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S.I.: MEDICAL KNOWLEDGE

Philosophers on drugs

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Abstract There are some philosophical questions that can be answered without attention to the social context in which evidence is produced and distributed. Abstracting away from social context is an excellent way to ignore messy details and lay bare the underlying structure of the limits of inference. Idealization is entirely appropriate when one is essentially asking: In the best of all possible worlds, what am I entitled to infer? Yet, philosophers' concerns often go beyond this domain. As an example I examine the debate on mechanistic evidence and then reevaluate a canonical case study in this debate. I show that for the assessment of actual evidence, produced in a world that is far from ideal, omission of the social aspects of medical epistemology (e.g. commercial drivers of medical research) leads philosophers to draw the wrong lessons from cases they take as paradigmatic cases for their views. I close by arguing that social epistemology provides an avenue to incorporate these complications and provides the necessary framework to understand medical evidence.

Keywords Medical epistemology · Social epistemology · Industry-funded science · Mechanistic evidence · Russo–Williamson thesis

> 'Scientific knowledge' may be regarded as subjectless. It may be regarded as a system of theories on which we do work as do masons on a cathedral.
> Karl Popper (1970, p. 57)

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Over the past decade philosophers of science have become increasingly interested in the evidential basis of sound medical decision making. A standard view assumed or promoted by epistemologists and philosophers of science stresses the virtues and promise of scientific research to transform the practice of medicine from an art into a science. The standard bearer for the promise of evidence-based medicine (EBM) has been Howick (2012), but many others (Cartwright 2007, 2009, 2010, 2011; Cartwright and Stegenga 2011; Fuller in press; Mayo and Spanos 2010; Solomon 2015a, b; Stegenga 2014; Worrall 2002, 2007a, b, 2010) have put forward alternative views on the nature of medical evidence. These philosophers have tended to conceive of medical epistemology as a good-faith effort by all members of a community to discover the truth by deploying the most rigorous methods in the most effective way. Because of this framework, philosophical disputes have centered on what levels of absolute and comparative confirmational significance should be assigned to particular types of evidence. Most crucially, these authors largely uphold Popper's vision of subjectless science: they ignore or abstract away from questions about who is actually making use of these methods or how.

In this paper I will evaluate previous accounts which have either ignored the effects of pervasive industry funding or largely brushed it to the side as a "sociological problem". Specifically, I will focus on philosophical arguments stemming from the work of Cartwright and Worrall which discuss "ideal randomized clinical trials (RCTs)" and use these idealizations to discuss the limits of inference. I will refer to any account which abstracts away worldly complications to consider ideal experiments *friction-free epistemology.* To an extent, such accounts are well-motivated. Abstractions are an excellent way to ignore messy details and lay bare some of the underlying structure of the limits of inference. In such cases, *friction-free epistemology* is entirely appropriate, as one is essentially asking: In the best of all possible worlds, what am I entitled to infer, given evidence of such and such? Idealizations are fine for ideal worlds.

Yet there are questions about non-idealized circumstances that philosophers sometimes take themselves to be addressing, such as: Was the meta-analysis performed by Patricia Crowley (1981) sufficient evidence to make treatment of infants with corticosteroids standard practice, despite the fact that experts judged that corticosteroids provided no benefit (Howick 2012, p. 161)? In general, Howick frames his book as "an evaluation of the EBM view of what counts as 'good evidence"' (Howick 2012, p. 24). Similarly, Worrall (2007a) views medical evidence as "a new area where philosophers of science could have enormous impact— both intellectual and (very unusually) *practical*" (p. 981, emphasis added). The question here is what actual doctors should make of actual evidence. For questions such as these, friction-free epistemology works only as well as the actual world approximates the ideal.

My central contention is that the way medical science works, and thus the epistemic reliability of science in these areas, is far from ideal. Specifically, I claim that industry funding and commercial imperatives are a deeply entrenched reality in medical research and thus any plausible account of medical knowledge must incorporate the fundamental antagonism between science and commerce. Moreover, because the effects of industry funding are both entrenched and pervasive, for an epistemology to be applicable these effects must be incorporated, not as an afterthought, but as a normal part of medical research.

