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Case histories as evidence

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Abstract. In courts case histories play a central part when a crime may have resulted from an effect of a prescribed drug; in civil cases where a person may have suffered damage from a drug; and in coroners' enquiries into the cause of unexplained deaths. The court must decide two important questions:

1. Can the suspected medication(s) cause this kind of effect?
2. Did it (or they) do so in this particular case?

Many judges and coroners have not addressed these questions clearly and have not used expert witnesses consistently, on occasion disregarding scientific evidence. Courts need to appoint experts to explain and interpret the scientific evidence. Few judges are equipped to resolve contradictions between different experts. Brief accounts of five cases from four countries illustrate these points. The reluctance of legal processes to implicate drugs as a possible cause of violent behaviour leads to injustice. Courts must be required to obtain appropriate expert evidence, and be given independent data on which drugs can cause such behaviour.

Keywords: Case history, expert witnesses, criminal court, civil court, coroner's court, medication-induced violence, homicide, suicide

1. Introduction

The case history is central in three quite different types of case:

a) Criminal cases, where a defendant's drug treatment may have caused or contributed to criminal behaviour that would otherwise not have occurred. Here the question is to what extent the defendant was responsible for the behaviour.
b) Civil liability cases, where a defendant is a person, usually a health professional, or an organisation, such as a hospital or a pharmaceutical company, for harm resulting from a drug. The question is whether the treatment caused the harm, and if it did, what compensation is just.
c) Coroners' inquests held to determine the cause of death, which often turns out to be impossible, so that the verdict must convey and explain the uncertainty. The process and the verdict is intended to assure the family and the community that the death has been thoroughly investigated so that lessons can be learnt from it.

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2. Criminal cases

A person who has unintentionally and involuntarily committed a crime under the influence of a treatment, usually a drug, is not a criminal and needs treatment, not punishment. The facts of the crime are not the primary issue, and are usually undisputed. The key question is whether the defendant used the drug responsibly or not. If the drug had been medically prescribed and used in accordance with the prescriber's directions, and the defendant was unaware of its possible effects on behaviour, then that can be a valid defence. The defence, the prosecution and the court have to rely on evidence from expert witnesses.

The court has to weigh the evidence on the effects of the drug against the evidence that other factors caused the crime. Unfortunately the basic legal principle that a defendant is innocent until proved guilty is liable to be misapplied to the drug: often the drug is considered innocent if not proved guilty. This happens because the courts and scientists understand and use the concept of likelihood quite differently. In court the phrase "more likely than not" describes a likelihood greater than 50%, which commonly means that the defendant is guilty. If the likelihood is below 50%, guilt is not proved - the defendant gets the benefit of the doubt. Lawyers tend to apply the same argument to the causation of criminal behaviour by drugs, demanding evidence that the drug was more likely than not to have caused the act. This is wrong: the relevant question is "Could the drug, in **this** person on **this** occasion have caused the behaviour?" If the answer is yes, then the doubt should benefit the defendant.

2.1. Case 1: Homicide by a depressed schoolboy – UK

A case in which AH was an expert witness for the defence illustrates the problem. Dr. Sameer Sarkar, a consultant in adolescent forensic psychiatry, was also called by the defence, which was led by Edward Rees QC. EB, a 16-year old schoolboy, killed his father in Dec 2007. In 2006 his GP had diagnosed 'endogenous depression' and in August 2007 prescribed citalopram. EB; felt it made him "remote from people, dreamlike", and wanted to stop it. Fluoxetine 20 mg/day was substituted; he found it "not really different". He sometimes forgot to take the fluoxetine, for up to 3 days in a row, and would then take the missed tablets in one go. Taking 3 made movements and actions exaggerated. He "felt funny" on the drug, "disconnected from everything", "nothing would affect me", didn't feel real, felt he could do whatever he wanted. Felt he was losing control, was waiting for someone to point it out and say 'stop'. "I haven't felt like me" any more; he can't put it into words. On 17 December "a sudden thing came up in my head and I had to do it" (kill father).

