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DRUG-INDUCED INJURY

Liability for drug-induced injuries did not become an issue of general concern until quite recently. However, a number of drug-induced problems, from thalidomide in the 1960s to antipsychotics and tardive dyskinesia in the 1970s and Oprelvekin in the 1980s, have caused widespread public disquiet and led to increasing awareness of issues to do with liability.²⁹ In psychiatry, the first big concern in the UK focused on the question of benzodiazepine prescribing, while in the USA the paramount issue was tardive dyskinesia in individuals taking antipsychotics. In both cases the arguments became highly emotive, with some commentators referring to the appalling frequency of drug-induced injury, while others comment on its astonishing rarity.

Drug-induced problems may stem from the toxic effects of a drug, from toxic effects caused by an impure additive, or from allergic reactions to the drug or its additives. Problems may also stem from overprescribing. For instance, in the case of someone who dies from a resistant bacterial infection, a relative could claim that the subject's death arose in part from the excessive prescription of antibiotics that contributes to the production of resistant infections. In

the case of the antipsychotics, problems may be brought about by the overuse of these drugs, promoted by drug companies on the one hand, but also stemming in part from the current politics of mental health, which can lead to deaths from rapid tranquillisation delivered by harassed staff in undermanned psychiatric units.

The question of liability is something of a rolling log on which companies, prescribers and drug takers try to maintain a footing. In addition to attempting to produce increasingly safe compounds, companies try to restrict liability by hedging their data sheets with warnings and lists of side effects, so that if something goes wrong either the prescriber or the consumer will be to blame, on the basis that they were warned beforehand if they chose to notice. The other side of this coin is that in the pursuit of markets, rather than make novel compounds, drug companies often manufacture drugs that are closely related to other compounds on the market in an attempt to gain a share of what is obviously selling well. This minor manipulation of a molecule may confer no additional therapeutic benefit, but may produce unsuspected side effects.

When it comes to determining whether a particular drug has been responsible for a particular injury, it can be extremely difficult to decide with confidence what has actually happened. Questions that arise are, for example, whether it is known that the individual actually did take the drug that supposedly caused the problem? Did they take anything else? Did the individual have any pre-existing disorder that made an unfortunate reaction to a compound more likely? The problems have been made worse in recent years because of company efforts to deny problems which have led to terming suicidal acts as emotional lability and withdrawal syndromes as symptoms on stopping.

The majority of drug-induced disorders resemble disorders that happen naturally anyway. For example, benzodiazepine withdrawal produces anxiety. Anxiety is common. One can

question whether all that is happening in the case of withdrawal is a re-emergence of the anxiety that led to the individual being put on treatment in the first instance. In the case of tardive dyskinesia, dyskinesias that are indistinguishable from those caused by the drugs occur in individuals who have never had antipsychotics. Even the limb deformities produced by thalidomide occur naturally. Drug-induced injury often involves a change in the frequency of something rather than an entirely novel development. For reasons such as these, some prescribers can have reasonable grounds to resist a linkage between treatment and an adverse event.

Even if it is agreed that the drug has caused the problem, questions arise as to whether the prescriber should have prescribed for the problem in the first instance. If not, then they share a part of the blame. Did the taker implicitly or explicitly agree to run the risk that is involved in all drug taking? Did they contribute to their own injury in any way – by altering the amount of salt in their diet, perhaps, while taking lithium?

In the case of a possible suicide consequent on antidepressant or antipsychotic-induced akathisia, for example, it is not clear exactly where blame might lie in individual cases. It may not be possible, given our current state of knowledge, to produce antidepressants or antipsychotics that will never produce akathisia or dysphoria, and hence the drug induction of suicidal behaviour is at present an inherent risk of drug taking. This puts an onus on prescribers to warn patients of this possible side effect and what to do should it develop. The particular interest in the cases of selective serotonin reuptake inhibitor (SSRI)-induced akathisia is explicit company denials that their drug could lead to akathisia or suicide. What do these company denials do to liability?

