EDITORIAL

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Litigation and the toxicity of psychotropic drugs

Brian E Leonard, PhD, DSc, MRIA, Professor of Pharmacology, Pharmacology Department, University College Galway, Galway, Ireland.

All drugs have side effects and given the increase in litigation for medical negligence that has occurred in Ireland in recent years, it would not be surprising to find that clinicians prescribing psychotropic drugs would also become the target for legal procedures if they fail to warn the patient about the possible side effects and toxicity of the drugs they are prescribing. The two extremes of the problem may be illustrated by the litigation carried out against some pharmaceutical firms and prescribers of benzodiazepines and the lack of such proceedings resulting from deaths of depressed patients who take an overdose of a prescribed antidepressant.

Benzodiazepines have been widely used for nearly 30 years, largely because of their presumed lack of toxicity as well as their efficacy in treating anxiety disorders and insomnia. By the early 1980s, there was clear evidence that dependence could occur at therapeutic doses. Lader identified a withdrawal syndrome amongst long term users of anxiolytic benzodiazepines and as over one million patients were taking benzodiazepines continuously for over one year, Lader claimed that benzodiazepine dependence represented an epidemic of alarming proportions.[1] There is ample evidence to show that many patients who become dependent on the benzodiazepines are 'dependent' personalities who are also likely to abuse alcohol and other drugs.[2] The situation becomes more complicated with the involvement of various consumer organisations and the media (particularly television). As an example of the exaggeration of the problem, the popular BBC television programme *That's Life*, claimed that 10 million patients were taking minor tranquillisers in the UK, of whom 50% were considered to be dependent on them.

Given the success of the plaintiffs in the thalidomide trial in the 1960s, it is perhaps not surprising that the legal profession could see benefits in taking up cases against the prescribers and manufacturers of the benzodiazepines. A Benzodiazepine Solicitors Group, comprising 320 law firms in these islands, was established to pressurise the manufacturers of anxiolytic benzodiazepine to establish a compensation scheme for those claiming benzodiazepine dependence. Not only did the expected number of benzodiazepine dependent patients fail to materialise but the litigation against two of the manufacturers of anxiolytic benzodiazepines (Wyeth, Roche) has been dropped largely on grounds of insufficient evidence to show that those patients claiming to be dependent were *de facto* clinically dependent.

It has been estimated that the risk of becoming dependent on a benzodiazepine is one per five million months of patient use.[3] Increasing awareness by clinicians of the problems that may arise with the benzodiazepine has led to a nearly 50% reduction in the prescription of the anxiolytic benzodiazepines in less than five years.[4] It is, however, interesting to note that the prescription of sedative-hypnotic benzodiazepines has increased by 5% over the same period. This situation raises a number of questions. Firstly, there is no significant pharmacological difference between the sedative-hypnotic and the anxiolytic benzodiazepines, yet only the latter have been perceived as causing major dependence problems. Secondly, it has been shown that unlike those dependent on opiates or alcohol, patients taking benzodiazepines seldom escalate the dose, but tend to reduce the dose taken.[5]

Thus the controversy over benzodiazepine dependence may be seen as an overreaction by some consumer and media groups, aided and abetted by part of the legal profession, that has caused an unfortunate reluctance in clinicians to appropriately prescribe these drugs. As a consequence of the fear of litigation, clinicians have been increasingly prescribing sedative tricyclic antidepressants (eg. amitriptyline) or neuroleptics (eg. chlorpromazine). Not only is there no convincing scientific evidence to show that these drugs alleviate anxiety, there is also ample evidence to show that these classes of drugs have a potential to cause more serious side effects even at therapeutic doses, particular in elderly patients who are the main recipients of the benzodiazepines. What sort of defence would a clinician have if he or she was sued for prescribing sedative tricyclic antidepressants or neuroleptics instead of the safer and therapeutically effective benzodiazepines? When balancing the risk of dependence on a benzodiazepine against the side effects of the tricyclic antidepressants or phenothiazines, the pendulum is weighted significantly in the direction of the former.

