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What are side effects?

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Abstract
Side effects are ubiquitous in medicine and they often play a role in treatment decisions for patients and clinicians alike. Philosophers and health researchers often use side effects to illustrate issues with contemporary medical research and practice. However, technical definitions of 'side effect' differ among health authorities. Thus, determining the side effects of an intervention can differ depending on whose definition we assume. Here I review some of the common definitions of side effect and highlight their issues. In response, I offer an account of side effects as jointly (i) unintended and (ii) effects due to the causal capacities or invariances of an intervention. I discuss (i) by examining the intentions or reasons behind therapeutic interventions, and I discuss (ii) by appealing to a manipulationist model of causation. The analysis here highlights that side effects are conceptually distinct from related outcomes like adverse events, adverse drug reactions, and placebo effects. The analysis also allows for reflection on the utility of 'side effect' as a technical term in medical research and practice.

Keywords Side effects · Adverse events · Adverse drug reactions · Placebo effects · Pharmaceuticals

1 Introduction

Side effects are common in discussions around pharmaceuticals, vaccines, screening procedures, and surgeries. Unforeseen, harmful side effects worry patients and clinicians alike; negative side effects cause an estimated 128,000 deaths annually (Lexchin, 2016; Rocca et al., 2020). From 2017 to 2020 the US Food and Drug

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Administration (FDA) issued around 200 'black-box' warnings – the strictest regulatory label for market-approved drugs – because of negative side effects.[1] The side effects of Vioxx (rofecoxib) caused tens of thousands of deaths only two decades ago. The negative side effects of OxyContin (oxycodone) have contributed to an ongoing opioid crisis. Tragedies from the negative side effects of diethylstilbestrol and thalidomide are still within public memory. Moreover, side effects are a core area of biomedical research, with well-over 100,000 papers published on side effects yearly from 2011 to 2019.[2] Philosophers and health researchers often appeal to side effects to problematize contemporary medicine's pre-market research process (Stegenga, 2016a, b), evidence hierarchies in 'evidence-based' medicine (Osimani, 2014; Vandenbroucke, 2008), mechanistic reasoning in clinical decision-making (Howick, 2011), regulatory policy (Stegenga, 2017), and a strictly biomedical model of disease (Gagnon & Holmes, 2016a, b). Side effects are a ubiquitous part of medicine and philosophical engagement with medicine.

However, even though we all have an intuitive idea of what side effects are, the technical definitions of 'side effect' given by health authorities and researchers differ. Moreover, explicit considerations of this fundamental concept are sparse.[3] The Center for Disease Control (CDC) and the FDA both define a side effect as an 'adverse reaction.'[4] The World Health Organization (WHO) defines a side effect as the 'unintended effect occurring at a normal dose related to pharmacological properties.'[5] Medical practitioners and researchers often define side effects as 'secondary' or 'unwanted' effects, or as 'all the unintended effects of a therapy' (Aronson & Ferner, 2005; Bresso et al., 2013). Notice that 'side effects' here are mainly referring to *pharmaceutical* side effects, which are the kinds of side effects highlighted moving forward though the account presented is intended to be generalizable to side effects in other kinds of therapeutic interventions.

[1] Data accessed from publicly accessible dashboards provided on the US FDA website: www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm.

[2] This is preceded by increases nearly every year since the late 60s, though there is 2020 drop, likely due to the impact of COVID-19; see: pubmed.ncbi.nlm.nih.gov/?term=side+effects&timeline=expanded.

[3] Some of the literature around the placebo effect considers the question of what side effects are, though usually indirectly in attempting to determine what placebo effects are, e.g., Adolf Grünbaum's (1986) relational model and its recent modifications by Jeremy Howick (2017) and Bennett Holman (2015). I will only briefly mention here that an issue with these models is that they can mistakenly categorize side effects as placebogenic (Blease & Annoni, 2019) or mistakenly posit unintended adverse drug reactions as *not* side effects. The model I offer here bears on the 'Grünbaumian' models, but address of that must wait.

[4] See: CDC: www.cdc.gov/vaccinesafety/ensuringsafety/sideeffects/; FDA: https://www.fda.gov/drugs/information-consumers-and-patients-drugs/finding-and-learning-about-side-effects-adverse-reactions.

[5] As of 2020, the WHO website no longer includes this definition on their website, due to 'migrating web content,' though it was originally accessible at: who.int/medicines/areas/quality_safety/safety_efficacy/trainingcourses/definitions.pdf. However, the vestiges of this assumed definition can be found in sources such as Aronson & Ferner (2005, p. 854). Either way, this is still a definition worth addressing since it does match onto general intuitions operative in drug research and in thinking about side effects. Important to note here is that along with the FDA and CDC definitions, the WHO definition is/was given on a relatively public-facing resource. Later discussed is that these definitions are given for a different purpose or in a different context than one directed at defining 'side effect' in a technically precise way.

Considering the above, an analysis of 'side effect' is warranted. Which of these definitions is correct? When it comes to drug research, which is the most useful or best describes research practices and motivations? Not only is providing clarity an important activity for philosophers of science and medicine, but without a clear understanding of what side effects are, research on side effects and related outcomes like adverse events, adverse drug reactions, and placebo effects can be problematic. It surely is not the case that drug researchers search *exclusively* for adverse reactions in hunting for side effects, since we know some drugs have *positive* side effects. I will show that the CDC, FDA, and WHO definitions of 'side effect' are faulty insofar as having straightforward counterexamples. In addition, I argue that defining side effects as the 'unintended effects of a therapy' or 'unwanted' is ambiguous unless we explain what it means for something to be 'unintended' and an 'effect' of an intervention in the first place.

I propose an account of side effects as (i) unintended and (ii) effects from the causal capacities or invariances or a drug. Condition (i) is explained by appealing to the reasons for taking or prescribing a drug. Condition (ii) is explained by appealing to a manipulationist model of causation. My account avoids the counterexamples the other accounts are susceptible to. Moreover, it posits clear distinctions between side effects and related outcomes like adverse events, adverse drug reactions, and placebo effects. 'Adverse drug reactions' and 'side effects' are *not* interchangeable terms, even though they often overlap. Finally, my account allows for reflecting on the use of 'side effect' as a technical term in medical research and practice.