In support of this contention, I will look at the philosophical literature on causal reasoning in medicine as an example of a philosophical debate that has been going on in the abstract (Sects. 1, 2). I will then examineo a case that EBM proponents take to illustrate to the dangers of causal reasoning (Sect. 3). I will argue that philosophers have misidentified the primary threats to medical knowledge in this case (Sect. 4) and that industry funding can neither be dealt with as an afterthought nor quarantined to "evaluative science" (Sect. 5). Before concluding the paper, I examine three prominent social epistemologies (Longino, Goldman, and Solomon) and show that each account successfully handles at least part of what is otherwise ignored as inconsequential. Though I do not endorse any particular view, I hold that each is a promising way to address precisely those questions that should matter most to our evaluation of evidential warrant.

1 Philosophers on drugs: Do doctors need causal theories to rationally prescribe?

Cartwright (2007, 2009, 2010, 2011) has put forward a case that EBM has come to rely too heavily on RCTs. Others have joined the chorus arguing for "EBM+", where mechanistic reasoning serves a complementary (reinforcing) function to RCTs (Clarke et al. 2014; Dragulinescu 2017; Illari 2017; Russo and Williamson 2007, 2011). Critics note that proponents of EBM often favor an atheoretical account of efficacy, a desire to let results stand alone without a narrative overlay about why such results occurred. For example, the Cochrane Collaboration, which has heavily influenced EBM, privileges highly controlled trials on the assumption that causes identified in highly controlled settings will continue to operate in the field.

The justification offered for a theory-free reliance on RCTs is that the relevant theories are controversial, ill-formed, or poorly supported, and thus should be eschewed. But as critics argue, an atheoretical account will not license the generalization from the experiment to the conclusion that the treatment will work in practice, which is the presumptive purpose of the experiment. The result of an RCT concerns the difference between two group means, but what is needed is a justification to act in a particular instance outside the experimental setting. For example, Cartwright argues that this requires three things: (1) Reason to believe that the effect observed in the RCT is the product of a capacity that will endure outside the experimental setting; (2) Reason to believe that the proper causal structure has been identified; and (3) An account of what it means for the cause to *contribute* in new situations. In short we need a theoretical account for what has been observed.[1]

The problem with causal mechanisms is that they are in some cases too much and in others too little. There are many cases in which we have good evidence that something works and no causal account of why (Broadbent 2011). For example, the cancer

[1] Similar arguments for the necessity of causal accounts for extrapolating from an RCT have been put forward by others (e.g. Clarke et al. 2014), though there remain fundamental philosophical differences between the views (Dragulinescu 2012). In this section and the next, I focus on Cartwright and Howick; however, the argument applies to any account that ignores industry funding and seeks to have practical application.

drug Cisplatin is widely regarded as one of the best antitumor drugs in the modern armamentarium. Despite possessing working hypotheses, decades after its approval "the molecular details of how it causes cells to die are largely unknown." (Fink and Howell 2000, p. 149). Though having a true causal account would aid rational use of treatments, it is clear that causal mechanisms are not the only warrant for employing a validated treatment in an individual case. Moreover, as the following example shows, sometimes relying on a causal account can be detrimental.

2 The danger of relying on causal theories: A philosopher's account of a medical disaster

In the early 1980s, people started dying in unexpected ways. At first only a few doctors noticed, but soon people all around the world were dying *en masse*. Faced with such dire circumstances, Ronald Reagan's NIH stepped in and orchestrated a multicenter trial employing thousands of medical professionals in 26 cities across the world. The randomized clinical trial, begun in 1987, became a flash point as ethicists debated the acceptability of giving half of the patients a placebo in lieu of treatment. By the late eighties tens of thousands of people were dying every year; estimates of the death toll for the decade are in the tens, if not hundreds of thousands for the United States alone. The cause of death was not AIDS, but the result of using class-I antiarrhythmic drugs.

The details of this story are crucial because the case serves as a paradigm example in the argument against a reliance on mechanisms (Howick 2012) as well as the defense of their use (Dragulinescu 2017). Moreover, a paradigm case such as this is intended to illustrate a problem, explain why it occurred, and identify what can be done to prevent future tragedies. In this section I will summarize the account as given by EBM proponents (Howick 2012; Straus et al. 2005) and then in section three, I will present a fuller narrative that illustrates how the standard account misidentifies the causes and thus the solutions to the arrhythmia disaster.

