venlafaxine increase the risk of upper gastrointestinal haemorrhage and other bleeding disorders, probably by altering platelet function.[29] A case-control study using the UK Health Improvement Network's database (www.thin-uk.com/) estimated that 2000 patients a year would require treatment with SSRIs for one case of attributable upper gastrointestinal bleeding. This risk was modifiable, increasing considerably (number needed to harm 250) with concurrent use of low dose aspirin or non-steroidal anti-inflammatory drugs, but reduced by use of acid suppressing drugs.[30]

Hyponatraemia

Hyponatraemia is a potentially serious adverse effect, which has been associated with most antidepressants but reported most frequently with SSRIs.[31] Reported incidence rates suggest that three to five cases of hyponatraemia induced by SSRIs per 1000 patients a year may be expected, but substantially higher rates have been reported in older people, particularly women. Hyponatraemia manifests with muscle cramps, fatigue, and confusion, and it may result in seizures. When it

Table 2 | Sexual dysfunction associated with four to 12 weeks of antidepressant use. Adapted from Serretti and Chiesa[24]

Drug	Prevalence (%)	Odds ratio (compared with placebo) (95% CI)
Citalopram	79	20.3 (14.6 to 29.9)
Duloxetine	42	4.3 (2.8 to 6.6)
Escitalopram	37	3.4 (2.3 to 5.1)
Fluoxetine	71	15.6 (13.0 to 18.8)
Imipramine	44	7.2 (2.6 to 20.1)
Mirtazapine	24	2.3 (0.8 to 6.8)
Moclobemide	4	0.2 (0 to 2.1)
Nefazodone	8	0.5 (0.1 to 1.6)
Paroxetine	71	16.9 (13.5 to 19.8)
Sertraline	80	27.4 (19.4 to 38.9)
Venlafaxine	80	24.8 (19.1 to 32.4)

95% CI= 95% confidence interval.

Risk factors for relapse of major depression

- Presence of residual symptoms
- Number of previous episodes
- Severity of most recent episode
- Duration of most recent episode
- Degree of treatment resistance in previous episode

TIPS FOR NON-SPECIALISTS

- Treatment with selective serotonin reuptake inhibitors should be regularly reviewed
- Ask patients about adverse effects
- People with risk factors for relapse should continue treatment for at least 12 months
- When stopping a patient's treatment with selective serotonin reuptake inhibitors, gradually reduce the dose over four weeks

ADDITIONAL EDUCATIONAL RESOURCES

For healthcare professionals

- National Institute for Health and Clinical Excellence. Depression: the treatment and management of depression in adults (update). 2009. (Clinical guideline 90.) http://guidance.nice.org.uk/CG90
- National Institute for Health and Clinical Excellence. Depression in adults with a chronic physical health problem: treatment and management. 2009. (Clinical guideline 91.) http://guidance.nice.org.uk/CG91. This document gives a comprehensive summary of potential drug interactions
- British Association for Psychopharmacology (www.bap.org.uk)—Evidence based guidelines for treating depression
- *Clinical Evidence* (http://clinicalevidence.bmj.com/ceweb/index.jsp)—Up to date review of research evidence; registration required
- UK NHS Evidence—mental health (www.library.nhs.uk/mentalHealth/)—Evidence based reviews, updates and monthly newsletter
- Cochrane Collaboration (www.cochrane.org/)—International network for preparation and updating of reviews of interventions using the best available evidence

For patients

- Depression Alliance UK (www.depressionalliance.org/)—Help and information about depression
- Royal College of Psychiatrists (www.rcpsych.ac.uk/)—A range of information leaflets on depression in several languages

is detected, antidepressants should be withdrawn immediately. Monitoring of serum sodium concentration is advisable in individuals aged 80 years or older, those with a history of hyponatraemia, or those receiving other drug treatments associated with hyponatraemia.[32]

Cardiovascular effects

In contrast to tricyclic antidepressants, SSRIs do not slow cardiac conduction, prolong the QT interval, or cause orthostatic hypotension[33] so are considered safe to use in cardiovascular disease. Observational evidence supports this, with no evidence of an increased risk of myocardial infarction or cardiovascular mortality with long term treatment.[34] Evidence from randomised trials has also shown no additional risk with SSRIs after myocardial infarction.[35]