The attitude of the media and the regulatory authorities regarding the benzodiazepines is in marked contrast to their relative indifference to the toxicity of the older antidepressants. There is evidence that suicide rates, particularly of the 25-34 year old group, are increasing in most countries. While the methods used to commit suicide vary from country to country, physical methods (shooting, stabbing, etc.) are increasingly being replaced by the use of poisons with or without alcohol. In the UK and many European countries, overdose of an antidepressant prescribed to prevent depression is now one of the main causes of death caused by chemicals.[6,7]

There is evidence to show that the toxicity in overdose of commonly prescribed antidepressants differs considerably. For example, figures for England and Wales show that the fatal toxicity index (number of deaths per one million prescriptions of the antidepressant) varies between approxi-

mately 50 for dothiepin and amitriptyline, to less than five for mianserin, and virtually nil for the selective serotonin reuptake inhibitors (SSRIs) and modified tricyclic antidepressants like lofepramine.[7] These figures relate to deaths by suicide and do not account for increased accidents due to cognitive impairment and sedation caused by the tricyclic antidepressants or to the effects of such drugs on cardiac function, which may occur after therapeutic doses.[8] Surely with the widespread use of the tricyclic antidepressants by both general practitioners and psychiatrists there should be more concern regarding the use of such drugs particularly now that equally effective and much safer second generation antidepressants such as the SSRIs are widely available. Does this mean that the medical profession only reacts to the threat of litigation in changing its prescribing habits rather than acting proactively to ensure that the efficacy of antidepressant treatment is combined with a better quality of life for the patient due to improved compliance and reduced drug side effects?

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COMMENTARY

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Patricia Casey, MD, FRCP(I), FRCPsych, Deptartment of Psychiatry, Mater Hospital, 62 Eccles St, Dublin 7, Ireland.

What is striking about Leonard's[6] clarion call to the litigants and the legal profession is that he made similar calls over the last number of years,[4,5] issuing dire predictions of the poor defence a hapless psychiatrist would have in the wake of a completed suicide as a result of an antidepressant overdose, when safer drugs were available. Such a spate of litigation has not followed nor, have the regulatory authorities expressed an interest in the matter. This is simply because a case against a doctor is unlikely to be successful when he or she is acting in accordance with a recognised body of practice within that profession, even though others hold the opposite view, provided of course there is no evidence of overt negligence such as failing to assess current suicidal ideation. Indeed in circumstances where active suicide ideation is present, to only prescribe an antidepressant, even if it were an SSRI, could be deemed negligent if suicide follows since such a patient should be hospitalised.

The comparison between the potential for litigation with fatal overdose of tricyclic antidepressants and benzodiazepines dependence is flawed since the source of the problems with benzodiazepines was their potential to cause dependence even with therapeutic doses. By contrast the problem with tricyclic antidepressants arises when they are taken in excess of the therapeutic dose. Notwithstanding the recognised and much publicised risks with benzodiazepines, the civil suits brought against the manufacturers have, to date, been unsuccessful. Moreover benzodiazepines can themselves be fatal in overdose but litigation for this has never arisen. If, as is claimed, older antidepressants are so dangerous and so toxic, is it not surprising that their prescription has not plummeted in a similar manner to that observed with benzodiazepines?

Whilst Leonard correctly states that the suicide rate among males in the 25-34 year old age group is increasing, it is inaccurate to attribute this increase to antidepressant overdose. For example, in 1992, of the 657 male suicides among the 25-34 age group, 22 (3.3%) died by antidepressant overdose alone.[7] A further inaccuracy is found in his claim that physical methods of suicide are being replaced by the use of poisons. In England and Wales poisoning accounted for 33% of suicides whilst this fell to 22% between 1990 and 1993. Moreover his perspective on the role of antidepressants in suicide is distorted since antidepressant overdose alone accounted for 18% of suicides by poisoning but for only 4% of suicides by any method.[8]

The fatal toxicity index of antidepressants is much cited as evidence for the danger of at least some of the older antidepressants. However, Leonard has failed to point out that a recent study by Jick *et al*[3] has demonstrated that the relative risk of suicide (suicide index) by any method is greater for at least one SSRI than for the tricyclic antidepressants. As this information is in the public domain, is a doctor who prescribed an SSRI for a patient who then dies by, say, hanging, potentially open to litigation also? It is likely that overdose toxicity is not the only link between antidepressants and suicide and undue focus on the overdose potential may detract from full and thorough assessment of suicide risk, irrespective of method.

The cognitive effects of psychotropic drugs and their potential to cause road traffic accidents is recognised. However, the direction of causality has never been established since patients with depressive illness are cognitively