Which antidepressant?

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SUMMARY. The prescription of psychotropic drugs, and particularly the use of antidepressants, has received considerable attention in the medical literature, the media and from legislative bodies in recent years. Medical practitioners are faced with a bewildering array of apparently efficacious drugs from which they must choose when prescribing for a depressed patient. This paper discusses the main parameters which guide this choice, namely clinical efficacy, adverse effects profile, safety in overdose and monetary cost. It concludes by making some recommendations for the prescription of antidepressant drugs.

Introduction

WITH the appearance on the market of several new antidepressants, and amid the current pressures to 'rationalize' our prescribing habits, deciding which drug to prescribe for a depressed patient becomes increasingly complex. It is perhaps timely, therefore, to review the major related issues and to make some tentative recommendations.

Four principal criteria determine one's choice of antidepressants; clinical efficacy, profile of adverse effects, degree of toxicity when taken in overdose and monetary cost of treatment. These criteria will each be discussed in turn.

Clinical efficacy

During the last 30 years, pharmacological modification of the basic tricyclic nucleus, of which imipramine was a prototype, has led to the development of agents with differing patterns of pharmacological activity and with increased selectivity. However, this has left the overall range of antidepressant efficacy unchanged. Somewhere in the region of 30% of depressed patients will respond to treatment with a placebo whereas 70–80% will respond to antidepressant medication.[1] Despite the development of the newer antidepressant agents little impact, if any, has been made on the remaining 20–30% of patients who do not respond to treatment. While there is no evidence that the newer antidepressant drugs are any less effective than the traditional tricyclic antidepressants, many trials of newer compounds may be criticized for employing patient numbers which are insufficiently large to demonstrate any small differences in efficacy.

Profile of adverse effects

The usefulness of the tricyclic antidepressants is greatly limited by their troublesome adverse effects profile.[2] The principal adverse effects associated with the use of tricyclics are those mediated by their anticholinergic activity; these present as symptoms such as dry mouth, constipation, urinary hesitancy and loss of visual accommodation. In addition, there is the potential to develop a central anticholinergic syndrome causing anxiety, delirium, hyperactivity, hallucinosis, and seizures. Tricyclic antidepressants are also noted for their propensity to induce orthostatic hypotension, tremor, a variety of cardiotoxic effects and carbohydrate craving which can result in troublesome weight gain.

In contrast, the second generation antidepressants have a very different profile of adverse effects.[3] With these compounds we do not encounter the constellation of symptoms mediated by the anticholinergic activity of the tricyclic antidepressants. Concern here is mainly focused on the rarer, idiosyncratic, but potentially fatal, adverse reactions affecting the liver, nervous system and haematological system. It has been these adverse reactions which have limited the usefulness of nomifensin, zimelidine and more recently mianserin. Nomifensin and zimelidine have been withdrawn from the market, but some authors have suggested that we may not have taken an adequately global assessment of the risks and benefits involved.[4] The case for the continued availability and use of mianserin has been eloquently put by Pinder[5] and Burrows and colleagues.[6] It is primarily this aspect of idiosyncratic drug toxicity on which the Committee on Safety of Medicines chooses to focus. The second generation antidepressant drugs have a much higher incidence of reported adverse reactions when compared with the conventional tricyclic drugs. However, the Committee on Safety of Medicines acknowledges that this is probably an inaccurate reflection of the true state of affairs.[7] In support of this, the data from two drug surveillance systems in West Germany have been analysed with a view to comparing the frequency and quality of adverse drug reactions associated with first and second generation antidepressants.[4] Very different profiles were found for first and second generation drugs, but no great differences within the groups. The authors draw attention to the impossibility of making fair comparisons between drugs when the various agents have been on the market for different lengths of time because the longer a drug has been on the market, the less likely it is that clinicians will report adverse reactions.

Perhaps the most topical example of concern over idiosyncratic reactions is that of the blood dyscrasias associated with the use of mianserin. Over a 10 year period up to May 1988, the following reports of dyscrasia associated with the use of mianserin were made: 185 non fatal white cell disorders (15 fatal); 29 non fatal red cell disorders (eight fatal); 12 bleeding/clotting disorders (personal communication, Bencard Pharmaceuticals).

Ancill[8] and Burrows and colleagues[6] have stressed the need to view these problems in the context of mianserin's comparative safety in overdose, and also its lack of cardiotoxicity and anticholinergic activity. It should also be noted that between 1964 and 1981 there were 83 reports of agranulocytosis associated with the use of amitriptyline. Of these cases, 18 were fatal.[9]

Doctors are sensibly cautious about prescribing new drugs. The extent and length of experience with some second generation antidepressants is now sufficiently long for them to be prescribed with confidence.

