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Annotation

The Safety of Antidepressants

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"It would be a good thing if there were a special remedy for each individual kind of insanity." Paracelsus, 1497–1541 (Sigerist, 1941)

It is no exaggeration to say that, in the 30 years since antidepressants were introduced, they have revolutionised the management of depression, thus fulfilling, at least for depressive illness, Paracelsus' prophetic wish. We now have a group of drugs which can induce remission in a disease which is disabling and not infrequently fatal. Despite intensive research, however, our understanding of the mechanism of action of these drugs is still largely hypothetical. Even our methods of evaluation are sufficient only to enable one to decide whether an antidepressant drug is effective or ineffective; there is no experimental method which can rank them in an overall order of potency, and perhaps this should not be the aim, since there must be subgroups of depressed patients who will respond differently to any one agent.

Some would argue that refractory patients need more appropriate doses or combinations of agents (Bridges, 1983; Paykel & Hale, 1986). In most cases, our understanding of the 'right' dose of drug, and how to tailor it to the individual patient, is elementary and empirical; this applies both to achieving therapeutic effectiveness and to avoiding unwanted effects. The decision about which drug to prescribe also appears to be subjective and arbitrary (Armstrong & Andrews, 1986). Although many doctors have a strong preference for some of the older tricyclic agents, a review of the literature shows that these are not clearly better than newer drugs (Chouirard, 1985; Young *et al*, 1987).

Because of this difficulty in distinguishing between drugs in terms of benefit, increasing attention has been paid in recent years to their risks, in order to put the overall usefulness of each drug into sharper perspective. As each new drug is developed, expectations of its effectiveness are accompanied by the anticipation of its toxicity, at first in animal models and later in man. It is relatively simple to decide when a drug is very toxic, but to establish its safety beyond reasonable doubt is more difficult and controversial. This applies both to safety in therapeutic use and to toxicity in overdose.

There is little problem in determining the percentage of patients who suffer from the different side-effects, but there are many difficulties in ascertaining the rare adverse reactions and their prevalence in the population, even after a drug has been on the market for several years – a large cohort of patients needs to be treated before an appreciable number of rare adverse reactions occur. This is illustrated in Table 1.

Table 1
Numbers of patients who would need to be treated with a drug for a defined number of cases of a given adverse reaction to occur with 95% probability (assuming no background incidence of the reaction)

Expected incidence of adverse reaction	Required number of adverse reactions			
	1	2	3	10
1 in 100	300	475	630	1 570
1 in 1000	3 000	4 750	6 300	15 700
1 in 10 000	30 000	47 500	63 000	157 000

After Lewis (1983).

With each suspected adverse reaction come the consecutive problems of recognising, reporting and recording, of establishing a causal link with the drug in question, and finally of deciding what should be done. Once an association is confirmed, the options are: to withdraw the drug; to issue a note recommending caution in prescribing (especially if a high-risk group, such as the elderly, can be identified); or to continue to collect reports on the drug in the absence of decisive data.

Careful monitoring resulted in the withdrawal of zimeldine in 1983 and nomifensine in 1986 owing to unusual and unacceptable side-effects. In 1990 L-tryptophan was withdrawn because of a number of reports of an eosinophilia–myalgia syndrome. It transpired that all implicated supplies came from one manufacturer, suggesting that a contaminant was to blame; this was confirmed when analysis of the drug taken by the affected patients showed an extra chromatographic peak (Belongia *et al*, 1990), and the offending substance has now been identified (Sakimoto, 1990). It should now be only a matter of time before the manufacturing process is corrected and L-tryptophan is reintroduced.

However, a number of recent examples may serve to illustrate some of the shortcomings of the process of gathering and interpreting data about uncommon adverse effects. Post-marketing surveillance of mianserin failed to demonstrate any cases of

agranulocytosis (Inman, 1988), yet Coulter & Edwards (1990), from New Zealand, cited an incidence of agranulocytosis with mianserin of 1 in 1354–1743 treated patients. Both reports met with criticism (Bateman *et al*, 1988; Farmer, 1990; Girard, 1990). The real risk of life-threatening agranulocytosis with mianserin must be very low, but it remains undetermined.

An early indication of drug-associated fatalities can cause great concern, and when the Committee on Safety of Medicines (CSM) mentioned that deaths had occurred in patients who had been prescribed fluvoxamine, the media coverage was such that the Committee had to issue a press release to clarify that no causal relationship had been established (*British Medical Journal*, 1988; Department of Health and Social Security, 1988). Continued monitoring has not revealed any particular toxicological problems, and the CSM subsequently removed the special reporting requirement indicated by the 'black triangle' from fluvoxamine in October 1990.