2 Problems with existing accounts of 'side effect'

Before addressing the problems with the definitions of 'side effect' from health authorities presented above and offering my account, one can ask what the value of such an account may be. Conceptual analysis is a useful tool for philosophers because, among other things, it allows us to draw distinctions between our concepts. However, stipulating such an account does not mean it is right, let alone useful. Maël Lemoine (2013) rightly points this out in an investigation into the use of conceptual analyses in the normative-naturalist debate around 'disease.' Say that some stipulated account of x picks out all the same entities in the world as a competing account of x. In that case, we must go beyond conceptual analysis to tell us which of the two accounts is better. Coming up with different accounts of x that posit the same set of things as x is not a useful case of conceptual analysis. When stipulated accounts free a concept from counterexamples, Lemoine (2013) claims that stipulated accounts can be useful. I think the account of side effects I offer here is a useful instance of conceptual analysis insofar as what I offer here picks out different things in the world as 'side effects' than the health authorities' accounts, the unqualified 'all unintended effects of a therapy' definition, and the 'unwanted' definition, while avoiding their counterexamples.[6]

[6] My thanks to Juliette Ferry-Danini for suggesting addressing this.

Let's look first at the CDC and FDA definitions of side effect: an 'adverse reaction.' It is not uncommon for researchers to say side effects are interchangeable with adverse reactions (e.g., Zielinski, et al., 2015; Uner et al., 2019). But are all side effects adverse reactions? Clearly not. 'Side effect' usually has negative connotations, but this is not the only sense in which we use it. For example, someone taking finasteride for their benign prostatic hyperplasia might be delighted to discover their hair gets thicker after treatment. The CDC and FDA definitions preclude non-adverse or positive side effects. Finasteride is just one of many therapeutic drugs that have side effects that are not considered adverse. To be fair, the definitions given by the CDC and FDA come from public-facing resources. Adverse side effects are the kinds of side effects people are most worried about. However, the side effects that are of most concern are not the only kinds of side effects out there, even if they are the ones we want to warn people about. The context of warning people about medication risks is different than the context of defining what a side effect is in the first place. These contexts are often blurred in the public-facing resources offered by health authorities.

The WHO defines a side effect as any unintended effect occurring at a normal dose related to pharmacological properties. The WHO definition does not make the same mistake as the CDC and FDA definitions insofar as it says nothing about the 'adverse' quality of a side effect. On the WHO definition, positive side effects are (correctly) possible. However, there is another problem with the WHO account. What is a 'normal dose' of a drug? This depends on which clinical guidelines are in place. That a drug at some dosage causes a side effect, but then that same effect is not a side effect when the dosage changes does not seem right. More damning for the WHO definition is that we often discuss side effects in cases where 'normal dosage' is not yet established like in 'first-in-human' phase I trials (e.g., Fisher, 2015, 2020). Also consider a case where I accidentally take too much of a drug – an 'abnormal' dose – and then an unintended adverse reaction occurs because of the pharmacological properties of the drug. This would not be a side effect on the WHO account; that does not seem right.

Much like with the CDC and FDA definitions, the WHO definition is given on a public-facing resource. It is understandable that the side effects we are most concerned about are those that occur in clinical settings at whatever 'normal' doses are specified by current clinical guidelines. These are where common everyday risks are most apparent and where most decisions are made about side effects. As with the CDC and FDA definitions, the WHO definition blurs the context of warning people about medication risks and the context of defining what a side effect is. Regardless, if we take the CDC, FDA, and WHO definitions to give conditions for what counts as a side effect, then there are straightforward counterexamples. Moreover, as above, it is probably not the case drug researchers hunting for side effects are looking *exclusively* for adverse side effects, though those might be important. Phase I researchers do look for side effects as well, even when 'normal dose' is not yet established. So, it would not be right to say these definitions are adequate for describing the side effect discovery process either.

Other definitions of 'side effect' include 'secondary' effects, 'unwanted' effects (e.g., Bresso et al., 2013), or 'all the unintended effects of an intervention' (Aronson & Ferner, 2005). Firstly, we could ask if 'secondary' is synonymous with 'unintended.' It does not seem like it must be so. However, a short example illustrates that when

discussing side effects, 'secondary' probably does mean 'unintended': 'Secondary' might not mean 'unintended' if it picks out the numerically distinct effects I intend in a treatment. I could intend two effects in taking some drug, and I could call the first intended effect the 'primary' effect, and the other the 'secondary' intended effect. In that case, we might say there are also possibly 'tertiary' effects when I intend three things. However, I think this example demonstrates that pointing out numerically distinct effects is just not what we commonly mean when talking about side effects as 'secondary.' Considering this, moving forward I will assume that 'secondary' in the context of side effects is synonymous with 'unintended.'

Are side effects necessarily 'unwanted'? Again, it is often the case that 'side effect' has a negative connotation, but beneficial side effects are well-known. As I will explain in Sect. 3, there might be beneficial effects of a drug that are foreseen but bringing about these foreseen effects is not *the reason why* the drug was taken. In that case, the foreseen beneficial effect is still a side effect. For example, one might take finasteride for their benign prostatic hyperplasia and foresee hair growth as a beneficial possibility without hair growth being *why* the finasteride was taken. So, to say side effects must be 'unwanted' is not quite right either.

Finally, are side effects 'all the unintended effects of an intervention'? Broadly, I think this definition points us in the right direction though it is at best incomplete. Depending on how we understand 'unintended' and 'effect' we could arrive at problematic definitions. For example, say I have a headache and take an aspirin. Say that my headache gets better, so I am in a better mood. In a better mood I leave the house to visit some friends, but I then get hit by a car. Being hit by the car was unforeseen and not something I intended in taking the aspirin. A naïve causal understanding of 'effect' might claim that since taking the pill caused me to leave the house, and leaving the house caused me to get hit by the car, getting hit by the car was an effect of taking the pill. This example shows us that an account of side effects must specify what kind of effect a side effect must be. I assume we want to say 'getting hit by a car' is not actually a possible side effect of aspirin. In response I will show that not all events that are unintended and causally downstream of an intervention are side effects. The WHO definition sheds light on how this could be done, claiming that side effects must be due to 'pharmacological properties.' But, how do we know that an effect is due to the pharmacological properties of a drug? Moreover, what does it mean to say that some effect is 'unintended'? If we can specify (i) what is meant by 'unintended' and (ii) give an account of which downstream events after taking a drug are actually caused by the drug, we can have a robust technical definition of side effects as 'the unintended effects of an intervention' that avoids the discussed counterexamples and better describes drug research. This specification of (i) and (ii) follows.