An evidence based approach to long term treatment with SSRIs and newer antidepressants

In adults with depression who have benefited from treatment with an antidepressant good evidence exists that they are at high risk of relapse, particularly in the first six months after recovery. Good evidence also exists that continuing antidepressant treatment reduces the absolute risk of relapse by about 50%. The trials on which guidelines are based come predominantly from secondary care settings with follow-up limited to three years. Longer term studies that include patients from primary care with less severe illness would inform clinical practice. Psychological treatments may augment the prophylactic effect of antidepressants, but much of the evidence for this has been inconclusive. Several studies have found that cognitive behavioural therapy combined with maintenance drug treatment significantly reduces rates of relapse compared with antidepressants alone, although whether this additional benefit is due to non-specific therapeutic effects is not clear.[36]

In summary, after a single depressive episode in the absence of specific risk factors for relapse (see the box on risk factors) people should be advised to continue treatment with antidepressants for 12 months after recovery. Treatment should be regularly re-evaluated, with the frequency determined by the severity of the episode. Individuals with risk factors for relapse, in particular those with several previous episodes or two episodes in the recent past, should be advised to continue with treatment for at least 12 months and consider long term maintenance treatment. With long term antidepressant treatment, regular reviews should take into consideration the social consequences of relapse for the individual, concurrent physical health problems, and the development of adverse effects, as well as patient preference.

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Competing interests: Both authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) (URL) and declare that all authors had (1) No financial support for the submitted work from anyone other than their employer; (2) No financial relationships with commercial entities that might have an interest in the submitted work; (3) No spouses, partners, or children with relationships with commercial entities that might have an interest in the submitted work; (4) SR is editor of the journal *Evidence-Based Mental Health*, and CB is a member of the editorial board of the Cochrane Collaboration Depression, Anxiety & Neurosis Group.

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ANSWERS TO ENDGAMES, p 767. For long answers go to the Education Channel on bmj.com

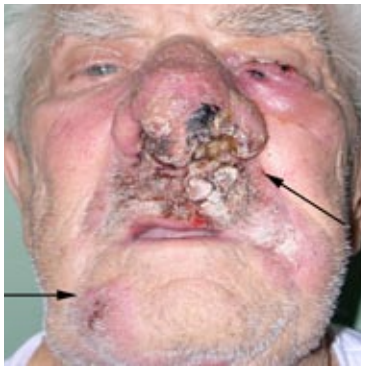
STATISTICAL QUESTION

Internal and external validity

Answer *c* can be concluded; answers *a*, *b*, and *d* cannot.

PICTURE QUIZ

Immunocompromised patient with an ulcerated nasolabial skin lesion



Patient with exophytic and crusted nasolabial facial lesion (right arrow), with extension to the nasal cruses. Some smaller lesions are located at the right mandible and cheek (left arrow)

1 The diagnosis is most likely to be cutaneous leishmaniasis.
2 The differential diagnoses are carcinoma, midline lethal granuloma, malignant tumours, granulomatous diseases, and infectious diseases.
3 Tissue biopsy, potassium hydroxide mount of a skin scraping sample, and ultrasound should be performed.
4 The first line treatment is pentavalent antimony compounds, such as sodium stibogluconate and meglumine antimony, administered for 20-28 days to a maximum dose of 850 mg a day. Second line treatment should be liposomal amphotericin B (3 mg/kg) for 5 days, with additional single doses on days 14 and 21.

CASE REPORT An agitated young man

1 The most likely diagnosis is neuroleptic malignant syndrome. The differential diagnosis should include encephalitis or meningitis, rhabdomyolysis, catatonia, drug toxicity, delirium tremens, serotonergic syndrome, and tetanus.
2 The patient should be treated in a medical unit. The causative drug(s) (in this case olanzapine) should be stopped and he should be rehydrated; consider giving dantrolene, baclofen, and ventilatory support if needed. Benzodiazepines can be used in severe agitation. Further investigations include blood tests, cultures, and urine toxicology. Chest radiography and neuroimaging should be performed.
3 This syndrome carries a risk of death and multiorgan failure, with estimates of mortality ranging from 5% to 20%. However, given adequate supportive treatment and no serious complications, the prognosis is good and there are usually no lasting neurological sequelae.