AH's report described reported effects of the drug on mood and behaviour, including violence, and noted their time course and possible mechanisms. During the 4½ weeks he had been taking it the concentration in his brain would have been near its peak. This could account for how he felt and for his evidently uncontrollable compulsive aggression. EB had earlier noted apparently inexplicable and disturbing feelings with citalopram, and the previous year with isotretinoin (prescribed for acne), on which he had auditory hallucinations. AH concluded that fluoxetine was on the balance of probabilities the main factor leading to his otherwise inexplicable act. Dr. Sarkar's very thorough assessment found that EB was mentally ill on the day of the tragedy.

The main experts for the prosecution were two psychiatrists and a clinical pharmacologist with special expertise in conducting clinical trials for pharmaceutical companies. They attributed EB's behaviour to 'Conduct Disorder' (although his case did not meet the DSM criteria for this), depression, self-harm, use of recreational drugs (which had ceased some three months previously), and lack of interest in school with poor performance. The pharmacological evidence was not considered. Much of the expert evidence

must have been difficult to understand, both for the judge and the jury. Early in 2009 they found EB guilty. Counsel explained to AH that an appeal against the conviction was not possible because the only test for the Court of Appeal is whether the conviction is 'unsafe'. There were no errors of law in the trial nor any arguable unfairness and he had no doubt that the Court of Appeal would have dismissed the appeal simply by saying the jury were able to hear the evidence and arguments on both sides and that their conclusions could not be considered unsafe. An appeal against the 18-year minimum sentence was rejected.

Such difficulties are bound to persist while the law and science consider evidence quite differently. Bradford Hill's 'guidelines on causation' which have been widely used for grading the reliability of evidence have recently been made simpler and easier to apply [1]. Three categories of evidence must be considered separately:

a) *Direct evidence* from studies that an apparent association is causal and not spurious;
b) *Mechanistic evidence* for the alleged causal process that connects the intervention and the outcome;
c) *Parallel evidence* that supports the causal hypothesis suggested in a study, with related studies that have similar results.

In the case of EB the *direct* evidence is that his mental turmoil, abnormal thinking, dissociation and emotional blunting, which culminated in killing his father, occurred after taking fluoxetine in adult doses for 4 weeks. This drug accumulates in the body and reaches a plateau concentration in about that time. Some months later after EB had stopped taking the drug his mental state had become normal. The temporal relationship fits.

That fluoxetine can cause mental turmoil, abnormal thinking and emotions is well documented. *Parallel* evidence comes from studies with other SSRI antidepressants, which are known to have similar effects.

This contrasts with the causes proposed by the prosecution. Bad conduct, use of recreational drugs, poor performance in school, and depression all occurred many months earlier and had ceased or waned before the tragic event. No direct or mechanistic link connects any of these with EB's behaviour. Their causal relationship is speculative and wispy – they are no more than possible contributory factors.

3. Civil liability cases

In civil cases the court determines both causality and damages, and contributory causes are more important than in criminal cases because responsibility for harm is more often shared by several parties and must be apportioned between them. Drug injury can result from prescription or supply of the wrong drug; an appropriate drug that is counterfeit or of bad quality; mistakes in dosage; harmful interactions with other drugs; or various other circumstances. A doctor, pharmacist, nurse, other health worker, the patient him- or herself, or an institution (e.g. a pharmaceutical company, hospital, or government agency) may have the main responsibility [2]. The same principles for assessing causality apply, but in what ways and to what extent other parties have contributed is often hard to assess.

3.1. Case 2: Suicide in Switzerland – life insurance liability denied

DL, a 36 year old businessman shot himself lying on his bed on 17 March 2006 while his wife was taking their children to school. He had shaved and dressed. DL had worries about his apartment and had felt stressed at work. He had gone to his GP, who had diagnosed moderate depression and prescribed

paroxetine and bromazepam. He took the first dose of each on 16 March and the second after getting up on the 17th. Neither his wife nor the GP thought the suicide was a deliberate act, but two psychiatrists advising the life insurers decided it was, and not related to paroxetine, so that the policy did not cover the death. Mrs L appealed this decision, supported by reports from two clinical pharmacologists, AH in the UK, EG in Switzerland, concluding that paroxetine was the most likely cause. A paper cited by the insurers in support of their argument dealt mainly with clinical trials and epidemiology which shed no light on the case of DL. Further, one author of that paper worked for a company making antidepressants and so had a strong interest in presenting these drugs as safe.