Higher reported rates of spontaneous adverse reaction are common with new drugs, and this source of bias can lead to undue anxiety about a drug's safety (Sachs & Bortnichak, 1986). Reports of raised levels of liver enzymes with lofepramine led to a CSM warning in 1988 (Committee on Safety of Medicines, 1988). However, it is apparent that liver enzyme levels may rise after giving any tricyclic antidepressant, and the CSM in May 1990 removed the 'black triangle' from lofepramine, indicating that the Committee no longer wished to be advised of minor adverse effects with this drug.

Teicher *et al* (1990) from the Johns Hopkins Hospital suggesting that six instances of suicidal ideation were caused by fluoxetine, calculated that it might be expected to occur in 3.5% of patients given the drug. This led to widespread media coverage in the US, which spilled over into a Channel 4 television programme in the UK, dubbed "trial by anecdote" by a well known medical journalist (O'Donnell, 1991). While some further anecdotal cases have been cited (Dasgupta, 1990; Hoover, 1990), a number of correspondents expressed their doubts about these findings (Miller, 1990; Berkley, 1990; Tollefson, 1990), and there seems to be little indication that this adverse effect occurs with any greater frequency with fluoxetine than with other antidepressants (Muijen *et al*, 1988; Beasley *et al*, 1991).

Each of these examples illustrates the difficulty in establishing the existence and the incidence of unusual or infrequent but potentially serious adverse effects. Researchers have to use the best methods available. The authorities have a delicate problem in deciding when to raise a warning, and the media have a serious responsibility to present problems concerning drug risks in such a way as to minimise anguish in patients taking the drug and – equally important – to avoid precipitating litigation and even withdrawal of a drug without sufficient foundation.

When we consider safety of antidepressants in overdose, the first objective is to view the problem in perspective. It is generally agreed that the lifetime risk of suicide in patients with depression is about 15%, but only 5% of those who commit suicide – that is, approximately 1% of all depressed patients – do so with drugs they have been prescribed for their depression. However, this is the extraordinary irony of antidepressant therapy. Many antidepressants, particularly the tricyclic drugs, are highly toxic in overdose. In many cases, a single prescription of an antidepressant drug is sufficient to cause death if taken in overdose. Often the patient puts the drugs on one side, only to take an overdose later on impulse. Although only a small proportion of suicides in depressed patients are a result of antidepressant overdose, these have attracted considerable attention because they can be measured and are to some extent preventable. However, there is no way of estimating how many of those patients would merely use another means to end their lives if a suicide attempt with a relatively non-toxic drug were to fail.

How can the relative toxicities of the different drugs when taken in overdose be estimated? It has long been clear that the early tricyclic antidepressants had considerable morbidity and mortality in overdose; it is now known that this is due to their cardiotoxicity (Pentel & Benowitz, 1986). A report by Frejaville *et al* (1966) gave a 20% mortality for patients presenting to hospital, but a collation of more recent reports gives a hospital mortality of 2.6% (Callaham & Kassel, 1985). This may be partly a result of improved management of tricyclic antidepressant poisoning, but it may also represent the wider use and greater availability of these drugs, with a higher proportion of suicidal gestures with token amounts.

However, hospital cases alone are not sufficient to give an accurate idea of the toxicity of a drug. About three-quarters of suicides by antidepressant overdose occur outside hospital (Crome & Newman, 1979; Callaham & Kassel, 1985), so that overall figures for fatalities rather than hospital admissions must be taken into account. National mortality data can be a useful indicator of toxicity, but must be compared with some measure of the availability of the drug in the community, such as prescription data. In this way, a comparative table of the fatal toxicity of the various antidepressants can be produced

(Cassidy & Henry, 1987), which shows that a figure of around 50 deaths per million prescriptions can be attributed to some of the older tricyclic agents, while many other drugs appear much less toxic. However, it may take several years to amass sufficient cases for the statistical significance to become apparent. The data produced also have to be viewed with caution because there are several sources of error. Despite this, they are a useful indication of differences in potential toxicities and are of value in the risk–benefit assessment of a drug. This aspect of drug toxicity was highlighted by a challenge in 1989 of the CSM's interpretation of the Medicines Act 1968. The ruling from the High Court, upheld by the Court of Appeal in 1990, was that safety in overdose may be taken into account when considering a drug's therapeutic safety.

Despite the recent interest in toxicity, it is apparent that there is a need to establish the relative benefits of the different drugs. It is also clear that we are still at the beginning of our attempts to characterise depressive illness into biochemical subgroups, and that response to different types of drugs cannot be predicted. While considerable progress has been made, further advances are still needed. The safety of antidepressants has rightly become a matter of concern, and here also we need better methods of identifying and quantifying their toxicity.

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