There are three principles that can be applied to all drug taking, as outlined in Box 25.1.^{30,31}

RISKS AND BENEFITS

The idea that one of the cardinal principles of medical practice is that a healer should ‘first of all do no harm’ is appealing, but it is a very poor description of medical practice. In the case of drug treatment, no treatment is possible unless risks are taken. No drug is safe. Treatment is a matter of weighing risks and benefits. The discovery of anaesthesia crystallised this dilemma. When first introduced, it was known that some people would die from the anaesthetic. Many had problems with the idea that some lives would intentionally be put at risk to benefit others, but this in fact is the situation with practically all treatments today. There is therefore a need to ensure that the person being treated is going to derive a clear benefit from treatment such that it is justifiable to take certain risks. For example, in the case of someone with cancer, it may be justifiable to take the very considerable risks associated with chemotherapy, but it would not be reasonable to give chemotherapeutic agents to someone with a cold or depression.

The antihypertensives provide a good case. There are very few people who absolutely need antihypertensives to lower malignant increases in blood pressure caused by hypertensive disease. However, there are legions of people who have some increase in blood pressure, and increased blood pressure is associated with an increased risk of heart attacks or strokes as a consequence. Some individuals may have raised blood pressure only as a result of the anxiety of attending their doctor. Increases in blood pressure are, furthermore, only an indication that a disease process may be operative. One option in such cases is repeated monitoring with a recourse to treatment only if the situation worsens. For those with minimal increases in blood pressure, the risk of likely problems is so small that one can legitimately ask whether the cost in side effects (impaired sexual functioning for instance and the hypochondriasis that goes with being on treatment) is worth it.

Until 1960 many calculations of risk and benefit were made primarily by the consumer. Since all drugs have been made available on prescription only, in the case of the antihypertensives for instance, these calculations have typically been made for patients by clinicians – who are often on automatic pilot. It is difficult for prescribing not to be almost automatic, when, for instance, the latest research indicates that hypertension is a risk factor for heart disease and there happens to be available a means of mitigating the risk. It takes considerable discrimination to appreciate that the risk may be quite minimal, and indeed less than the risks posed by the drug. An even greater skill is needed to impart this state of affairs to the patient. In such circumstances it behoves all the members of a health team (and not just doctors) to have a good grasp of what drugs can and cannot do, as some may be better able to influence particular patients than others.

The issues have become particularly salient in the treatment of the elderly where in order to meet targets physicians put many patients on statins with no evidence that they are likely to benefit and a good deal of evidence that they may be worse off. There is no discussion about what the patient might prefer to die from – a heart attack or a cancer or other problem. Patients are not informed and their consent is not sought. This is happening increasingly across medicine – and it is hard to know when or where the chickens will come home to roost³².

CLINICAL TRIALS AND LEGAL JEOPARDY

The Prozac story

In clinical studies before its launch in 1988, Prozac was associated with akathisia and agitation, occurring with sufficient frequency and intensity to lead to recommendations that benzodiazepines be co-prescribed with it in clinical trials.³³ Leading textbooks on the clinical profile of psychotropic agents mention Prozac's well-known propensity to cause akathisia.

Akathisia has been implicated as a mechanism whereby Prozac may, in certain circumstances, lead to violence and suicide (see Ch. 4). The physiological mechanisms by which this happens are relatively well understood, yet Lilly's presentation of the side effects of Prozac from their clinical trials database contains no mention of akathisia.

Emotional flatness or blunting is a not infrequent side effect of treatment reported by patients on Prozac. Arguably, this effect is all but intrinsic to the mode of action of the drug, which generally reduces emotional reactivity. It has been reported in observational studies, where it has been linked to other potentially harmful behaviours, yet nothing resembling emotional blunting appears in the clinical trials side-effect database for Prozac.

