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Prevention of relapse and recurrence of depression: newer versus older antidepressants

J. Guy Edwards

In a 17- to 19-year follow-up study it was shown that patients admitted to the Maudsley Hospital, London (whose index episode marked their first psychiatric contact) had a 50% chance of readmission during their lifetime; those with previous admissions had a similar chance of readmission within three years. Less than one-fifth of the patients had remained well, and over one-third suffered severe chronic distress and handicap or had died unnaturally (Lee & Murray, 1988). Similar gloomy pictures were reported in a 15-year follow-up study of patients in London and Sydney (Kiloh *et al*, 1988) and an 11-year follow-up study of patients in Montreal (Lehmann *et al*, 1988). As a result of such findings, much emphasis is now put on the importance of continuation and maintenance treatment of depression.

Continuation treatment is given to help consolidate recovery from an episode of depression and to prevent relapse, whereas maintenance (prophylactic) treatment is given to help prevent a recurrence of depression. A relapse is a worsening of an ongoing or recently treated episode, whereas a recurrence is a new episode of depression. When there is a long interval between episodes, the distinction is easier to make but, when the interval is short, the distinction is to a certain extent arbitrary and may not reflect underlying pathogenic processes. There is agreement among researchers that four to six months' remission (during which time the patient's affective state returns to its premorbid level) should occur before a further depressive episode is regarded as a recurrence.

Many trials of continuation and maintenance treatment have been carried out. Over the years, larger numbers of patients have been included in trials and the methodology has improved. The placebo-controlled studies undertaken during the past decade are shown in Table 1. It is difficult to make meaningful comparisons between older and newer antidepressants because of differences in the patients included in trials of older and newer compounds and differences in methodology. However, the studies have included patients who meet conventional diagnostic criteria, such as those in DSM–III–R, and who have defined scores on rating scales for depression. Most subjects included have been responders to open treatment with the drug being investigated, or those who have responded during a controlled trial of shorter-term (acute) treatment with the drug. Relapse or recurrence was defined as a worsening or return of depression with a predetermined increase in a score on a rating scale. However, there are a number of methodological difficulties that have to be taken into account in the interpretation of the results of long-term trials (Box 1).

Notwithstanding these difficulties, the studies suggest that about 60% (range 22–76%) of those who respond to an antidepressant and are then switched to placebo remain in remission for up to

Box 1. Methodological problems in studies of long-term treatment

- Difficulties in defining remission, relapse and recurrence
- Small sample sizes
- Matching on all variables, including number of previous episodes of affective disorder
- Effect of previous treatment
- Effect of concomitant treatment
- Drop-outs
- Difficulty tracing patients
- Difficulty obtaining accurate follow-up data

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Table 1. Placebo-controlled studies of antidepressants in the prevention of relapse and recurrence of depression

Study	Age range (months)	Duration of study	Antidepressants	Patients (*n*)	Relapses or recurrences (*n*)
Montgomery *et al*, 1988	n.s.	12	Fluoxetine 40 mg	88	23 (26%)
			Placebo	94	54(57%)
Georgotas *et al*, 1989	>55	12	Nortriptyline n.s.[1]	13	7 (54%)
			Phenelzine n.s.[2]	15	2 (13%)
			Placebo	23	15 (65%)
Rouillon *et al*, 1989	18–78	12	Maprotiline 75 mg	385	62 (16%)
			Maprotiline 37.5 mg	382	92 (24%)
			Placebo	374	131 (35%)
Frank *et al*, 1990	21–65	36	Imipramine mean 200 mg	28	6 (21%)
			Imipramine + IPT	25	6 (24%)
			Placebo	23	18 (78%)
Robinson *et al*, 1991	>18	24	Phenelzine 45 mg	12	4 (33%)
			Phenelzine 60 mg	19	5 (26%)
			Placebo	16	13 (81%)
Doogan & Caillard, 1992	18–70	11	Sertraline 50–200 mg	184	24 (13%)
			Placebo	105	48 (46%)
Kupfer *et al*, 1992	21–65	24	Imipramine mean 200 mg	11	1 (9%)
			Placebo	9	6 (67%)
Jacobi & Lunn, 1993	>60	24	Dothiepin 75 mg	33	10 (30%)
			Placebo	36	20 (56%)
Montgomery & Dunbar, 1993	23–65	12	Paroxetine 20–30 mg	68	11 (16%)
			Placebo	67	29 (43%)
Montgomery *et al*, 1993	18–70	24	Citalopram 20 mg	48	4 (8%)
			Citalopram 40 mg	57	7 (12%)
			Placebo	42	13 (31%)
Anton *et al*, 1994	n.s.	12	Nefazodone 100–600 mg	139	12 (9%)
			Imipramine 50–300 mg	66	5 (8%)
			Placebo	71	18 (25%)
Robert & Montgomery, 1995	19–70	6	Citalopram 20–60 mg	150	21 (14%)
			Placebo	74	18 (24%)
Total			*Antidepressant*	*1723*	*302 (18%)*
			Placebo	*934*	*383 (41%)*