The insurers' defence also relied on the argument by the generic manufacturer Mepha (since then taken over by Cephalon, based in the USA) that their information for doctors and patients complied with regulatory requirements, and that therefore the drug could not be blamed. However two months after DL's death the company changed its warning notice for patients in Switzerland, and in July 2010 amended the warning again stating that it can cause suicide. In late 2011, 5½ years after DL's death, the judge in Geneva decided that the suicide was a deliberate act, not the result of an irrational and uncontrollable act. Mrs L must now take her case to the Swiss Federal Court.

3.2. Case 3: A suicide in USA

A series of civil cases in the USA, brought by families of suicide victims mainly during 2001–2006, illustrate many of the features outlined above. One such case, that of a 52 year old man who killed himself several days after commencing sertraline, is typical. In this case, the deceased's family sued the manufacturer (Pfizer), the physician's assistant who provided a free 'starter pack' of sertraline, and the medical doctor responsible for supervising the assistant. Lawyers for Pfizer, distinct from those retained by the doctor and his assistant, challenged virtually every assertion made by the plaintiff's lawyer and his expert witnesses (DH and DM) which linked the ingestion of sertraline to suicide. In this case, the clinical history (specific causation) was very clear of a man who, although experiencing job stress and anxiety, had never been suicidal before using sertraline and became so in the setting of markedly abnormal thinking and behaviour shortly after starting the drug.

Pfizer's lawyers were, if anything, even more stalwart in rejecting evidence that sertraline, like other SSRIs, could cause suicide in a vulnerable subgroup of consumers (general causation) – despite the FDA's mandated **black box** warning of this risk in 2004, before the index event. Much of the defence argument in this and similar cases hinged on the repeated assertion that there was no 'statistically significant' indication of increased suicide risk in clinical trials of sertraline and other SSRIs. This argument ignores the fact that no antidepressant clinical trials have yet been designed (or powered) to detect such an effect, which is generally seen after initiation or changes in dosage. This relationship is not seen in the summary analyses of drug exposure typically presented by companies and their lawyers. Equally important, adverse events and their causation are more reliably determined from case-reports and post-marketing surveillance than from clinical trials [3, 4]. Because of this confusion, lawyers defending pharmaceutical companies have sometimes succeeded in excluding or discounting plaintiff's evidence on the basis of argued *Daubert* (or *Frye*) standards for 'scientific' evidence [5].

Civil cases involving adverse effect causation thus depend on both epidemiological and clinical evidence; these are different and complementary. It follows that both general and specific causation must be considered; regardless of how compelling specific causation might appear, many lawyers and expert witnesses (including the authors) are reluctant to become involved in cases with inadequate evidence, or plausible mechanisms, for general causation. An interesting wrinkle on this tension between general

and specific causation also appeared in the index sertraline-suicide case introduced above. Pfizer lawyers presented evidence from a re-analysis of FDA suicide data which indicated that sertraline may be less prone than other SSRIs to provoke suicidality [6] – notwithstanding their earlier assertion that SSRIs did not cause suicide anyway! Nonetheless, these data showing a possible reduced risk relative to other SSRIs did not invalidate the overall general causation argument or postulated mechanisms; combined with the abovementioned evidence of specific causation, the overall argument that sertraline was a proximal cause of suicide in this case remained strong.

