New or old antidepressants?

New is better

Glynn Harrison

This is the ninth in a series of articles examining some of the difficult decisions that arise in medicine

To justify a claim that a new drug is much better than old and well tried formulations it is necessary to show greater effectiveness, fewer side effects, or significantly reduced costs to the purchaser. There is no evidence that the "new" antidepressants, such as lofepramine and the selective serotonin reuptake inhibitors, are any more effective than older treatments, but they are certainly equally effective.^{1,2} Some of the new antidepressants have already been in use for several years and acquired a sound track record in general clinical experience. Though further prospective trials are needed in severe and chronic forms of depression,³ experimental evidence for tricyclic antidepressants in these conditions is similarly limited.

Benefits of new drugs

The advantages of the new treatments are that they have fewer unpleasant side effects.⁴ Because of the absence of antimuscarinic effects, most of the new antidepressants have few of the troublesome effects of dry mouth, constipation, blurred vision, and tachycardia, and sedation is less of a problem because new treatments cause little blockade of histamine receptors. Less ataxia and incoordination in elderly people reduce the risk of falls, and postural hypotension is uncommon because of the absence of α_1 receptor blockade. Weight gain and carbohydrate craving, a serious concern of many patients, are much reduced. These side effects are always unpleasant for patients, sometimes distressing, and occasionally fatal.

Tricyclic antidepressants are a well recognised cause of cardiotoxicity and death in overdose. The selective serotonin reuptake inhibitors and other new antidepressants have weaker membrane stabilising properties at high doses and are thus much safer in patients with cardiac disease and those at risk of overdoses, which includes almost all depressed patients. Safer drugs offer incalculable benefits in terms of the human cost of suicide.

The main drawback of safer antidepressants is the higher incidence of nausea and gastrointestinal side effects. These complaints are often relatively mild, however, and tend to lessen with continued use. Data suggesting that fluoxetine increases violent and suicidal thoughts or that selective serotonin reuptake inhibitors are more likely to precipitate mania are not convincing.⁵

Compliance with treatment

The benefits of the newer antidepressants in terms of side effects are evident to all but those still clinging to the dubious view that "if it isn't hurting it isn't working." The critical issue, however, is whether they actually affect the way patients comply with treatment. Between 0 and 14% of patients taking placebo drop out of clinical trials because of emerging side effects (median 5%) compared with 7-23% (median 15%) taking selective serotonin reuptake inhibitors and 7-44% (median 21%) taking tricyclics.⁴ An increased rate of compliance of around 6% seems modest but

represents recovery in around 4-5% of depressed patients (assuming a partial response rate) who would otherwise fall out of treatment.

In addition, drop out rates for patients who have been recruited to clinical trials on the basis that they will take part in placebo controlled treatment conditions may not represent the rate among ordinary general practice attenders. People who are not on the conveyor belt of a clinical trial are likely to be much more sceptical about their drugs and more sensitive to side effects and therefore more likely to drop out. If less toxic treatments are prescribed first appreciable inroads could be made into the 30% of patients who probably do not comply with treatment at all⁶ and the 25% of patients placed on inadequate doses by doctors worried about side effects.⁷

Because many modern antidepressants, especially the selective serotonin reuptake inhibitors, can be given in a one tablet daily dose without the need for increments, treatment is straightforward and easy to follow. This further increases the potential for compliance and fewer patients are given subtherapeutic doses. Few reliable data are available for rates of compliance with either new or old antidepressants in the maintenance treatment of depression (often required for up to 12 months and longer). But giving such patients drugs with fewer side effects especially less sedation means that they can return to work and resume driving.

There is growing concern about road safety and the use of psychotropic drugs. In the United Kingdom recent draft guidelines from the medical advisory branch of the Driver and Vehicle Licensing Agency suggest that drivers suffering from "serious psychoneurotic episodes" (including depression) affecting or likely to affect driving should be advised not to drive and notified to the agency. All patients must be warned about the possible effects of drugs on fitness to drive. People who drive in the course of their work should stop driving until symptom free and "off all psychotropic medication." Concern also exists about the sedative effects of older tricyclic antidepressants and fitness to drive, even where they are prescribed for less serious psychoneurotic episodes. Though considerable caution is required in translating experimental data, such as choice reaction times, into estimates of risk for car accidents, the impairment produced by tricyclic antidepressants is greater than that produced by blood alcohol concentration over 80 mg/100 ml (the legal limit in Britain).⁸ Lofepramine, although a tricyclic antidepressant, does not possess the same degree of sedative effect, and neither do selective serotonin reuptake inhibitors and reversible monoamine oxidase inhibitors. In addition, most of the newer antidepressants do not augment the sedative effects of alcohol, further reducing the risk of road traffic accidents.