n.s., not specified.
1. Dose n.s. – adjusted to maintain plasma nortriptyline levels at 190–648 mmol/l.
2. Dose n.s. – adjusted to maintain plasma platelet inhibition at >70%.

two or three years. If instead the patients continue with the treatment to which they have responded, they have overall a 20–25% better chance of maintaining their improvement. Some of the studies referred to have also revealed advantages of antidepressant over placebo in the time to onset of relapse or recurrence and in the depression scores of those who do not relapse. The studies cited are important in showing the efficacy of continuation and prophylactic treatment, but there is a paucity of knowledge on variables which may predict benefit for individual patients.

Which antidepressant?

Few long-term comparative studies have been carried out and most of these were comparisons of tricyclic antidepressants (TCAs) and lithium. The choice of drug in long-term treatment, therefore, has to be based on the results of short-term trials, epidemiological studies of untoward effects, pharmacological experiments and impressions gleaned from studies of continuation and maintenance treatment.

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Therapeutic effects

Meta-analyses have shown that there are no significant differences in effectiveness of different types of antidepressants during short-term treatment (Anderson, 1997, this issue), although data from some individual trials suggest that selective serotonin reuptake inhibitors (SSRIs) other than fluvoxamine could be less effective than TCAs in the treatment of severely melancholic in-patients (Anderson, 1997, this issue). As there are insufficient data on long-term treatment (merely hints of a possible lower relapse rate on SSRIs than TCAs), there is no strong reason based on effectiveness for choosing one antidepressant rather than another for maintenance treatment.

Adverse effects

The choice of antidepressant (or antidepressant class) for continuation or prophylactic treatment is therefore based on its tolerability (adverse effect profile), toxicity in overdose and cost. Many unwanted effects of both new and old drugs have been reported, but only those that occupy a dominant place in the new-versus-old antidepressant debate will be discussed here. Conspicuous among these are anticholinergic and anti-α-adrenoceptor effects and sedation.

There are problems in comparing drugs because of difficulties in defining common effects (which are often identical to the symptoms of depression) and because of differences between studies in the way adverse effects are elicited, recorded and related to treatment. Notwithstanding these problems, the newer antidepressants have been shown to cause less sedation and autonomic effects than older TCAs. Thus, they produce fewer anticholinergic effects, such as decreased salivary flow and gastrointestinal mobility, which lead to dental caries and constipation, respectively, and less anti-α-adrenoceptor effects, which may result in postural hypotension (causing falls and injuries). Accidents may also be caused by over-sedation. On the other hand, the newer drugs cause other effects, such as gastrointestinal symptoms and CNS excitatory effects in the case of SSRIs (see Henry, 1997, this issue). In the case of both older and newer antidepressants adaptation to unwanted effects, such as sedation and nausea, may occur.

Compliance

These various reactions influence compliance, which in turn may have an effect on relapse and recurrence. Meta-analyses of compliance with continuation and maintenance treatment have not been carried out, although comments in trials of long-term treatment with TCAs and newer antidepressants imply that both types of drugs are well tolerated. Clinicians are therefore influenced in their choice of drugs by the results of meta-analyses of short-term treatment. These show, for example, no difference between SSRIs and tricyclics in drop-outs due to inefficacy, but a small significant difference (4.4–4.7%) in drop-outs due to side-effects (Anderson & Tomenson, 1995; Montgomery & Kasper, 1995; Anderson, 1997, this issue).

Much is made of this difference but more important is the overall drop-out rate, as it is often difficult to be sure exactly why patients stop their treatment. Drug-induced dysphoria (a side-effect) may be misinterpreted as lack of effectiveness, while patients may not tolerate side-effects that they would otherwise accept, or drop-out for other reasons, due to their depression failing to respond to treatment. Overall drop-out rates in meta-analyses do not show a significant difference between SSRIs and TCAs.

