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Diagnosis, Verdict, Conclusion, and Causality

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This article presents two clinical scenarios based on antidepressant-induced deaths, which make clear that there are a number of intervening processes in between the valuable data Read and colleagues present and the verdicts that come out of inquests. The manner in which inquests and court cases are structured means that it is very rare for even clearly-proven prescription drug induced deaths to result in a verdict that the drug has caused the death. Instead, a growing number of drug-induced deaths fuel perceptions of a need for more and better drugs.

Central to this situation is a question about how to determine causality in drug-induced injury cases. The idea that randomized controlled trials are the way to establish causality needs to be revisited. Unless there is reform, people caught in situations like the two described here would be better placed holding their own inquests, and finding ways to promulgate the resulting verdicts, rather than "trusting" in a process that is biased against them.

Keywords: adverse effects of psychiatric drugs; biological psychiatry; antidepressants; biological psychiatry

Before the emergence of controversies about suicides on selective serotonin reuptake inhibiting (SSRI) antidepressants, the standard way to determine cause and effect clinically was to describe treatment and an effect and attempt to diagnose on the balance of probabilities whether an SSRI, for instance, was the likely cause of an effect like suicidality in a specific case.

The act of determining causality involved close clinical observation, a chance to examine and cross-examine the patient, full access to their prior medical history, along with an ability to run laboratory tests and clinical tests such as increasing the dose, or dechallenging and rechallenging the patient with treatment, or introducing an antidote. Doctors can enlist colleagues to examine the patient and their case details in person, or make case presentations to a number of colleagues, to establish if a diagnosis other than drug-induced is more probable.

This process for diagnosing an adverse event is endorsed by the 1994 Federal Judicial Manual for establishing adverse events (Federal Judicial Center, 1994). It also conforms to judicial norms, which enjoin juries to arrive at a balance of probabilities verdict based on the examination and cross-examination they see in front of them, abjuring hearsay or other materials that cannot be examined and cross-examined.

Teicher et al. (1990) adopted this process in an *American Journal of Psychiatry* article, when laying out the details of six clinical cases in which it appeared that fluoxetine had

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induced suicidality (Teicher et al., 1990). The problem cleared when treatment stopped and reappeared in those who were rechallenged.

In response, Eli Lilly analyzed their fluoxetine clinical trials and claimed these trials showed no evidence that fluoxetine made people suicidal (Beasley et al., 1991). This claim was made even though the suicide event rate was higher in those on fluoxetine than on placebo. It later became clear that if an event from the run-in phase of the trial, which was designated a placebo event although the patient had not been randomized to placebo was excluded, the suicidal event rate was statistically significantly higher on fluoxetine than on placebo (Healy, 2004).

In both academic and lay media, Lilly argued that clinical trials are the science of cause and effect. Lilly portrayed traditional assessments of a link as case reports, which even if replicated, were anecdotal and irrelevant. Portraying media reports of drug harms as anecdotes is one thing, but applying the term to published case reports undercuts the basis for making diagnoses in medicine and verdicts in court cases.

In 2004, regulators put Black Box Suicide Warnings on SSRI and related antidepressants used by children. These warnings were not tied to either convincing case reports or clinical trial data, which at this point showed a statistically significant doubling of suicide event rates on active treatment. The warnings were adopted in part because there was not sufficient evidence of benefit, against which to offset any risks; however, we opt to determine their causality.

This article offers two scenarios bearing on the question of how to decide whether a treatment has caused death or is causing a problem in clinical practice. Those faced with the task of making decisions like this include people who are on a drug and think they might have a problem, as well as prescribers. This matter is also something for the health systems that encompass all of us. At present, health systems leave many believing that someone else, such as regulators, coroners, or guideline makers, establishes what we can say about cause-and-effect determinations in respect of treatment-related adverse events.

This position taken here is that doctors and patients make a mistake in deferring to these other elements of the system. There is a need to reverse the position taken by Beasley et al. (1991) when defending fluoxetine against charges that it can make some people suicidal. They argued that clinical trials are the appropriate way to determine cause and effect.

SCENARIO 1

A 16-year-old boy, A, after a review in the mental health services, was diagnosed with obsessive-compulsive disorder. The disorder was relatively mild, and he had no prior nervous problems. An initial psychotherapeutic approach offered no immediate benefit and his parents sought medical input. This input from Dr. X led to A being put on paroxetine 20 mg. On paroxetine, his condition deteriorated. He became more disorganized and aggressive, had trouble sleeping, and had other problems. His doctor increased the dose of paroxetine to 40 mg, which led to further deterioration. A phenothiazine antipsychotic was added. This did not help. A committed suicide at a train station soon afterward.