3 Condition (i): side effects are unintended

3.1 Intended v. unintended

The first condition of the offered definition of 'side effects' is that they are unintended. In this section I explain what that could mean and, importantly, what is entailed. Let's start with a simple example: if you take an aspirin to relieve a headache, and headache relief follows, that is the *intended* effect. However, imagine that after you take the aspirin for your headache, you develop a rash. Aspirin does sometimes cause rashes, but let's say you did not know that. So, you could not have intended the rash. The rash is unintended and, intuitively, that is what seems to make it a side effect. But what does it mean to say you did not intend the rash? I think to say that the rash is unintended is just to say that 'causing the rash' was not among the reasons why you took the aspirin. We can say that what makes some effect unintended is that bringing about that effect was not among the reasons why you took the drug. This means when you take the aspirin with the sole intended effect of headache relief, the non-headache-relief effects[7] like the rash that follow are unintended; they are side effects. This also means that when you take the aspirin solely intended for headache relief, blood-thinning (another actual effect of aspirin) is not among the reasons why you took the aspirin and is therefore a side effect. Intentions belong to agents or users, and users can have different intentional relationships to the same event, e.g., the outcomes from taking an aspirin. Imagine that you have a friend who takes aspirin for its blood-thinning properties. In your friend's case, blood-thinning is not a side effect, since bringing about or causing blood-thinning is the reason why your friend takes aspirin. In your case, blood-thinning was unintended, i.e., was not the reason why you took the aspirin. But in your friend's case, blood-thinning was intended, i.e., was not a side effect. You both bear different intentional relationships to aspirin-caused blood-thinning. If you take the aspirin intending headache relief and blood-thinning concurrently, neither are side effects because neither are unintended. Because side effects are unintended, when different people have different intentional relationships to an event, it could be intended (or unintended) by one and not by another. The unintended nature of side effects entails they are fundamentally relative to *users* and *uses*.

Moreover, the intentional relationship to some effect can differ between a prescriber and patient. Say some pill *P* has two well-known effects, *PE1* and *PE2*. Imagine a case where a patient wants *P* for *PE2* but knows their clinician will probably only prescribe *P* for *PE1*. That patient might approach their clinician seeking *P* under the false pretenses of wanting to bring about *PE1*. In this case, because of the unintended nature of side effects, *PE1* would be the side effect of taking *P* for the patient and *PE2* would be the patient's intended effect. For the clinician, in contrast, *PE1* would be the intended effect and *PE2* would be the side effect. Additionally, pharmaceutical companies intend particular indications for their drugs. If a drug is approved and marketed as a painkiller, reducing pain is its intended use from the perspective of the drug company. Whether or not the intentional relationship is the same between

[7] As specified in Sect. 4, 'effects' here are the effects caused by the causal capacities of the aspirin.

a pharmaceutical company, whoever gives the drug, and whoever takes the drug will change case-by-case.[8]

We might think it is odd to call blood-thinning a side effect since it is one of the most common reasons why aspirin is taken. This is odd only if we fail to see that the possible side effects we want to warn people about, i.e., the side effects we commonly list in pamphlets or communicate when discussing treatment risks, are different than the conditions by which something is a side effect in the first place. As above, these two contexts are different. The contexts of warning people about the possible harms that can come about from a drug or educating people about what a drug is effective for are different than the context of defining side effects. As I will discuss later, I think discussing 'side effects' highlights an interesting tension between these contexts, specifically that 'technical precision' may function differently as a desideratum in each context.

Since side effects are unintended, I cannot intend a side effect. If I intend some effect from a drug, i.e., bringing it about or causing it is among the reasons why I take the drug, it is intended. And since side effects are unintended, that effect being among the reasons why I took the drug means the effect is not a side effect. At first this might seem strange. Aren't some drugs taken *because of* their side effects? In cases like these, given the account presented, we can see what people mean when they say they 'take a drug for its side effects' is that they take the drug for reasons that are either (1) not the same reasons as most other people who take that drug as recommended by their physicians or (2) reasons outside causing those effects the drug was market-approved for. If side effects are necessarily unintended, that means in cases (1) and (2) the speaker is misusing the word 'side effect' in a strictly technical sense. Notice that this is not just the case for the definition of side effects I offer here. If people take drugs for beneficial side effects, this violates the CDC and FDA definitions of side effects as 'adverse,' it violates the WHO definition in that side effects are unintended, and violates the idea that side effects are somehow essentially 'secondary' or 'unwanted.' In that case I will maintain, strictly speaking, that one cannot intend a side effect. When one 'takes a pill for its side effects' those effects are not side effects for the person taking the pill, but they might be side effects from the perspective of a prescriber or regulatory body. It is not the most felicitous use of the term 'side effect' given side effects being inherently unintended, but we still know what someone means when they say it. It is not *false* that someone 'takes a pill for its side effects,' it is just a misunderstanding of whose intentions matter in determining what side effects are.[9] The account I offer here is the only one that can 'make sense' of such a case.

That side effects are inherently relative may seem a little strange, though I think this is just what is entailed by side effects being inherently unintended. One could try

[8] In the case of the patient and the prescriber, we might imagine 'side effects' could be a metric for success in shared-decision making, insofar as shared intentions between parties. If an effect arises that is a side effect for one party and not the other, that would indicate the intentions between parties were not shared at the outset of giving/taking some medication.

[9] Granted, the technical account presented here does entail that the claim 'I take a drug for its side effects' is not *straightforwardly* true. Insofar as that is the case, it may serve as a counterexample to the presented account similarly to how it is a counterexample to the FDA, CDC, and WHO definitions.

to prevent this relativity of 'side effect' by arguing that the only intention that matters is the intention of drug regulators.[10] The intentions of patients and prescribers would have no bearing on which effect of a pill was a side effect. However, this only pushes back the problem of the relativity of side effects. Drug regulation changes from country to country. Drugs that are legal in some countries are illegal in others, and drugs are approved for different indications in different countries as well. Consider the case of pemoline, a stimulant used to treat ADHD that was withdrawn from the US in 2005. After its withdrawal in the US, it was still available in Japan as a narcolepsy treatment (Shrader, 2017). In the US, not only was the use of pemoline withdrawn, but treating narcolepsy would be a side effect, where in Japan it was the intended effect. The relativity of 'side effect' is inherent given the inclusion of intention as a criterion.[11]

One might still ask why we ought to include *patient* intentions in the definition of side effect. I do think that it is important to include patient intentions in determining side effects other than just for the fact that relativity seems inescapable. Consider a case where someone is taking a drug that was not prescribed by a health care practitioner like in 'over the counter' (OTC) cases or cases where a therapeutic drug is not approved by a regulatory body. St. John's Wort is not regulated as a therapeutic drug, yet some people take it for their depression. In those cases where it is taken for treating depression alone, are photosensitivity, insomnia, dizziness, diarrhea, etc. caused by St. John's Wort *not* side effects? I think it would be strange to say they are not. I think including patient intentions is necessary, because a patient or patients seem to be minimally necessary for making something a therapeutic intervention in the first place. One might respond that the St. John's Wort case is not strictly speaking a therapeutic intervention. Though, admittedly, that may rest on a particular definition of 'therapeutic' or 'medical' which is beyond my scope to address here.