It is possible that overviews obscure differences between individual drugs. For instance, in a comparative trial there were 10% less drop-outs due to inefficacy and side-effects during treatment with paroxetine than imipramine (Dunbar *et al*, 1991), whereas in a small meta-analysis there were 9.6% less drop-outs due to adverse effects during treatment with dothiepin than SSRIs (Donovan *et al*, 1993).

Meta-analyses focus on trials in which highly selected patients are included. It is not known whether the apparent advantage of SSRIs also exists in the real world of general practice where most depressed patients are treated, or whether there is a lower discontinuation rate during longer-term treatment when adaptation to adverse effects might be expected to occur. Nor is it known whether the advantage would be upheld in populations of patients given better information and reassurance about side-effects, which is known to improve compliance.

Behavioural effects

The older TCAs (and some other antidepressants, e.g. mianserin, trazodone) have been shown to cause more impairment than the newer antidepressants (including lofepramine) in laboratory tests of cognitive and psychomotor function (Hindmarch *et al*, 1992). The older tricyclics have also been shown to cause impairment in driving tests, whereas SSRIs, reversible inhibitors of monoamine oxidase A (RIMAs) and nefazodone cause little or no impairment (Louwerens *et al*, 1986; Raemaekers *et al*, 1994; Robbe & O'Hanlon, 1995; Van Laar *et al*, 1995).

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Although these findings support the use of the newer drugs for long-term treatment, the predictive validity of psychomotor tests has been questioned (Parrott, 1987; Freeman & O'Hanlon, 1995). Many skilled tasks can be performed without undue effort and with spare processing capacity left available, and it has been suggested that information-processing tasks are measures of competence (potential) rather than actual performance (Parrott, 1991).

Furthermore, most of the investigations were carried out after short-term administration of drugs (sometimes in single doses), rather than during longer-term treatment, when adaptation may occur. Adaptation to the effects of TCAs on driving has, in fact, been demonstrated (Ramaekers *et al*, 1994; Robbe & O'Hanlon, 1995; van Laar *et al*, 1995). Perhaps these considerations explain why TCAs were found in the body fluids of only 0.2% of people who died in traffic accidents, compared with alcohol in 35% and other drugs liable to affect the CNS in 7.4% (Everest *et al*, 1989).

Consistent with the observations that older TCAs cause psychomotor impairment, is the finding that elderly drivers treated with these drugs have an increased risk of vehicle crashes in which injuries are sustained, and that there is a relationship between the risk and dose of drug (Ray *et al*, 1992; Leveille *et al*, 1994). This suggests that the drugs contribute to the accidents, although inability to control for all potentially confounding variables does not allow for definite conclusions to be reached.

The extent to which antidepressants cause or contribute to road traffic and other accidents is not known. Nevertheless, the aforementioned concerns should be taken into account in the choice of drug for long-term treatment. Although the risk may be greater when treatment is first introduced, it should also be considered when the dose is increased or when antidepressants are taken with other substances that affect cognition and psychomotor performance. For patients thought to be at high risk of accidents, including those who experience persistent sedation when taking TCAs or drug combinations, it is sensible to err on the side of safety and prescribe non-sedative antidepressants.

Drug interactions

The more receptors and enzymes affected by a drug, the greater the number of potential interactions. Thus, older monoamine oxidase inhibitors (MAOIs) and TCAs cause more interactions than newer drugs, such as RIMAs and SSRIs. However, SSRIs interact with other drugs that affect serotoninergic transmission and they inhibit hepatic enzymes involved in the metabolism of a wide range of other compounds. Fluoxetine and paroxetine, for instance, are powerful inhibitors of CYP2D6, a specific cytochrome p450 isoenzyme which catalyses the metabolism of many other drugs. Concurrent treatment with SSRIs may lead to increased plasma concentrations of these drugs (Spina & Perucca, 1994; Edwards, 1995). However, the evidence for some interactions is weak; many are of more theoretical than practical interest; and similar numbers of potentially hazardous interactions occur with SSRIs as with TCAs (Edwards, 1995; Henry, 1997, this issue). Such interactions can be avoided by the careful choice of drugs.