A's family contacted GlaxoSmithKline (GSK), the makers of paroxetine, asking them to comment:

> on the causality between the treatment taken by A and the symptoms he developed (sleep disorders, irritability, violent attacks, mood disorders, thought disorders, emotional instability, disinhibition, impaired discernment), and on the causality between the treatment and his suicide.

GSK responded that they could not comment on this case given that A was on another treatment as well and had a condition that led to anxiety, and some irritability even before starting the treatment.

They sent the family the paroxetine label at the time of A's death, which made clear that paroxetine was not approved for children of this age. They drew attention to the several warnings on the label about the suicide risk, based on the increased rates of suicidal events on active treatment in clinical trials. The label in addition notes that despite these warnings your doctor might think that paroxetine can help you. The label advised children (whose mental state might be disintegrating on this treatment) to tell their doctors if they appeared to be having any problem linked to the drug.

The company stated that fulfilling their obligations in respect of A, they had reported the case to the medicines' regulator. Up to around 2,000 companies understood they had a legal duty not just to report an adverse event to regulators but to attempt to establish a causal relationship to the effect. This was ordinarily done by accessing the patient's medical record and making inquiries of his doctor and possibly others in order to make an informed judgment. Companies no longer do this. Companies now simply report to regulators that events have been reported to them, without adding a diagnosis. Regulators have never had a duty to establish causality and ordinarily do not seek out a person's medical record or contact their family.

Clearly, GSK is not in a position to attempt to establish causality in this case without interviewing A's family, as well as the doctor who treated him, and without full access to his medical record. Establishing a likely link between treatment and effect involves weighing the clinical experience of the prescriber in general, and with this patient in particular, assessing the possible motivation of the prescriber for the view they now offer. It also requires a consideration of the lived experiences of the patient's family and friends who were witnesses to a transformation, if there was one, and an assessment of their motivation for making the link.

Equally as clear, it is not possible to say that just because there is evidence of a doubling of suicidal events in trials of this treatment for this condition that the treatment has therefore caused the suicide. While less obvious, the converse is also true, that even if trials show a reduction in suicidal event rates on treatment, the best explanation in an individual case may be that the treatment caused the event (Healy et al., 2013).

However, there are some notable aspects to this situation.

GSK appears to have *de facto* conceded that the doctor and family are best placed to determine causality in an individual case. If a doctor and family concur in view of the evidence from the case that treatment has caused a problem, a third party, such as a pharmaceutical company, is less likely to be able to make a credible case that the treatment did not cause the problem. If, however, the third party assesses the case in

detail and offers a credible alternate diagnosis based on overlooked or newly discovered details, as with all good science, and legal process, the doctor and family might be expected to change their diagnosis/verdict.

In the case of paroxetine, as of 2004, the clinical trial data in minors showed a statistically significant increase in suicidal events on it compared to placebo. Had these events shown an increase in events on paroxetine that was not statistically significant, would it have been credible to claim the trials had not shown scientific evidence of a problem and simply on that basis the verdict on the individual case should be overthrown?

This question becomes more acute in the light of other trial data such as depression rating scale scores, which, even in the presence of an increased rate of suicidal events on active treatment, tend to show a fall with active treatment when aggregated across all participants in the study. One of the problems, in this case, is that the depression rating scales ordinarily do not permit a distinction between treatment-induced and condition-induced suicidality. The rater is typically enjoined to simply ask the question about suicidality without delving into the reasons for an increase.

The position the company has taken here constrains the company medical director, if called to an inquest in this case, and asked whether paroxetine can cause suicide. To answer Yes leaves them free, but if then asked did it cause this suicide to answer No, then the patient's illness likely caused the problem.

The prescribing psychiatrist, advised by a medical defense union, if asked the same question and after hearing the company medical director's answer, can say (and have said) they do not believe the drug can cause suicide.

SCENARIO 2

Anxious about forthcoming professional examinations, B went to his family doctor, Dr. Y, requesting citalopram, an SSRI antidepressant. B was 25 years old. He had minimal health issues and no prior history of nervous problems. He was in a steady relationship, had no debts or other problems, and was expected to do well in the forthcoming professional exams rather than have difficulties passing them. He was almost a healthy volunteer.

Dr. Y reluctantly prescribed citalopram. A week later B hung himself. In the days prior, he had features consistent with SSRI-induced suicidality. For instance, his computer indicated that shortly after starting the treatment he had investigated symptoms of schizophrenia. His death came as a shock to his family and Dr. Y.

No medical condition or circumstance later came to light that could have explained B's death. The clinical features and timeframe of his death map out the fingerprint of an SSRI-induced suicide. Like A, he was within the age covered by Black Box Warnings of suicidality for this drug.

