Title: Causation in Evidence-based Medicine: Reply to Strand and Parkkinen

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Abstract

Strand and Parkkinen criticise our dispositional account of causation in medicine for failing to provide a proper epistemology of causal knowledge. In particular, they claim that we do not explain how causal inferences should be drawn. In response, we point out that dispositionalism does indeed have an account of the epistemology of causation, including counterfactual dependence, intervention, prediction and clinical decision. Furthermore, we argue that this is an epistemology that fits better with the known fallibility of even our best-informed predictions. Predictions are made on the basis that causes dispose or tend towards their effects, rather than guarantee them. The ontology of causation remains a valuable study for, among other reasons, it tells us that powers do not always combine additively. This counts against the mono-causality that is tested by RCTs.

Introduction

In response to our 'Causation and evidence-based practice: an ontological review' [1], Strand and Parkkinen claim that 'philosophical accounts of causation are pertinent to EBM [Evidence-Based Medicine] when they help us to understand, evaluate and optimize the role of causal knowledge in inferences from evidence to clinical decisions' ([2] p. 1); a statement with which we agree. They proceed to add that:

> EBM should not get entangled in ontological aspect of causation that transcend the issues of causal inference and causal epistemology but focus on systematizing the best possible evidence, and providing the best possible framework for making and evaluating inferences to clinical decisions from this evidence. ([2] p. 1)

This second claim, we do not accept. We should not proceed to systematize the best possible evidence for causation, and then infer to clinical decisions, without a grasp of the ontological issue of what causation is. Our view of the nature of causation determines what we take to be its evidence. If one takes a cause to be a difference maker, for example, the randomised controlled trials (RCTs) at the centre of EBM constitute good evidence of a cause and inform clinical decisions. But suppose a

cause isn't simply a difference maker. Shouldn't that affect how we understand the importance of RCTs? We think so. In general, we take it that ontological considerations about the nature of causation can guide our methodology and epistemology in the right direction.

Difference making and interventions for dispositionalists

Strand and Parkkinen argue that the dispositional theory that we have advocated [1] does not adequately account for the causal inferences we need to draw in medicine, especially following RCTs, and they then suggest that a counterfactual dependence or difference making theory does much better. We deny this assessment of the relative merits of the two theories and the extent to which they can explain our epistemological practices. Dispositionalism makes far better sense of the nature of prediction (and explanation), for instance. In particular, dispositionalism shows why prediction is defeasible and, although reliable to some degree, not reliable entirely.

The difference-making account is advocated by Strand and Parkkinen in which causation is analysed in terms of dependency relations, such as variation under an intervention. Intervene on one variable and another alters with it. This trades on the intuitive idea that causes makes a difference. As they state it: 'A is a cause of B if and only if there is a possible intervention on A that would lead to a change in B.' ([2] p. 2) We would say this fails as an analysis among other reasons because the notion of *leading to* that is invoked itself looks causal, hence assuming the notion it is meant to analyse. Many proposed analyses of causation have this sort of problem because it seems very difficult to analyse causation into something else, such as difference-making under possible intervention. While most causes do make a difference, for example, not all do: not in cases where effects are overdetermined by more than one sufficient cause. There is at least some conceptual gap, then, between our notions of cause and difference maker. There has been extended debate on the prospects of understanding causation the way Strand and Parkkinen suggest, though we will not recount all the details here.

They go on to say 'Causal information concerns what *would* happen if things were different' ([2] p. 2, their emphasis), and 'On difference-making accounts, causal dependence entails claims about what *will* happen in counterfactual scenarios ([2] p. 2, our emphasis). What they overlook is that the dispositionalist does indeed have accounts of counterfactuals, intervention and counterfactual reasoning readily at their disposal ([3] ch. 6); and, we would claim, they are more credible accounts.

Counterfactual reasoning, for instance, will be understood as being about what *tends* to happen if one other thing does. We cannot say for sure what definitely will and won't happen, given a particular counterfactual assumption. But when Strand and Parkkinen say that 'even the dispositionalist would have to adhere to dependence aspects of causation' ([2] p. 2), it is not something we deny. Most effects will indeed depend upon the causes that produced them, with the exception of aforementioned overdetermination cases.

The dispositionalist thinks that causal factors tend to some degree, but no more than tend, towards certain effects. Some of those factors might tend quite strongly in a certain direction but, we argue, they do not necessitate them in any case because of the possibility of additive interference. A may cause B but also might not do so if accompanied by C, where C is an additive interferer with respect to this causal connection. This makes us reluctant to say, as Strand and Parkkinnen do, that causal claims are about what *would* and *will* happen in certain circumstances. They are instead about what is *disposed* or *tends* to happen. We will see the significance of this later but the immediate point is that this certainly permits counterfactual reasoning, inference, prediction and, in the medical case, clinical decision. We know, for instance, that if the cause occurs then the effect is disposed to occur, where there may be a strong or only a weak tendency towards it. We know that we can predict an effect, more or less reliably, on the basis of what tends to happen and we can also make a clinical decision. Smokers tend to develop cancers more than non-smokers, for example, and this can be the basis for a recommended course of action, such as to stopping smoking.

Much of what Strand and Parkkinen claim as strengths or their account thus carry over to the dispositional theory. But, we argue, the dispositional approach has the advantage over the difference making account. In particular, the theory of causal reasoning they offer does not adequately account for the defeasibility in prediction, where prediction is the basis for clinical decisions. The dispositional account allows that we can reason perfectly correctly from all the known information but still find our causal inference lets us down. A prediction can be disappointed, usually when some factor is at work that was not previously understood or because the known factors in play interacted in some way that was not anticipated. We take it as a datum that the prediction of effects sometimes fails, in medicine as in anything else, and so any theory of causal inference needs a good explanation why.