4. The coroner's court

Coroners are responsible for investigating violent, sudden or suspicious deaths, and hold inquests to consider the evidence. Unexpected deaths need investigation and explanation to reassure the family and friends of the deceased, and the public, that these events are being taken seriously and that future preventive measures will be considered and recommended whenever appropriate. Coroners are either medically or legally qualified, and can ask experts to give evidence in cases that seem to require it. They rarely need to investigate cases in great depth, and do not generally examine complex causality in detail. If a case raises no important issue for prevention or public safety, the affected family and the public may be best helped by a bland narrative verdict which indicates no blame for anyone. There is however some risk of unjustified reassurance, especially where medicines are involved. As shown below, some manufacturers anxious to avoid bad publicity for their products may also be able to influence coronial proceedings.

4.1. Cases 4 and 5: Homicide and suicide

DH was an expert witness in both inquests, the first in Ireland in 2010, the second in England in 2011. The coronial systems are virtually identical.

SC, a 23 year old, with no prior history of nervous problems or psychotropic drug use, upset after the breakup of a relationship, was told by his doctor this was normal and would pass. A week later another doctor prescribed citalopram. He attempted suicide a little over a week later. The citalopram was continued and after a further 10 days he stabbed his ex-girlfriend and her new boyfriend, killing him, and then stabbed himself repeatedly to death. Lundbeck, the makers of citalopram, and a grouping of all senior academic psychiatrists in Ireland, issued public statements that the drug could not cause such an effect. The inquest jury of conservative middle-aged landowners, refused to support a suicide verdict (and by implication homicide verdict), accepting that the known effects of citalopram and observed effects on SC made it difficult to be certain he intended suicide or homicide.

YW, a 42 year old woman, with no prior history of nervous problems or psychotropic drug exposure, anxious as her marriage broke up, was prescribed citalopram by her doctor, who diagnosed anxiety disorder and noted she was at no risk of suicide. Over the following 6 weeks, the dose was increased from 10 to 20 mg, and then to 40 mg/day. As it was increased YW was noted to have become suicidal, and then attempted suicide, before finally committing suicide. When the coroner asked if citalopram could have contributed to her death, the doctors who prescribed denied that it had or could. When the coroner asked a medical representative for Lundbeck (CM) if citalopram could have contributed to her death, he denied that it had. When the coroner asked specifically if citalopram can cause suicide, CM stated that it can. (The US 'label' warns that adults treated with citalopram "should be observed for ...

suicidality, especially during the initial few months of a course of the drug therapy, or at times of dose changes".)

When asked a direct causal question, companies are legally obliged to state that the drug can cause suicide, but they are rarely asked this and in stating repeatedly that they have no reason to think their drug caused this suicide or homicide or other adverse event, they can give the impression that they do not accept it can in any circumstances cause the adverse event in question. Companies also can and do defer to academics or clinicians who are not debarred legally from stating that antidepressants cannot cause suicide or homicide. As a result, in recent years inquests have become contested in a way that was unusual hitherto. Furthermore a rise in narrative or open verdicts as in these two cases is giving rise to growing problems with suicide data [7].

5. Conclusion

The deep trench that separates the law from forensic pharmacology is unfortunate and causes injustice, largely invisible to the legal profession. Legal processes generally seem reluctant to implicate the drugs, for whatever reason, preferring instead to look elsewhere. This unexplained bias needs to be examined. Even if people are in general prepared to accept the evidence, many cannot bring it to bear in specific cases.

The gap can be bridged only by educating, training and informing all involved: judges, prosecutors and others. A sophisticated approach is required, since some criminals, and perhaps unscrupulous lawyers, will learn to construct histories to suit their cases and expertise is necessary to detect this.

The task is urgent, not only in Britain but internationally.

Two steps could be taken now. First, legal administrations in all countries should ensure that courts under their control obtain appropriate expert evidence from a forensic psychiatrist or pharmacologist in all cases where a prescribed drug could have caused violent or other criminal behaviour.

Second, criminal courts and coroner's courts should be supplied with an annotated list of drugs that can cause violent behaviour. That need not take long because solid building blocks for such a list have recently been compiled from national pharmacovigilance databases in the United States [8] and in France [9]. The list should be updated regularly.

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