A further issue which is associated with the adverse effects profile of medication is that of compliance. In the case of tricyclic compounds, this can be seen principally as a consequence of the troublesome anticholinergic activity. One might reasonably assume that those antidepressants with a superior adverse effects profile, the newer agents, probably enhance patient compliance rates.[10] As Lader[11] points out, 'this is important in the real world of antidepressant drug usage'.

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Toxicity in overdose

With regard to toxicity in overdose, the magnitude of the problems posed by deliberate self poisoning has been extensively reviewed.[12,13] Deliberate self poisoning has become the single most common reason for acute medical admission of women to hospital and it is second only to ischaemic heart disease for men.[14]

Forster and Frost[15] present evidence of a clear correlation between the prescription of psychotropic drugs and the incidence of medicinal self poisoning. Brewer and Farmer[16] note the recent decline in the incidence of self poisoning which parallels the decline in the prescription of psychotropic drugs. While the main reduction has been in the prescription of the benzodiazepines, 10–20% of cases of self poisoning still involve antidepressant medication.[17] Often, these antidepressant drugs are prescribed shortly before the overdose. Indeed, Hawton and Blackstock[13] showed that in as many as 63% of cases of parasuicide the patient consulted their general practitioner within four weeks of the overdose. Skegg and colleagues[18] showed that the highest rates of self poisoning are in those individuals who are prescribed antidepressant medication. Unfortunately, most of the commonly prescribed antidepressants are extremely toxic when taken in overdose.

Cassidy and Henry[19] have taken a close look at the relative toxicity of the major antidepressant drugs used in the UK, calculating toxicity indices for each. These data show striking differences between the first and second generation antidepressants, with the traditional tricyclic antidepressants resulting in many more deaths from overdose. Pinder[5] has taken this a stage further, actually comparing estimated numbers of deaths owing to idiosyncratic reaction with those owing to overdose (Table 1).

Table 1. Number of deaths owing to poisoning and adverse drug reactions.

	Fatal poisonings per million prescriptions	Fatal adverse drug reactions per million prescriptions
Dothiepin	50.0	<1
Amitriptyline	46.5	<1
Trazodone	13.6	not known
Mianserin	5.6	2–3
Nomifensin	2.5	7

(From Pinder[5]).

From Table 1 it seems clear that we place depressed patients at substantially greater risk by prescribing amitriptyline or dothiepin than by prescribing trazodone, mianserin, or even nomifensin, if this were still available.

Cost of treatment

While there are insignificant differences between antidepressants in terms of their clinical efficacy, there are major differences in monetary cost. If we take 150 mg as an average 'treatment dose' of amitriptyline and compare it with similar 'treatment doses' of newer antidepressants we find the following. For lofepramine, 210 mg is approximately seven times more expensive, 300 mg of trazodone is approximately 10 times more expensive and 200 mg of fluvoxamine is approximately 16 times more expensive (hospital pharmacy pricing). Thus, the newer drugs are considerably more expensive than the older ones.

Given the current political climate in the UK, and particularly following the publication of government plans for reform of the NHS,[20] doctors are likely to have to take even greater account of the cost of their treatments. As illustrated above, there are considerable differences in cost between the conventional tricyclic antidepressants and the second generation compounds. However, if we place undue emphasis on cost rather than on toxicity, then we shall undoubtedly contribute to significant numbers of deaths which probably could otherwise be avoided.[21] As a profession, doctors are not good at predicting which patients will attempt suicide[22] and it is therefore illogical to attempt to differentiate between our patients in terms of suicide potential when it comes to choosing antidepressants.

Conclusion

We would suggest that, particularly in general practice, prescription of antidepressants should be limited to the use of second generation agents such as trazodone, mianserin and lofepramine. Preliminary data suggests that fluvoxamine may be prescribed with equal confidence.[23] The selection of these antidepressants would permit matching of drugs to individual patients with regard to symptom profile. Lofepramine is particularly well tolerated by the elderly[24] whereas mianserin should probably be avoided since the great majority of serious blood dyscrasias have occurred in patients over the age of 65 years.[25] Trazodone and mianserin, which are both sedating, would be suitable for patients in whom anxiety and sleep disturbance were major features. Fluvoxamine and fluoxetine, as specific serotonin reuptake inhibitors, would be available for depressive disorders where obsessional symptoms predominate.[26] For illnesses refractory to this group of antidepressants, phenelzine, lithium and clomipramine should be considered but these should probably only be prescribed and treatment supervised, by psychiatrists. With the exception of these latter drugs, each of these antidepressants are safe in overdose, relatively free from cardiotoxic effects, free from marked anticholinergic activity and are efficacious in treating depression. They should be replacing tricyclic antidepressants as the first line of treatment in depression, especially in the primary care setting.