Lethality in overdose

Antidepressants introduced before 1970 have a higher fatal toxicity index (the number of deaths due to overdose per million prescriptions) than those introduced more recently (Henry *et al*, 1995; Henry, 1997, this issue). Despite the limitations of the methodology (especially uncertainty over the cause of death; the quantities of drugs and other substances taken; and the medical condition of the patients), the results show that death due to overdose of antidepressants is more likely to occur if older drugs are taken. This is consistent with the known cardiotoxic effects of older TCAs and the relative freedom from these effects of the newer antidepressants.

On the strength of these observations, it has been recommended that the newer antidepressants should be used routinely as first-line treatment of depression. However, the risk of death from overdose has to be seen in perspective. Only about 4% of all suicides are due to overdose of single antidepressants (Office of Population Censuses and Surveys, 1975–92) and it is not known what proportion of these are taken during treatment (when choice is more relevant).

Furthermore, different suicide rates among patients prescribed different antidepressants may be influenced by their doctors' perception of suicidal risk. It has been shown, for instance, that amitriptyline is prescribed more often for patients with severe depression and depression associated with severe insomnia, which in turn could be associated with an increased propensity for suicide (Isacsson *et al*, 1994). Also, patients treated with TCAs may not be at greater overall risk of suicide (by any method) than those treated with less toxic drugs, as those who have their minds set firmly on killing themselves will choose a method of doing so. In keeping with this are two other findings: first, deaths due to self-poisoning in England and Wales have decreased since safer antidepressants have been more widely used, while those due to more

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Table 2. National Health Service prescriptions for antidepressants and their costs (England 1995)

Antidepressants	Prescription items ('000s)	Net ingredient cost (£'000s)	Average cost per prescription (£)
TCAs and related antidepressants	8610.9	36 439.4	4.23
Amitriptyline	2461.7	1890.0	0.77
Imipramine	437.1	438.9	1.00
Dothiepin	3308.3	13 963.0	4.22
SSRIs	3793.9	103 230.9	27.21
Total for all antidepressants	13 227.2	146 832.9	11.10

Drug classification as in British National Formulary (September 1994). Data refer to all NHS prescriptions dispensed by community pharmacists and dispensing doctors. The net ingredient costs are the costs of drugs before discounts; they do not include dispensing costs or fees. The data are published with permission of the Statistics Division of the NHS Executive.

violent methods have increased (Office of Population Censuses and Surveys, 1975–92); second, the incidence of suicide by any method during treatment with the newer and older antidepressants in general practice is similar (Jick *et al*, 1995).

There is need for more epidemiological research. Until the results of this are available, it is advisable to avoid, or reduce access to, the older antidepressants that are more lethal in overdose in patients at high risk of suicide.

Relative costs and benefits

Purchasers of health care who have limited budgets have to weigh the direct and indirect costs of expensive new treatments against the benefits. A balanced view (Box 2) suggests that the benefits of the newer over older antidepressants may not be as clearly defined or as large as some believe. New drugs are expensive (Table 2). If there were a total shift in prescribing to SSRIs, in England alone the cost to the National Health Service at 1995 prices and consumption volumes would be almost £350 million per annum more than treating the same patients with amitriptyline. The purchases that can be made from this additional cost are often overlooked. They include, for instance, the employment of 2.8 million days of in-patient or 6.9 million days of day-patient treatment or 4.1 million out-patient attendances per year for patients with mental health problems (calculated at 1994/5 costs). As an alternative, almost 22 million hours of community psychiatric nurse time could be bought. Outside psychiatry, the additional costs of SSRIs would allow for the purchase of a wide variety of operations ranging from about 12 000 heart or bone marrow transplants to 770 000 D & Cs.

Opinions on the advantages and disadvantages of the newer and older drugs are polarised, but there is

Box 2. Advantages and disadvantages of SSRIs compared with older TCAs and related antidepressants

Advantages

Tolerance: 3.4–4.9% fewer drop-outs from trials due to side-effects

Unwanted effects: less sedation; less anticholinergic effects; less weight gain; possibly fewer accidents

Toxicity in overdose: less likely to be lethal

Disadvantages

Unwanted effects: more gastrointestinal side-effects; long-term toxicity unknown

Cost: more expensive

Comments

Tolerance: no significant difference in overall drop-out rate; not known whether advantage exists in routine clinical practice

Unwanted effects: more epidemiological data are needed

Toxicity in overdose: suicide rate by any method among patients treated with different antidepressants is similar

Cost: extra expense means less money available for other areas of medical care

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little place for dogmatism. The most objective view is that based on scientific evidence, rather than a frustration with the relative lack of effectiveness of antidepressants in general, novelty and hype.

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