Since 1960, it has been known that antidepressants can trigger suicide. Since 1980, it has been known that SSRIs can trigger suicide in healthy volunteers in exactly the timeframe found in B's case. For nearly two decades, antidepressants have come with warnings of suicide.

Stunned at the death of their son and reaching out for explanations for what had happened, B's family found guidelines for SSRIs that recommend a review within a week

of starting an SSRI. At a meeting with Dr. Y and colleagues, the family raised this recommendation for a review after a week and asked whether they should have been informed their son was on treatment.

As an expert in this inquest, I reviewed Dr. Y's responses to their questions and the approach to B's care. He seemed like a good doctor to me. He offered no view about the cause of B's suicide other than the drug.

No guidelines clearly state that these drugs can cause suicide, even in healthy volunteers. They steer doctors and patients toward a notion unsupported by evidence, that if a person becomes suicidal their condition is likely the cause of the problem. Unless the guideline explicitly states that patients may be suffering from SSRI toxicity rather than depression, doctors facing a worsening situation may diagnose depression and perhaps increase the dose of a problem medicine making suicide even more likely.

The problem has been further obscured for doctors by the virtue of the fact that most articles purporting to represent the results of trials of these drugs have been ghost-written with suicidal events hidden under coding rubrics like emotional lability, and with all data from these trials sequestered.

The problem is also obscured by the fact that coroners cannot return a verdict against a prescription drug. Faced with a good doctor who does not implicate the drug, rather than return a medical negligence verdict, coroners will blame the mental illness the patient had or must have had. Coroners have actively steered me in this direction.

I was retained by B's family as an expert in the case. I wrote to Dr. Y prior to the inquest, outlining the data behind the Black Box Warnings, the record of suicidality and suicides in healthy volunteer trials of these drugs in the 1980s, and the fact that all articles on these drugs are ghostwritten with the trial data sequestered. I indicated that I had written to the doctor's minister of health and chief medical officer making these points, and that neither they, nor those who wrote the guidelines that he and B's family appealed to, had demurred on any of these points.

I also indicated that I had made it clear to the family that Dr. Y was now their best ally, and that if anyone should later take an action against him for this death, he could count on me as a witness on his behalf.

He responded that he had been advised by his medical insurer not to engage with me – on grounds of confidentiality, even though at this stage I had all relevant records including the clinic notes of his meeting with the family and I had talked extensively with the family.

Dr. Y was not in a good position to argue as an expert on the details of clinical trial data or the adequacy of the warnings, but he was in a position to agree (as he implicitly appeared to have done in his meeting with B's family) that the drug was most likely to be the prime factor in their son's death.

Dr. Y's defense union provided a lawyer to represent him at the inquest. The lawyer presented the case that depression is a serious illness and suicide is a leading cause of death in people of B's age. Dr. Y said nothing.

My report stated that there was a convincing case to implicate citalopram, both on the specifics of this case and the data supporting a general causation case that this drug, while useful for many, can unequivocally cause suicide.

In the United Kingdom, coroners cannot implicate a prescription drug in a death, whereas they can finger a street drug. Coroners can, however, submit a Regulation 28 report to the medicines' regulator drawing attention to the drug, implying the drug has

caused the problem, and suggesting that in the interests of general safety something needs to be done, perhaps about warnings (Aronson, 2022).

The case was sufficiently clear cut that, despite Dr. Y's silence, the coroner filed a Regulation 28 report raising the drug and its warnings. The Medicines' Regulator responded that Dr. Y had not implicated the drug and without his input, the regulator could do nothing (Courts and Tribunals Judiciary Ref, 2022).

I wrote to the relevant minister of health, copied the Medicines' Regulator noting a problem with the inquest process. The stated mission of medical defense companies is to support doctors to practice good medicine, but as a business, their interests lie in closing off any opening to further legal actions against their clients. They generally advise doctors in Dr. Y's situation, as they have advised me, not to implicate the drug.

I wrote to the two leading medical defense companies in the United Kingdom putting the case outlined here to them, offering them a chance to respond. They acknowledged receipt of the letter but did not respond. Off the record, lawyers for medical defense companies have endorsed the point I am making.

It is not bad clinical practice to have a patient injured or killed by an avoidable hazard of a drug, especially if the hazard has been hidden from the doctor. Doctors are in a uniquely strong position to promote the safety of others by acknowledging, on a balance of probabilities basis, that certain harms seem likely to have resulted from a treatment they have given in a specific case.

The staff at Britain's drug regulator, the Medicines and Healthcare products Regulatory Agency, have no clinical training in establishing adverse effects and without an examination of the case in detail are not in a position to come to a diagnosis/verdict. They have never contacted B's family or reviewed his records. A treating doctor, like Dr. Y, is better placed to offer a diagnosis and it would appear sensible to have doctors like him lead on safety, rather than bureaucrats.