References

1. Montgomery SA. Chemotherapy of affective disorders: future prospects. *International Medicine* 1986; (suppl 11): 30-32.
2. Blackwell B. Adverse effect of antidepressant drugs. Part 1. *Drugs* 1981; **21:** 201-219.
3. Coccaro E, Siever L. Second generation antidepressants: a comparative review. *J Clin Pharmacol* 1985; **25:** 241-260.
4. Schmidt LG, Grohmann R, Muller-Oerlinghausen B, *et al.* Adverse drug reactions to first and second generation antidepressants: a critical evaluation of drug surveillance data. *Br J Psychiatry* 1986; **148:** 38-43.
5. Pinder RM. The benefits and risks of antidepressant drugs. *Human Psychopharmacology* 1988; **3:** 73-86.
6. Burrows GD, Norman TR, Dennerstein L, Davies BM. Antidepressant therapy: benefits and risks in perspective. *Acta Psychiatr Scand* 1985; **72** (suppl 320): 43-47.
7. CSM update. Adverse reaction to antidepressants. *Br Med J* 1985; **291:** 1638.
8. Ancill RJ. Mianserin and blood dyscrasias. *Br J Psychiatry* 1987; **150:** 569-570.
9. Clink HM. Mianserin and blood dyscrasias. *Br J Clin Pharmacol* 1983; **15** (suppl 2): 291-93.
10. Johnson, DAW. Non-compliance with antidepressant therapy — an underestimated problem. *International Medicine* 1986; (suppl 11): 14-17.
11. Lader M. Fluoxetine efficacy versus comparative drugs: an overview. *Br J Psychiatry* 1988; **153** (suppl 3): 51-58.
12. Kennedy P, Kreitman N. An epidemiological survey of parasuicide (attempted suicide) in general practice. *Br J Psychiatry* 1973; **123:** 23-24.
13. Hawton K, Blackstock E. General practice aspects of self poisoning and self injury. *Psychol Med* 1976; **6:** 571-575.

14. Office of Health Economics. *Studies of current health problems. No. 69: suicide and deliberate self harm.* London: OHE, 1981.
15. Forster DP, Frost CEB. Medicinal self poisoning and prescription frequency. *Acta Psychiatr Scand* 1985; **71:** 567-574.
16. Brewer C, Farmer R. Self poisoning in 1984: a prediction that didn't come true. *Br Med J* 1985; **290:** 391.
17. Platt S, Hawton K, Kreitman N, *et al.* Recent clinical and epidemiological trends in parasuicide in Edinburgh and Oxford: a tale of two cities. *Psychol Med* 1988; **18:** 405-418.
18. Skegg K, Skegg DCG, Richards SM. Incidence in self poisoning patients prescribed psychotropic drugs. *Br Med J* 1983; **286:** 841-843.
19. Cassidy SL, Henry JA. Fatal toxicity of antidepressant drugs in overdose. *Br Med J* 1987; **295:** 1021-1024.
20. Secretaries of State for Health, Wales, Northern Ireland and Scotland. *Working for patients (Cm 555).* London: HMSO, 1989.
21. Matthews K, Eagles JM. Toxicity of antidepressants. *Br J Psychiatry* 1989; **155:** 420.
22. Barraclough B, Bunch J, Nelson B, Sainsbury P. A hundred cases of suicide: clinical aspects. *Br J Psychiatry* 1974; **125:** 355-373.
23. Banerjee AK. Toxicity of antidepressants. *Br J Psychiatry* 1989; **155:** 267-268.
24. Dorman T. The management of depression, and the use of lofepramine in the elderly. *Br J Clin Pract* 1988; **42:** 459-464.
25. Inman W. Blood disorders and suicide in patients taking mianserin or amitriptyline. *Lancet* 1988; **2:** 90-92.
26. Goodman WK, Price LH, Rasmussen SA, *et al.* Efficacy of fluvoxamine in obsessive-compulsive disorder: a double blind comparison with placebo. *Arch Gen Psychiatry* 1989; **46:** 36-44.

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