3.2 Unintended, not unintentional

Positing that side effects are *unintended* is not necessarily the same as saying that side effects are *unintentional*. And, if we want to be clear on what it means that side effects are 'unintended,' this distinction is worth understanding. Firstly, 'unintended' can either mean 'intending to not x' or 'not intending to x', and it is the latter sense in which I mean 'unintended' moving forward.[12] Secondly, that some effect *E* is intentional only when *E* is among the things I intend is often called the 'simple view' of intention. I might only intend pain relief in taking an aspirin on the simple view, and on the simple view only pain relief occurs intentionally. However, there are challenges to the simple view. Michael Bratman (1984) posits that what is intentionally done is not constrained by what is intended. Instead, if you intend *E*, and while

[10] My thanks to an anonymous reviewer for this helpful case, which further illustrates the inescapability of side effects' relativity when 'being unintended' is a core component of the definition.

[11] One might worry that this outcome will prevent any possible litigation around drug side effects. I am skeptical of this, however, as I am hesitant to posit that litigation is completely powerless in determining intentions around particular actions in case-by-case scenarios.

[12] My thanks to an anonymous review for highlighting this.

bringing about E another effect E_1 occurs that is necessary for bringing about E, then E_1 occurs intentionally (1984, p. 378).[13] Bratman uses the example of jogging: the wearing down of my shoes (E_1) is not among the things I intended when deciding to go for a jog (E), though the wearing down of my shoes might still be done intentionally. On this challenge to the simple view, if I solely intend the aspirin to alleviate my headache (E) but knew that blood-thinning (E_1) causes my headache to be relieved, blood-thinning might be intentionally done even if it was not among the things I intended, i.e., my reasons behind taking the aspirin.

I do not aim to defend the simple view here. Rather, I contend that the first condition (i) of the posited account I propose solely concerns the reasons for taking a drug. In other words, even if on Bratman's view blood-thinning is intentional, it remains correct to say that blood-thinning was not among the things I intended. If one *assumes* the simple view, blood-thinning is unintended, and is unintentionally done. If one *rejects* the simple view, blood-thinning was not among the things I intended – i.e., unintended – even if the blood-thinning is intentional. Regardless of the unintent*ional* status of blood thinning, it remains unintend*ed*. One can adopt the presented account of side effects regardless of one's position on the simple view. Something being unintended is meant to reflect something only about the reasons behind taking a medication.

3.3 Decisions and side effects

One can ask if side effects really do not play a reason behind my taking a drug. Consider a case where I am presented with two different drugs to treat some illness. Drug A has minor possible side effects, and drug B has more severe possible side effects. Is it not the case that when I pick A over B, something about the side effects of B plays into the reasons behind taking A? If so, it might not be right to say that side effects must be the effects that were not included in the reasons behind taking some drug. One might say that by picking A over B I am choosing to take something because of the possible side effects it brings about or picking a less intense combination of possible side effects over the other.

One response is that 'reasons for taking A' are different than 'reasons for taking A instead of B.' In the latter case, it is avoiding the possible side effects of B that are my reasons. B's side effects do play a role as reason for my action, but that reason is not to bring them about.[14] My second response is that even in picking A because of its less severe side effects, this is different than intending whatever side effects might occur by taking A. Say I take a drug intending to treat an illness. If the therapeutic effect from the drug does not occur, something has gone 'wrong'. My intentions have been foiled, by whatever means. If I pick drug A because it has less severe possible side effects, and then those side effects do not occur, has anything about my intention been foiled? It does not seem so. Even in weighing different treatment options because of possible side effects, choosing a drug because of its less severe side effects

[13] Bratman discusses this formalization of the challenge to the simple view while speaking of 'actions' rather than 'effects,' I have switched these to match the context more clearly.

[14] My thanks to a reviewer for highlighting this as a possible response.

is different than intending those effects to come about. Thus, if they do arise, they are still (or can be) unintended and remain side effects.

Before moving on to the second condition of side effects, a summary of the above is useful. The first condition of side effects is that they are unintended. This means that the effects that come about that were not the reason why you took a pill are side effects. Since intentional relationships can differ between people, the same effect might be a side effect for some, and not for others. You cannot intend a side effect, since once an effect is intended, it is no longer unintended due to your intentional relationship to the effect. Regardless of one's position on the 'simple view' of intention, side effects remain unintended. Finally, in considering different treatments, having 'less severe possible side effects' be a reason behind a decision is different than intending those effects. Therefore, I take it an address of condition (i) is offered. Notice that condition (i) is alone insufficient to call something a side effect. Consider again the car accident after taking aspirin case. I did not intend getting hit by a car as a downstream effect of taking the aspirin. This might fit condition (i) but is intuitively not a side effect. So, we now need to explain the second condition (ii) of what makes an effect a side effect.

4 Condition (ii): what effects can (or can't) be side effects?

Where condition (i) posits that side effects are essentially unintended, condition (ii) addresses that side effects must be a certain kind of effect. Effects come from causes, so determining which cause-effect relationship produces side effects is necessary. Think back to the aspirin-rash example. You took the pill, and then experienced a rash. If the rash was caused by the aspirin and unintended, the rash was a side effect. So, we can initially posit that the effects that can count as side effects are those effects caused by the intervention.[15] However, not all things that occur downstream of an intervention are side effects. We intuitively would say that getting hit by the car is not an effect of the aspirin. To explain this in the context of pharmaceutical side effects, I appeal to a manipulationist model of causation explicated by James Woodward (2003). In what follows I present a model of side effects as effects that arise from the causal capacities or invariances of an intervention. This model allows us to understand condition (ii), which when paired with condition (i) gives us a technical and robust definition of side effects that avoids the problems with the other presented definitions of side effect.