There is a good deal of published and unpublished evidence that SSRI use is associated with a higher rate of suicidal ideation early in the course of treatment than other antidepressants, strongly suggesting that treatment may induce suicidality in some. Whether or not the reader believes that an antidepressant could induce suicidal ideation, it is a fact that treatment-emergent suicidal ideation is not recognised by any code in current clinical trial systems. It is not recorded as a side effect of Prozac in Lilly's database.

These examples point to a number of problems with the side-effect data from clinical trials. One is the failure of systems to cope with 'new' problems. Another is the current dependence on self-reporting methods for the collection of data on side effects. In the case of the SSRIs it would seem that these methods detect only one in six of the side effects detected by systematic checklist methods.³³

If the side-effect profile of a drug drawn from clinical trials were used just for marketing purposes, there might be little problem with this state of affairs. We could all take them with a grain of salt. After all, although clinical trials indicated that sexual dysfunction on SSRIs

occurred at a 5% rate no one believed this and in fact the true rate is probably closer to 50%. These side-effect profiles have, however, also been used in academic debate and for legal purposes to deny that claimed adverse effects are happening.

Against this background, it would seem that any patients entering into any clinical trials of any kind of medication where side-effect data are collected by spontaneous reporting methods are putting individuals who may subsequently suffer a drug-induced adverse event into a state of potential legal jeopardy. The consequences for prescriber liability are also uncertain.

Health-service professionals have been in the business of encouraging patients to participate in clinical trials, arguing that it is almost a civic duty to do so – although they are much less likely to participate themselves in trials or to encourage their own family members to do so. But, in fact, participation of any of their patients at present is probably doing everyone an injury given that pharmaceutical companies are prepared to argue that, because data on a particular side effect were not collected in their clinical trials, this proves the side effect does not happen. It may be time to stop participating in these trials that often yield thousands of pounds per patient for the clinician running the study, but only increased legal jeopardy for the rest of us.

A refusal to participate might have many positive benefits. At present companies are reluctant not to have a European arm to their studies. If it becomes difficult to perform trials in Europe, the companies are likely to amend their consent forms to include a statement that side effects collected by current methods could be used for marketing, but for no other purposes. Alternatively they could introduce better side-effect collection methods, which would both enhance the scientific information provided by clinical trials and minimise the risks of jeopardy.

Another way forward might be for ethics committees and patient advocacy groups or others to transform the informed consent form into a contract between patients and investigators

and companies giving rights of access to the raw data. This is not an issue just to leave to patient groups within mental health. It applies across medicine and applies as much to those who are not at present patients as it does to those at present in treatment. This is a matter for lawyers and politicians to consider closely as it is their friends and families who are being put in a state of legal jeopardy should treatment lead to drug-induced injury.

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Box 25.1 Principles of drug taking

First Principle

<p>No drug or drug treatment can be guaranteed in advance to be entirely safe. Risks are inevitable and justifiable provided they are not disproportionate to the purpose that the treatment is supposed to serve.</p>
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<p>At present, society as a whole deems that risks such as tardive dyskinesia may be justifiable against the backdrop of an otherwise irremediable illness such as schizophrenia. But what of</p>

tardive dyskinesia consequent on the prescription of an antipsychotic for anxiety or a sedative antipsychotic as a hypnotic, or given to a child for a vague behaviour problem?

Second Principle

No party can reasonably be blamed for doing their best, even if injury is one of the consequences.

The issue here, of course, may depend on being able to show that one has done one's best; herein lies the importance of documenting advice given.

Third Principle

Responsibility is carried by anyone on whom one is entitled to rely.

This includes the nurses who hand out medication who have a responsibility to get the drug and dose right, the pharmacist to dispense the right medication, and potentially anyone who acts as an authoritative source of advice regarding the benefits or hazards of medication, including mothers, and these days anyone who accesses the Internet and the pharmaceutical companies who engineer what appears on the Net.