In defending RCT as the correct method for understanding causal knowledge, Strand and Parkkinen acknowledge a number of ways in which it can go wrong. The randomisation might not be genuine,

for instance, or an individual within the trial might have had some prior exposure to the treatment ([2] p. 3). However, if the RCT is conducted correctly, avoiding these experimental and methodological errors, every indication is given that a prediction will be perfectly reliable. Causal reasoning is presented as following logically from the outcome of such a well-conducted trial because it allegedly reveals the causal dependencies. The dispositionalist is castigated, on the other hand, for offering only 'gestures' of 'how the inferential aspects of causal knowledge' are assessed. We would defend the idea of causes no more than gesturing towards their effects, rather than guaranteeing them under any circumstances. We have to allow the possibility that a causal inference can be based on a perfectly well-conducted RCT and still be mistaken so that we can explain the defeasibility of prediction. A dispositionalist in contrast states that well-based predictions are reliable to a degree – sometimes quite a high degree – but that there is always the possibility that they be disappointed. To understand why this occurs, we need to understand better the nature of the RCT and how it does not accurately capture some vital features of the ontology of causation.

Mono-causality

Strand and Parkkinen give an accurate and fair description of the method of RCT. What it shows is that RCT is a single-factorial test for causality. As they say: 'On this method, one isolates a factor of interest in a system and proceeds to vary it in specific ways, while detecting whether the putative effect changes as a result.' ([2] p. 2) RCTs assume and underscore a mono-causal account of causation, whether it is in medicine, biology, economics or elsewhere. This suggests, at least if we think that such knowledge can be clinically valuable, that we can find the effect of a single factor and then, once established, are warranted in inferring that the factor has that same effect in every other case in which it appears, including those in which it is not the only causal factor in operation.

Such an inference is unsafe. All causation is complex and multi-factorial. That matters for two reasons. One is that there are ways of preventing a cause from having its effect in particular cases. Where the cause occurs also with a preventer or interferer, then the expected effect might not occur. In an RCT with a large enough population, it might be thought enough that a trial drug showed an increased rate of recovery, to conclude that it has the intended effect. There may be some cases of prevention of that effect, for some individuals, but with a large enough sample, the statistics should be able to nevertheless reveal the effect. However, we still have no guarantee that the effect revealed in the RCT will be duplicated when a trialled drug is made commercially available.

While the treatment group and placebo group will be as alike as matters, if the population is divided in two in a genuinely random way, the population using the commercial product need not be like the trial population. There is a simple explanation. For ethical reasons, we cannot always involve the vulnerable in the trial. We cannot include the sick and very elderly, for example, because it might be thought to put them at risk. Yet these are often the people who then take the drug once available [4].

That might be thought of as a practical problem but the second reason it matters than causation is multi-factorial is a more ontological one about the nature of causation. If we test single factors and then make inferences about the same effect of those factors in other cases, it is to assume that when causes compose into a complex that they do so additively. But it is possible and seems likely that there are many cases of causation that compose nonlinearly. A most striking example that illustrates the issue is clonidine and beta-blockers such as propranolol. Individually, both these drugs are antihypertensives, disposing towards the lowering of blood pressure. This disposition can be revealed in their difference making. However, when taken in combination, they have the opposite effect. They dispose towards the raising of blood pressure (see [5, 6]). This is known as an antipathetic composition ([3] p. 91). We cannot simply add up causes that have a known effect through RCT, then, because those factors are capable of interacting with each other and changing the other's causal behaviour. Perhaps some composition of causes is perfectly linear (additive and subtractive) but it seems there are at least some cases where a combination of causal factors forms a new whole with a new set of tendencies.

Causes are clearly not to be understood as factors that have exactly the same effect in every context in which they appear, therefore. Causes that have been identified through RCTs carried out to perfectly acceptable standards, and clearly suggesting of a certain prediction and clinical intervention, could nevertheless fail to produce their expected effect. When one looks to the ontological matters of causation, one sees that this further consideration, concerning context and composition, can be highly significant. Adding together a combination of drugs, for instance, each of which has been found to have a safe, positive effect in RCT, in theory could possibly produce a 'cocktail effect' that is unsafe. Again, this explains why causal inferences are fallible. They are based on an assumption of a finite number of operating factors. An unknown factor could effectively be an additive interferer, for some expected effect. Worse still, it might be a factor that composes nonlinearly with the presence of the other factors to produce an antipathetic effect.

Conclusion: defeasible inferences for dispositionalists

Strand and Pekkinen concentrate on the 'inferential aspects of causal knowledge'. They say that their difference-making theory explains those causal inferences while the dispositional account does not. They argue for this conclusion without considering the ontological issues at stake. Indeed, they suggest those considerations are not relevant. Our point, in [1], was to show that it would be beneficial to unveil some of the shortcomings of current causal models for the complexities of medical phenomena. Strand and Parkkinen deny this simply by asserting that if the RCT is conducted correctly, without experimental error, then predictions should be forthcoming that are simple, exact and unfailing. We know this to be false. Any account of causal inferences has to respect the obvious datum that our predictions are fallible and defeasible. Dispositionalism offers an explanation of prediction and inference within a fallibilist framework in which dispositions tend to produce their effects but might not always do so. Strand and Pekkinen are thus wrong to say that an epistemology of causal knowledge 'does not flow from the dispositionalist ontology'. What does not flow is an epistemology in which inferences can be drawn with deductive certainty, which seems exactly as it should be.

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