4.1 Modeling side effects

Figure 1 is a simple causal model of a medical intervention. Causal models allow us to describe the relations, regularities, and influence of causally related variables (Hitchcock, 2009). Let me first describe the model and then explain how it relates to the second condition of the presented account of side effects.

[15] One might say that this is caused by the intervening, not the intervention. I make a distinction later in Sect. 5 that explains the difference and why the use of 'intervention' is proper here.

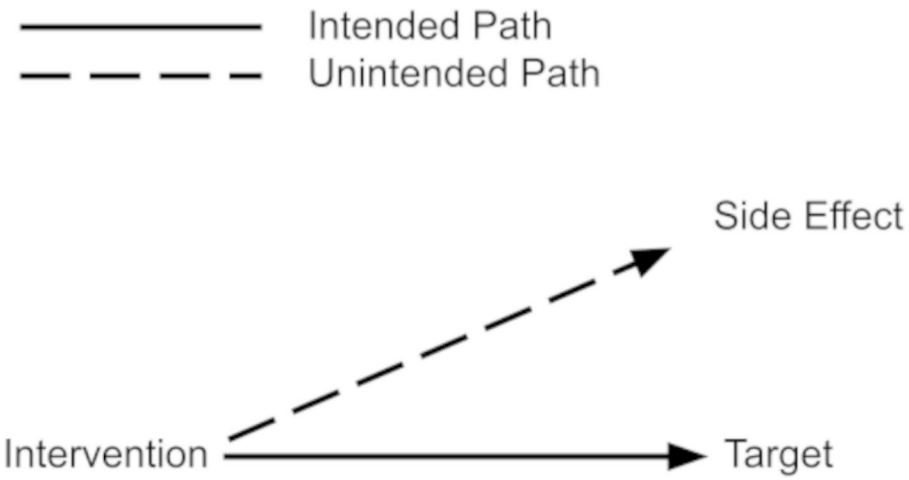

Fig. 1 Side effect causal model

There are two different kinds of causal pathways on Fig. 1. There is firstly a causal pathway going from the intervention to the target of the intervention. In the aspirin case, the target of the intervention can be your headache when you take the aspirin for headache relief alone. You take the aspirin (the intervention) with the intent of relieving your headache (the target). The causal pathway from the intervention to the target is the intended causal pathway, since the target is your intended effect, i.e., why you took the aspirin. If you take aspirin for things in addition to headache relief, those are also included in the target. The other causal pathway goes from the intervention to the side effect. These are the unintended things the intervention causes. What this model shows is that side effects arise in cases where interventions are not precise or 'surgical.' Surgical interventions (not in the sense of medical surgery) are those in which no causal paths outside the intended causal paths are manipulated (Woodward, 2003). 'Surgical' interventions are those where only the variables intended to be varied are varied. And, since pharmaceutical interventions rarely only affect the intended variables, it is likely there are numerous benign side effects that occur without our noticing. A pharmaceutical intervention causes a plurality of effects within the body, depending on its metabolization. Some of these may manifest into *noticeable* side effects, and many will go without notice or are 'neutral' side effects that we do not posit as plainly 'good' or 'bad.' Side effects can be plainly neutral or benign.

In short, the candidate cause-effect relationships that produce side effects are the 'aspirin plus effects from the causal capacities of aspirin' types of relationships. However, how do we know which of the phenomena that follow taking an aspirin are effects due to the causal capacities of aspirin?[16] If this cannot be accounted for, then

[16] We do possess clinical tools to help determine if an effect was caused by a drug, e.g., the Naranjo Algorithm. The Naranjo Algorithm gives some probability that an effect was caused by the drug, based on factors like if the side effect stops when the patient stops taking the drug, and if the side effect comes back upon resuming drug use. Bradford Hill criteria also allow us to posit if some suspected effect is actually an effect of some cause, as would biomechanistic information, though that might not be available in clinical settings. Why something like the Naranjo Algorithm works, I posit, has to do with how side effects come about from the causal capacities of interventions.

the proposed cause-effect relation that constitutes the second condition of side effects is vague.

4.2 Manipulation and effects

Consider again the example where I get hit by a car after taking aspirin to treat my headache. This is a downstream, unintended event that occurs after I take the aspirin. We intuitively do not want to call this a side effect of aspirin. In giving an account to justify this intuition by relying on a manipulationist model of causation, the cause-effect relationship that constitutes the second condition of the presented account becomes explicit.

Using a manipulationist conception of causation gives us one way[17] to solve this problem. We can look at a similar case discussed by Woodward (2003). Consider the case where a dog bites off my right forefinger, which I was going to use to detonate a bomb.[18] The next day, I detonate the bomb with my left forefinger instead. If I had not lost my right finger, I would have used the right finger to detonate the bomb. The bite causes me to use my left finger instead, which causes the bomb to explode. It seems strange to say the bite caused the explosion. Woodward unpacks this by assigning three variables to the dog bite problem: *B* specifying if the bite occurs or not, *L* specifying if the left ring finger is used, right finger is used, or the button was not pressed, and *E* specifying if the bomb explodes or not. Woodward says that there is a causal path in the example from *B* to *L* to *E*, but we can posit that *B* does not cause *E*:

> "The changes in the value of *L* on which the value of *E* depends are completely different from the changes in the value of *L* that are influenced by the value of *B*, so that there is no overall sensitivity of the value of *E* to the value of *B* along the only route connecting *B* to *E*: manipulating the value of *B* does not change the value of *E*. I believe that it is this fact…that makes us judge that *B* does not cause *E*…" (2003, 57–59).

The dog bite does not manipulate the explosion, so the explosion was not a causal effect of the bite. This exemplifies a core tenet of a manipulationist theory of causation: there is no causal difference without a difference in manipulability relations, and there is no difference in manipulability relations without a causal difference (Woodward, 2003, p. 61). The manipulation of *B* values does not change *E* values, so *B* does not cause *E*.

This approach gives us a way to show how my being hit by a car is not even an effect of aspirin in the first place (placating our intuitions) and thus is not a side effect. Mirroring the dog bite case, there is a path from the aspirin to the car hitting me. Along that path is the alleviation of my headache and my leaving the house. I might represent taking the aspirin as a variable *A*, the alleviation of my headache and leaving the house as *H* and getting hit by the car as *C*. *A* has two values, that (0) I take the

[17] I do not take it that a manipulationist theory of causation is the only theory that can get around these kinds of concerns.