Both the narrative offered by EBM proponents and the one I will detail below begin by noting that sudden cardiac death is one of the most frequent causes of fatalities in the prime of life. With the invention of the defibrillator and the ability to reverse ventricular fibrillation, it was discovered that sudden cardiac death often occurred independently of any underlying cardiac disease and that patients who were reached quickly often subsequently lived long and healthy lives.[2] However, given the difficulty of reaching most people in time, the medical community began searching for ways to prevent cardiac deaths. However, from this common ground, the narratives then diverge.

In order to provide the EBM narrative of this episode for the reader, I quote at some length:

> Consider a rather famous case of mechanistic evidence involving antiarrhythmic drugs to reduce mortality in patients who had suffered myocardial infarction

[2] Studies had shown that 25% of patients that died suddenly had no symptoms of heart disease. The treatment population at issue below, on the other hand, were patients thought to be at risk for sudden cardiac death because they had both asymptomatic arrhythmias and had suffered from a myocardial infarction.

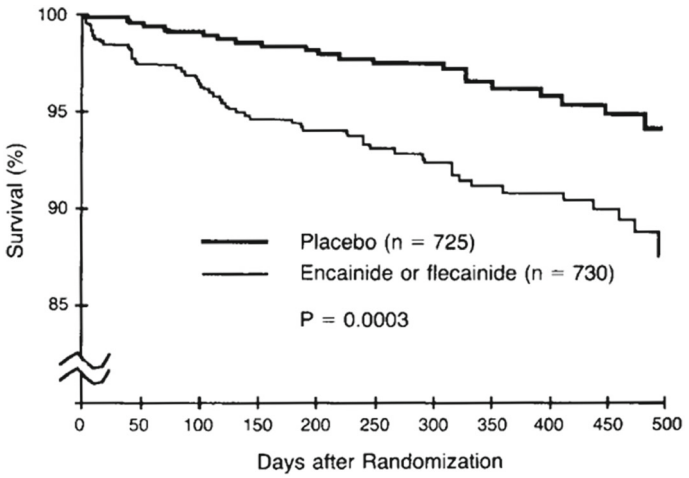

Fig. 1 Mortality in the CAST I trial. This charts survival in the two groups regardless of the cause of death. By the end of the trial the relative risk for death by any cause was 2.5 (95% CI 1.6, 4.5). The deleterious effect is even more dramatic when the analysis is restricted to the outcome the drugs were intended to prevent; at the time the trial was halted the relative risk for arrhythmic death was 3.6 (95% CI 1.7, 8.5).

> (heart attack). Myocardial infarction often damages the muscle and electrical system in the heart, leaving it susceptible to arrhythmias. A common type of arrhythmia, ventricular extra beat (VEBs) occurs when the left ventricle contracts before it has time to fill completely. The heart then fails to pump sufficient blood. Without treatment, lung, brain, and kidney damage ensues. Worse, VEBs can also degenerate into ventricular fibrillation in the absence of electrical shock. Large-scale epidemiological studies suggested that between 25 and 50% of sudden cardiac deaths were associated with arrhythmias. Based on this understanding of the underlying mechanisms, several drugs were developed and found to be successful for regulating VEBs. The drugs became widely prescribed in the belief they would reduce cardiac deaths (Howick 2012, pp. 126–127).[3]

Given the widespread use of antiarrhythmic drugs, the NIH convened a study (CAST I) to test the arrhythmia suppression hypothesis. Midway through the study, the advisory committee was convened and because the data were highly significant and unlikely to change, it was deemed unethical to continue the trial. When the advisory group was unblinded, it was discovered that the group with more deaths was the treatment group, not the placebo. At the time the trial was halted, 56 of the experimental patients had died (compared to 22 on placebo—see Fig. 1). The FDA was called and the *New England Journal of Medicine* expedited the manuscript showing how dangerous

[3] The various terms used in the medical literature for this phenomenon were "premature ventricular complexes," "ventricular premature complexes," and "extrasystoles." I have chosen to stick with Howick's acronym for the sake of simplicity.

doctors' causal reasoning had been. The results were subsequently confirmed in a second study (CAST II).[4]

Howick (2012) contends that such cases show the frailty of relying on mechanistic reasoning:

> The mechanism(s) involved in antiarrhythmic drug action might include swallowing and gastric emptying, metabolizing circulatory and binding mechanisms. The mechanisms involved in getting the orally administered drug to its pharmacological targets on the cells are relatively (but not completely) well understood and referred to in the medical literature as ADME (mechanisms for absorption, distribution, metabolism, and excretion). Once the drug reaches its cellular target, antiarrhythmic drugs reduce the frequency of VEBs by modifying the heart's electro-chemical mechanism. Finally, a reduction in VEBs (allegedly) reduces the risk of sudden death… Mechanistic reasoning involves *inferring* from knowledge of the mechanism(s) to the claim that an intervention has its putative effects. I might know about the ADME, heart and brain mechanisms, but to move from there to the claim that antiarrhythmic drug will reduce mortality, I must be able to predict what happens to each of the mechanisms under intervention. (127f)

This challenges Cartwright's position by pointing out that we rarely have knowledge about a drug that is sufficient to determine how it will interact with biological mechanisms. This complexity makes causal reasoning based on mechanisms an unreliable source of evidence. Of course, we do rely on causal reasoning when we use surrogate endpoints (like suppressing VEBs) to evaluate drugs, but these can be sources of significant tragedies. The problem arises when "some but not all of the relevant mechanisms involved in mechanistic reasoning are based on sound evidence… [in this case] the impact of the drugs on mortality was not based on sound evidence" (138). If Howick is correct, then it is not so much that mechanistic reasoning was relied on, but that the mechanistic reasoning for the patient-relevant outcome (mortality) was not "high quality."

This analysis identifies the cause of the tragedy as the reliance on low-quality mechanistic reasoning. Howick suggests that if doctors simply paid closer attention to the epistemic grounds of the arrhythmia suppression hypothesis, they would have seen that it was not fully warranted. Because it was in fact partially warranted (the drugs did stop VEBs), it had the "aura of acceptability, which in turn [led] to more prolific use of a harmful treatment" (pp. 139–140). The solution to the problem is to educate doctors not to trust low-quality mechanistic reasoning and in most cases to insist on RCTs of clinically relevant outcomes before a treatment is widely used.

[4] Figure 1 (and the death toll estimates) does not include a large number of patients who died in the first 2 weeks of the trial, when all patients were on an antiarrhythmic drugs to establish the effectiveness of VEB suppression in that patient. Of the first 91 deaths in CAST I, 41 occurred during the 2-week titration phase of the trial (during which there was no placebo group for comparison). These deaths were not included in the analysis. In CAST II, with another class I antiarrhythmic drug, a placebo group was added to the initial phase of the trial. Before this trial was stopped, researchers recorded 17 deaths during titration compared to 3 on placebo. Antecedently, the drug studied in CAST II was thought to be the "most benign" member of the class. Since the initial dose given was low and high doses increase risk, the results "may be considered a minimal estimate of the risk of the initiation of drug therapy" (CAST II, 1992, p. 230).

Unfortunately, such an analysis is specious. In the next section, I will show that Howick's narrative is oversimplified. Delving into the arrhythmia case in greater detail will illustrate how the commercialization of medical knowledge served as the wellspring that fed the widespread success of the deadly medicine. The fuller story underscores why medical epistemology cannot be separated from the "sociological problems" caused by commercial imperatives. A corollary is that philosophers have misidentified the dominant forces threatening a sound medical epistemology. It bears repeating that such problems occur throughout medicine (Angell 2004; Avorn 2004; Brody 2007; Elliott 2010; Healy 2012; Kassirer 2005; Krimsky 2003). Moreover, there is now a growing body of research that investigates the methods pharmaceutical companies use to manipulate medical judgment (e.g. Cosgrove et al. 2016; Holman and Bruner 2015, 2017; González-Moreno et al. 2015; Jureidini et al. 2016; Sismondo 2007, 2009, 2017; Vedula et al. 2012; White and Bero 2010).[5] The crucial point is that because such problems are pervasive, they can be identified even in cases that are selected as paradigm examples for other analyses. The fuller account of the arrhythmia disaster will take us into the details of medical history, but the philosophical payoff depends on understanding how the account given by EBM proponents falls short.