Cost issues

At first glance the newer antidepressants lose out on costs. A 20-30 times higher price seems hard to justify if new treatments differ only in terms of side effects and

Academic Department of
Psychiatry, Mapperley
Hospital, Nottingham
NG3 6AA

Glynn Harrison, professor of
community mental health

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better compliance. Is it worth saving one life through the prescription of non-toxic drugs if the overall increase in costs averages at several hundreds of thousands of pounds? More lives might be saved for the same outlay on, for example, kidney transplantation or health education. Costs are therefore central to the debate about new versus old.

On closer scrutiny the cost advantages of the cheap tricyclic antidepressants may be more apparent than real. Firstly, the cost differentials, although wide, are starting to narrow. Secondly, the costs of treatment abandoned because of unwanted side effects of tricyclic antidepressants, failures of recovery, and the increased risks of suicide must be taken into account. Thirdly, the side effects of tricyclic antidepressants could result in extra expenditure on treatment for dental decay, hip fractures, and trauma from road traffic accidents. A simulated costing analysis based on data available from clinical trials estimated that when the cost of drop outs and poor compliance are taken into account, the selective serotonin reuptake inhibitors are no more expensive than tricyclics, despite the higher initial prescription costs.⁹

Of course, an old friend such as amitriptyline is not

yet ready to be pensioned off completely. Not all patients respond to their first antidepressant treatment and certain depressed patients may require a broader spectrum of synaptic blockade than that offered by the selective serotonin reuptake inhibitors. Tricyclics will continue to form an important part of doctors' armoury. But for the first line treatment of patients seen everyday in surgeries and psychiatric clinics, new is better.

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Benefits of new drugs are exaggerated

David Owens

Lately there has been a good deal of clamour from those who think that the recent additions to the antidepressant drug list known as selective serotonin reuptake inhibitors (fluoxetine, fluvoxamine, paroxetine and sertraline) should replace older, largely tricyclic, antidepressant drugs as the treatment of choice for depressive illness. How strong is their case?

Effectiveness

Randomised trials have shown the new drugs to be more effective than placebo, but the debate is about trials comparing serotonin reuptake inhibitors with tricyclic antidepressants. Selected studies have found greater recovery with serotonin reuptake inhibitors and are widely quoted by enthusiasts. However, several influential reviews have concluded that efficacy is about equal.¹⁻³ A recent systematic review of 64 randomised controlled trials comparing serotonin reuptake inhibitors with established antidepressant drugs found similar benefit from new and old treatments; where data could be pooled in a meta-analysis no clear difference was found.⁴

Because the treatment trials have mainly examined depression in primary care, specialists may be premature to count on equal effectiveness when treating patients referred to clinics and hospitals. Interest is shifting towards other clinical situations and we will soon be (or already are being) treated to claims that serotonin reuptake inhibitors are ideal for severe depression, resistant depression, continuing treatment, prophylaxis, and so on. In view of the lack of extra benefit so far shown, canny clinicians will look for independent systematic reviews in each of these areas before changing practice.

Unwanted effects

No more effective, but do the serotonin reuptake inhibitors prevail when it comes to unwanted actions: either troublesome side effects or toxicity in overdose?

The side effects of new and old drugs have little in common. For example, serotonin reuptake inhibitors are less likely than tricyclic antidepressants to cause sedation, anticholinergic actions, and cardiac arrhythmias. On the other hand, serotonin reuptake inhibitors commonly affect the gut (especially causing nausea and diarrhoea) and may affect the central nervous system producing insomnia, agitation, extrapyramidal symptoms, and withdrawal effects.

It is a common assertion that serotonin reuptake inhibitors are less troublesome to patients, thereby improving compliance and wellbeing. This claim does not, however, bear close scrutiny. As with tricyclic antidepressants, many patients find serotonin reuptake inhibitors unpleasant to take. When drop out rates from 58 trials were reviewed systematically there was no clinically important difference between the new drugs and tricyclic and related antidepressants; when the data were pooled one third of patients dropped out of each drug group.⁴

Antidepressant poisoning accounts for about 5% of suicides. Serotonin reuptake inhibitors are probably safer in overdose than older tricyclic antidepressants. Some clinicians have already argued that this should affect routine choice of antidepressant⁵ and that tricyclic antidepressants should be consigned to second or lower choice.⁶

There were around 3600 deaths due to overdose of single antidepressants in the United Kingdom between 1975 and 1989—an average of 240 deaths each year.⁷ But substitution of serotonin reuptake inhibitors for tricyclics is unlikely to eradicate all these deaths. Firstly, a few people have already committed suicide using serotonin reuptake inhibitors; precise figures for fatal toxicity in overdose will emerge only after several more years of use. Secondly, serotonin reuptake inhibitors, like older drugs, are often not tolerated or are ineffective; some patients at risk of suicide will necessarily be switched to other drugs. Thirdly, where self poisoning with a prescribed drug has not been fatal an unknown proportion of suicidal patients will substitute another method.

Division of Psychiatry and
Behavioural Sciences,
Leeds University, Leeds
LS2 9LT
David Owens, senior lecturer