[18] This example is originally from M. McDermott (1995).

aspirin or (1) that I do not take the aspirin. *H* has four values, that (0) my headache does get better and I do not leave the house, (1) my headache does get better and I do leave the house, (2) my headache does not get better and I do not leave the house, and (3) my headache does not get better and I do leave the house. *C* has two values, (0) I get hit by the car and (1) I do not get hit by the car. If we can show that a manipulation of *A* does not change *C* values, that means that *A* does not cause *C*. If *A* is set to (0) and *H* is set to (0), then *C* is (1). If *A* is set to (0) and *H* is set to (1), then *C* is (0). If *A* is set to (1) and *H* is set to (2), then *C* is (1). If *A* is set to (1) and *H* is set to (3), then *C* is (0). So, the value of *A* can be either (0) or (1) and have no determination on the value of *C*. The manipulation of the *A* values does not change the *C* values, so *A* does not cause *C*. Getting hit by the car was not caused by my taking the aspirin, thus it is not properly a side effect.

Woodward (2003) discusses the role invariance plays in establishing cause and effect. If the causal relationship between two variables is sensitive to context, then whichever variable is antecedent is a poor causal explanation for the consequent. The relationship between *A* and *C* is not invariant; contextual details could differ and the relation would not hold. The relation between *A* and *C* is overly sensitive. Woodward further mentions that when relationships are invariant and stable, this can indicate an object's causal capacities (2003, p. 313). 'Capacities' here refers to the power of something to produce certain effects. This is how we usually think about aspirin; aspirin has the capacity to relieve headaches, to thin blood, cause rashes and rare allergic reactions. Aspirin does not have the capacity to cause me to get hit by cars as demonstrated by the manipulationist response. Philosophers also often think about reliable cause-effect production in terms of mechanisms. Mechanisms are the entities and activities that underlie phenomena and produce regular behavior (Machamer et al., 2000) and this regular behavior can be explained in terms of *ceteris paribus* laws (Cartwright et al., 2020). There is no ceteris paribus law or mechanism in the aspirin-car example. Any one that could be constructed here would be overly variant on the manipulationist picture.

With condition (ii) above, we now have a robust account of side effects. What makes something a side effect is that it (i) is unintended and (ii) is an effect caused by the capacities or invariances of the intervention. Are these discussions of what it means for something to be 'unintended' and an 'effect' the only ways to meet these conditions? I do not assume so. One might be averse to a manipulationist theory of causation, but still be able to determine effects from non-effects of an intervention by whatever means. Whatever we posit as sufficient for determining side effects, it will have to address both the reasons behind interventions and what downstream events are actually the effects of an intervention.

5 Applications

5.1 Events, effects, and expectations

Given the presented account of side effects, we can distinguish side effects from other treatment outcomes. The standard measure of harm in clinical trials is the 'adverse

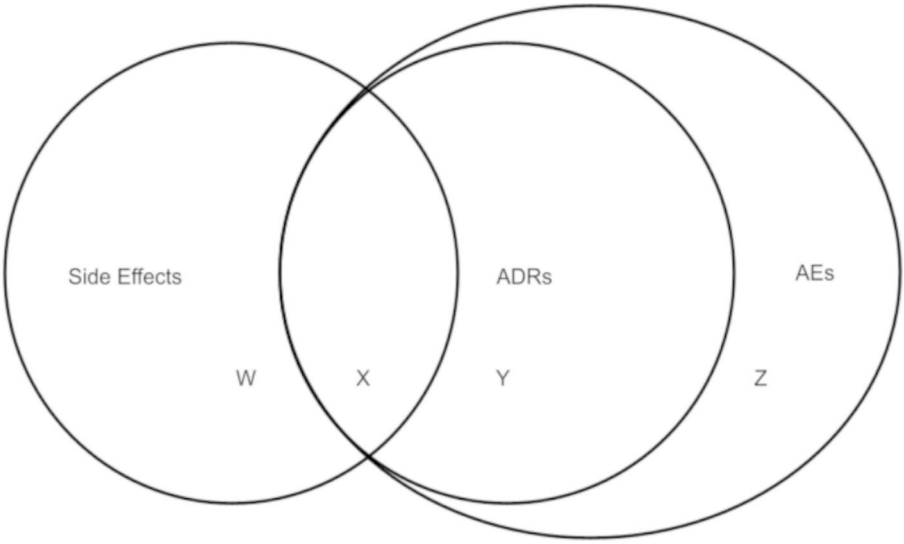

Fig. 2 Proposed relation of side effects, adverse drug reactions (ADRs), and adverse events (AEs)

event.' Adverse events are often defined as injuries related to medical management or care (Jung et al., 2019). Adverse events include a variety of things, ranging from transport errors, wrong-patient operations, technical and skill-based errors, and emergency room re-admittance before set time thresholds (Forster et al., 2007; Thomas et al., 2000; Ferner & Aronson, 2006). Adverse events, therefore, are not necessarily due to an intervention's capacities. Furthermore, not all side effects are adverse. Adverse events and side effects are related, but distinct concepts.

Another related outcome is the 'adverse drug reaction' or 'adverse drug effect.' Adverse reactions are a subset of adverse events that are attributable to a medication's causal powers (Ferner & Aronson, 2006). The unwanted rash you receive after taking aspirin is an adverse drug reaction. Like adverse events, adverse drug reactions are adverse. As above, not all side effects are adverse. Moreover, side effects are necessarily unintended. Adverse drug reactions, theoretically, can be brought about intentionally. In other words, something that conceptually distinguishes side effects from adverse drug reactions – i.e., what makes them not plainly interchangeable – is that I *cannot* intend a side effect and I *can* intend an adverse drug reaction. Say that I know some medication has a common adverse effect. I can take or give that medication intending to bring about that adverse reaction, say poisoning, perhaps maliciously or to trick someone. However, when I intend to bring about an adverse drug reaction, it is not a side effect. As soon as one intends an effect, it is not an unintended effect and thus not a side effect. In short, side effects are conceptually distinct from adverse events and adverse drug reactions firstly on the grounds that side effects need not be adverse, and secondly on the grounds that side effects cannot be intended. A concrete way to think about the relation between side effects, adverse events, and adverse drug reactions is Fig. 2.