The regulators of medicines and others have played down the warnings on antidepressants, and likely many other medicines, stating explicitly that they do not wish to deter people from seeking the benefits that can come from treatment.

DISCUSSION

While there are Black Box Warnings for suicide on antidepressants in the United States, they contain no explicit statement that these drugs can directly cause suicide, and have done so in healthy volunteers, for instance. Current warnings did not deter Dr. X or Dr. Y from prescribing, nor B from asking for citalopram, or A and his family from taking and continuing to take paroxetine over a period of months in the face of a steady decline in his mental state.

There is little evidence that warnings deter people from seeking treatment. But a clear statement that a drug can trigger dangerous effects might have been explained to B or to A's family what was happening after treatment began, and enabled B or A's family to come to a diagnosis that could have saved a life.

Clinical care is not possible without evaluations of treatment effects, both good and bad effects. No one argues when a patient and doctor agree that a drug is working. In these cases, there is a general endorsement of the standard medical approach to determining causality or making a diagnosis as it can also be termed.

Indeed, unless this standard approach "works," it is difficult to see how medical care can happen. Care cannot be solely underpinned by algorithms, eliminating any place for judgment calls about specific effects. An exercise of judgment is central to care, especially when there is a threat to a patient's health or life.

When adverse effects enter the legal domain, expert reports commonly refer to general causation and specific causation. Can this drug cause this problem? Did it cause this problem in this case? This distinction has only been drawn since approximately 1990, following legal cases involving birth defects on Bendectin, and connective tissue disorders linked to breast implants, along with Lilly's (1991) defense of fluoxetine. Prior to that, an expert report from a clinician offering a balance of probabilities diagnosis, based on specific evidence that could be examined and cross-examined, was taken as legitimate scientific evidence.

Controversies in U.S. cases about Bendectin and birth defects created a Daubert Rule, whereby courts were required to ensure that experts were not peddling junk science (Healy, 2004). Daubert hearings offered a platform for company lawyers and medical experts to argue that the plaintiffs' experts proffering views not supported by statistically significant clinical trial evidence have no basis for arguing that a drug had caused a problem even if a jury or coroner might be inclined to make a link to treatment.

Companies have managed to get cases against them dismissed on the basis that negative evidence from randomized controlled trials is equivalent to a high-powered scan that shows no lesion in the organ the plaintiff's expert claims has been damaged. But the argument becomes incoherent when on the same basis, companies claim both that their drugs work even though there are more dead bodies on active treatment than on placebo and that their drugs have no side effects (Hudson I Deposition of Ian Hudson in Tobin v SmithKline Beecham, 2000). In 2000, Ian Hudson was the chief safety officer for GSK; in 2013, he became chief executive of Britain's Medicines Regulatory Agency.

For over 30 years, companies however, have largely generated the evidence to which they appeal. This evidence appears in ghostwritten articles, some of which have been demonstrated to be fraudulent, and the trials in question have not been designed to investigate whether this drug (an SSRI) can cause that problem (suicidality).

There is also a lack of access to trial data. The apparent evidence is, therefore, largely hearsay, and hearsay is ordinarily inadmissible in court on the basis that it cannot be interrogated.

A second problem is that while there is a logic to company distinctions between general and specific causation, the distinction as currently deployed invalidates diagnoses, and legal verdicts. Specific causation is a new term that essentially translates into clinical diagnoses, legal verdicts, and coronial conclusions. Scans and other tests can assist diagnoses in medicine, but have we reached a point where traditional medical diagnoses no longer count? And if that is the case for diagnoses, can the case for legal verdicts be far behind?

Finally, as things stand, doctors are commonly advised by medical defense unions to refrain from offering views they believe to be accurate, that might offer succor to bereaved families and might save the lives of others. This advice is shaped by the business interests of these insurers.

There is a complex nexus of interests here that needs addressing. At present our "systems" default into supporting pharmaceutical companies rather than patients. This

is not just a matter for inquests in that it becomes harder for doctors to make the kinds of judgments needed for clinical care when all the apparently best evidence is stacked against them. This also becomes a problem for patients and families if they are not listened to when they make judgments, which may be critical to saving a life.

We have a problem when the people best placed to offer a reasoned view on cause-and-effect are encouraged to remain silent. The legal process makes it clear names count. Examinations and cross-examinations cannot happen if there is no named person who can be brought into court, or if the named person is advised on legal grounds not to comment. We risk compromising the safety of all if we prohibit judgments about cause-and-effect based on an examination of specific case, in which the question is, did this drug cause that effect?

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