Figure 2 shows a relationship of side effects to adverse drug reactions and adverse events based on the presented account. Recall that side effects as I explain them here are unintended and effects from the causal capacities of the intervention. Adverse drug reactions are also actual effects from the intervention, but can be intended and are necessarily adverse. Adverse events are adverse things that happen to patients under care that are not necessarily due to the causal capacities of some intervention. With that in mind, notice that there are four categories or sets of membership in the diagram: W, X, Y, and Z. Things in category Z are things that are strictly adverse events, these include examples above like wrong-patient operations or re-admittance to emergency rooms before set time thresholds. Adverse drug reactions are a subset of adverse events, and things in category Y are adverse, intended, happen under medical care, and are due to a therapy's causal capacities. In other words, things in category Y are intentionally brought about adverse drug reactions. This would be something like the malicious poisoning case above. Though these occurrences are (thankfully) rare under clinical care, that does not preclude the existence or possibility of this category. Things in category X are adverse drug reactions that are unintended, that is, adverse side effects. There can be overlap between adverse drug reactions and side effects when the side effect is adverse or the adverse drug reaction is unintended. X is where most adverse drug reactions exist, but not necessarily where most side effects exist, since benign or neutral side effects (in category W) likely outnumber adverse side effects.

Category X is comprised of the things we are also likely most concerned about in medicine, which is why the CDC and FDA definitions of 'side effect' describe category X. That is not to say adverse events in category Z are of no concern to researchers; these are often explicitly measured in trials.[19] The CDC and FDA definitions do not allow for an analysis about the differences between the categories in Fig. 2. As mentioned before, pointing out the side effects we are concerned with is different than defining what side effects are in general. Finally, things in category W are side effects that are not adverse in virtue of having no overlap with adverse drug reactions and adverse events. This includes beneficial side effects like the case of finasteride and hair growth above, or the numerous unnoticed or 'neutral' side effects that occur as effects of the drug in and on the body. Even though most of the harms we care about in medical care probably fall under category X, which is the overlap category of side effects and adverse drug reactions, it is wrong to assume without qualification that adverse drug reactions and side effects are interchangeable and point out the same phenomena. Though they have overlap in X, they are conceptually distinct concepts insofar as side effects need not be adverse and cannot be intended, and neither of those conditions necessarily apply to adverse drug reactions. Moreover, it is not just things in category X that are monitored for in pharmacovigilance, though monitoring for adverse side effects is a primary function. We can (and do) look for positive side effects of drugs. In that case, the account I offer here does a better job describing all the kinds of things monitored for in drug research.

It is also worth pointing out that given the account of side effects presented, we can also distinguish side effects from another possible treatment outcome: placebo

[19] My thanks to an anonymous reviewer highlighting the need to include this.

effects. Side effects have been defined with two conditions: they are (i) unintended and (ii) effects due to the causal capacities or invariances of a drug. Placebo effects, on the other hand, are thought to arise from expectation or conditioning mechanisms (Friesen, 2020). It is not something about the drug itself, but something about the act of being intervened upon in a medical setting that brings about placebo effects. In that sense, I make a distinction between *interventions* (aspirin) and *intervenings* (taking an aspirin in a medical setting). Side effects arise because of interventions, where placebo effects arise from intervenings.[20] It is the intervening in a psychosocial context, not the causal capacities of some intervention, that causes placebo effects. Even in contexts where a pill's color influences a placebo effect, that is less about the intervention and more about the psychosocial context and conditioning. The difference is therefore a difference in the second condition of side effects, namely, the cause-effect relationship that produces side effects. Side effects must arise from the capacities or invariances of something like a drug. There is also a difference in the first component, as a physician might intend a placebo effect, further precluding overlap with side effects since side effects are unintended.[21] Unintended placebo effects are not side effects on this account since they do not arise from the capacities of the intervention but are from the context of intervening. Regarding Fig. 2, We might add 'nocebo effects' as intersecting with category Z. Placebo effects would not intersect with W, X, Y, or Z as described. Side effects, adverse events, adverse reactions, and placebo effects are all related notions, and the presented account of side effects can clearly distinguish them.

5.2 Revisiting the CDC, FDA, and WHO definitions

With the presented account of side effects, we can see where and why the received definitions went wrong. The CDC and FDA definitions are too restrictive in precluding positive or neutral side effects. Furthermore, the CDC and FDA definitions fail to include the first component, that side effects are tied to the reasons behind an inter-

[20] This line might be blurry considering an interpretation of the biopsychosocial model of health where medical interventions are not 'merely' biomedical. My response is that on such an interpretation of the biopsychosocial model of health, interventions can have biopsychosocial properties. If that is the case, the conditions here for side effects still work. Side effects would still be unintended, and effects of a particular cause. That cause would just be a biopsychosocial cause, and those effects would be those invariant or from the capacities of the cause. Moreover, on the biopsychosocial model I still assume we can make a distinction between biophysical and psychosocial mechanisms of action. In that case, we would still have clear cases of side effects that are not due to psychosocial mechanisms like expectation or conditioning that underlie placebo effects. That is not to say there would not be 'gray' areas. Given those gray areas, conditions (i) and (ii) might no longer be taken as a sufficient condition of side effects, but they will remain necessary.

[21] Consider a case where there is an unintended placebo effect in the case of psychotherapy. Is this a side effect since in a case like this, the intervention and intervenings line is quite blurry? I would argue no. Psychotherapy acts on psychosocial mechanisms, and psychosocial mechanisms are at fault for placebo effects, but we cannot assume that these are the same mechanisms. The mechanisms underlying something like cognitive-behavioral therapy (CBT) might not be identical to the mechanisms that underlie placebo effects. In that case, there is still the causal capacities/invariance of the intervention (CBT) and then the broader psychosocial context of intervening via CBT that could cause unintended placebo or nocebo effects. My thanks to a reviewer for encouraging me to consider such a case.

vention. Something that the CDC and FDA get right is that, on a generous reading, we can interpret 'adverse reaction' as a reaction that comes from the capacities of whatever intervention we have in mind. So, there is a kernel of truth in these definitions, but there are clear counterexamples and shortcomings. Importantly, the model here that addresses both conditions of side effects can show where and why those shortcomings arise.

The WHO definition does include that side effects are unintended, but without an account of what 'unintended' means like the one provided in Sect. 3, determining which effects are side effects is still vague. This is also the case with the common definition of side effects as 'secondary' or just 'all the unintended effects of an intervention,' which can run into issues considering condition (ii). The WHO account is also too restrictive on what cause-effect relationships produce side effects. On the WHO account, taking aspirin does not cause side effects when the dosage of aspirin falls outside some pre-determined dosage. This precludes side effects in instances like the St. John's Wort case, or within therapeutic contexts where 'normal dose' is undetermined. These needless qualifications are not included in condition (ii) presented in Sect. 4. Moreover, when it comes to drug research that looks for side effects, the accounts given by the CDC, FDA, and WHO are not descriptive of what effects might be monitored for. Granted, the contexts in which the health authority definitions are given are public facing, not necessarily driving research. However, given the ubiquity of conflating side effects and adverse effects in drug research, this is still something to consider. The proposed definition does a better job of mapping onto what drug researchers do look for in looking for and confirming side effects: things both good and bad that are actually (or suspectedly) caused by the drug and unforeseen (and likely unintended in whatever experiment or trial is operating).

One possibly strange outcome of the model of side effects presented here is that *death* is a possible side effect for just about every single drug. If one takes too much aspirin, death is possible, and it would be correct on my account to call 'unintended death' a side effect. The same follows for 'no therapeutic change' occurring as a side effect if one takes a miniscule dose and intends therapeutic change. On this account, anything caused by the intervention that is unintended, even if unnoticeable by the patient or physician, counts as a side effect.[22] However, these are not the kinds of cases physicians and patients typically have in mind in day-to-day treatments. When patients are concerned with safety, they likely do not care about the banal effects like those that occur through drug metabolization but instead want to know about anything potentially harmful (things in X in Fig. 2). This, likely, is why the CDC, FDA, and WHO definitions are what they are. These definitions care less about what a side effect is, and more about the kinds of things to keep an eye out for. My offered account here does show where these definitions go wrong, but also offers a justification for them being what they are (i.e., warning about things in X on Fig. 2).

[22] I do not think these are tantamount to counterexamples, as they do not contradict the model presented. For example, with the 'side effects are adverse effects' definition, we can plainly say, "No they aren't, look at the positive side effects of finasteride." This is different than an intuition that it is odd that 'death' is a side effect of all drugs. We know drugs can have fatal side effects. There's nothing contradictory in saying 'death' can be a side effect of (foreseeably) any drug like there is in using finasteride's positive side effect of 'hair growth' to prove 'side effects are adverse effects' is false.

One might infer this means 'technical precision' of definitions is something that is a desideratum in terms of theory, but maybe not for other goals. When it comes to wanting to warn people about harmful drug effects, maybe 'adverse effects' is a sufficient way to communicate about side effects. But, if 'technical precision' is a desideratum in theoretical contexts, is it right to say it is not a desideratum, to some degree, in other contexts like public education?[23] I do not think so. We cannot advocate for *imprecise* definitions. Precision – to some degree – remains a desideratum around educating the public about concepts, though one may be less 'weighty' than in the purely theoretical context. That being so, I do not think my definition presented here is too technical for public education. Side effects just are the things a pill causes that you did not explicitly take that pill for. They can be good, they can be bad, and you might not even notice them at all.

Before moving on, it is worth highlighting that research done with incomplete definitions may have detrimental concrete outcomes. Research strictly assuming the CDC or FDA definitions would only focus on adverse reactions and might fail to measure or notice beneficial unforeseen effects. Research strictly assuming the WHO definition would look for side effects when normal doses are not set. Does my offered account fix these possible problems? It could, yes. However, it just *is the case* that pharmacovigilance and drug research in general *does* look for or monitor non-adverse effects in addition to adverse effects and is not tied to 'normal' dose, e.g., phase I trials. I contend that my offered account better describes the ongoing process of drug research than the other accounts discussed insofar as where and how side effects are monitored for.

5.3 Reflecting on the utility of 'side effect' as a term in medical research

Before closing, let me address a final feature highlighted by my account. 'Side effect' covers a large set of things that occur after taking a pill, most of which go by without notice. Considering something similar to this, some have argued that we ought not use 'side effect' as a technical term in medical practice and research that looks for adverse drug reactions (Aronson & Ferner, 2005; Ferner & Aronson, 2006; Edwards & Aronson, 2000; Aronson, 2012). This argument says that when it comes to safety we are more concerned with things that are plainly adverse and effects of some drug, e.g., the kinds of things in category X in Fig. 2 that we could call either 'adverse side effects' or 'unintended adverse drug reactions.' So, we can see that 'side effect' might be needlessly broad when discussing the research on drug harms. Thus, one might say that we can eliminate 'side effect' completely when specifying an adverse reaction as an 'unintended adverse drug reaction.'

However, someone who disagrees might respond that we should eliminate 'unintended adverse drug reaction' when we specify that effect is an 'adverse side effect.' The term 'side effect' is ubiquitous as a colloquial term in medicine (Britten, 2012, p. 574). My purpose here is not to advocate for using 'negative side effect' over 'unintended adverse drug reaction,' or to say why 'side effect' remains an important term for contemporary medicine and medical research. Any such argument may sup-

[23] My thanks to an anonymous reviewer for recommending addressing this.

pose the analysis here, but it is beyond the analysis here to argue for such a claim. I will say that 'unintended adverse drug reaction' and 'negative side effect' pick out the same kinds of things in the world, i.e., things in category X in Fig. 2. And, as we know from the discussion of conceptual analyses from Lemoine (2013), we must go beyond conceptual analysis to select between competing accounts like these. My purpose here has only been to offer a technical answer to the title of this paper considering the counterexamples and ambiguities with existing definitions.

6 Conclusion

By examining the issues with existing definitions of 'side effect,' I offer a technical account that, among other things, avoids those issues. I argued that side effects are (i) unintended and (ii) the effects from the causal capacities or invariances of an intervention. Condition (i) was explained as related to the reasons behind an intervention. Condition (ii) requires that we are able to determine which downstream occurrences after an intervention are causal effects of that intervention. With this definition in mind, we can cleanly distinguish side effects from other kinds of therapeutic intervention outcomes like adverse events, adverse drug reactions, and placebo effects. The account highlights why adverse drug reactions and side effects are often thought to be interchangeable, though this is mistaken. The account here also better maps onto contemporary drug research. Moreover, the account presented allows for reflection about the utility of 'side effect' as a technical term in medical research.

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