3 This time with friction: How commercial forces contributed to the antiarrhythmic drug disaster

The account given by EBM proponents locates the source of the arrhythmia disaster in the reliance on causal reasoning. The example is invoked to demonstrate the unreliability of causal reasoning and challenge philosophers who stress the necessity of identifying mechanisms in warranting treatment (e.g. Cartwright and Hardie 2012; Russo and Williamson 2007). In this section I will develop this case study and show how the commercialization of medical evidence contributed to the arrhythmia disaster.[6] I claim it is these factors and not a reliance on poorly supported causal reasoning that is at the heart of the problem. Thus, to the extent that philosophers take themselves to be addressing threats to actual inferential practices, they are addressing the wrong issues.

First and foremost, it was not the acceptance of the arrhythmia hypothesis *per se* that caused the disaster. The hypothesis gained attention after Harvard Professor Bernard Lown devoted his keynote address to it at the annual gathering of America's cardiologists (Lown 1979). Lown's early work on prevention led to his development of the defibrillator and made him a giant in the field. His vision was to prevent such episodes altogether. Several decades of research suggested that VEBs precipitated

[5] My thanks to the anonymous reviewer for their suggestion to add such citations and for bringing the Jureidini et al. (2016) study to my attention.

[6] This account draws heavily on the book *Deadly Medicine* (Moore 1995) referenced by the EBM advocates as their source for information on arrhythmias. I will indicate where my account differs from Moore's rendition in footnotes.

cardiac arrest even after controlling for underlying structural damage to the heart and for Lown this was the key for his prophylactic campaign.[7]

Lown separated arrhythmias into five different grades and contended that it was only for the two most severe grades that the benefit of treatment outweighed the risks (Lown 1979; Graboys et al. 1982). Lown repeatedly emphasized that VEBs, even when they are frequent, "require no treatment at all other than the physician's affirmation of their ubiquity and benignity. Therapy is needed in only a minority of patients, who usually have ischemic heart disease and a life-threatening or symptomatically disabling arrhythmia" (Lown 1979, p. 321). This concern was born out by studies showing the troubling propensity of the drugs to have arrhythmogenic effects (i.e. to worsen arrhythmias). In roughly 11% of patients, the drugs could precipitate cardiac arrest that was unusually hard to reverse and unlike anything doctors had seen before (Velebit et al. 1982; Winkle et al. 1981). Had the medical profession restricted the use of antiarrhythmic drugs to the most severe cases, the tragedy would not have occurred. Thus, the central question is why the patient pool to be treated was far outside what the doyen of the cardiac world first proposed. I will tackle this question by first examining the decision by the FDA to accept a surrogate endpoint as a measure of efficacy and then explore how medical knowledge circulated within the medical community after antiarrhythmic drugs were approved.

3.1 VEBs as a surrogate endpoint: Manufacturing consensus

While the FDA requires a company to provide *evidence* of efficacy from adequate and well- controlled trials, the *criteria* for efficacy are determined by expert consensus. When a variable of interest is difficult to measure or would take years for a trial to establish, experts sometimes decide that it is fair and responsible to use a surrogate endpoint in place of the clinically relevant outcome.[8] The CAST trials showed that had companies been required to use death as a primary outcome, the drugs would not have been approved. This section examines how this decision was arrived at despite

[7] Moore suggests that the cardiac suppression hypothesis was only based on simple correlation and that it was equally plausible that heart arrhythmias and subsequent cardiac arrests had a common cause, but were not themselves causally related: "Every doctor has been taught that an association between two events does not prove a causal link. In this case it was equally plausible that premature beats were nothing more than a telltale indicator of underlying permanent damage" (p. 49). Howick repeats this claim: "The available evidence suggested an epidemiologic link between VEBs and mortality, but association is not causation. Moreover, even at the time there were good reasons [he does not specify what these were] to believe that after myocardial infarction, the heart is damaged in a way that both causes VEBs and raises the risk of sudden death" (p. 138). The supposition that the arrhythmia suppression hypothesis confused correlation with causation is simply untrue. For example, in the very speech in which Lown described his theory, he addressed the topic: "It may be argued cogently that prognostic implications are not determined by the ventricular premature complex [VEBs] but by the extent of cardiac disease because the grade of ectopic activity is largely an expression of the severity of the disease. A corollary inference is that the attempt to control ventricular arrhythmia is futile because the ultimate outcome is determined by the extent of heart disease. A recent study of Schulze et al. contradicts such a conclusion" (Lown 1979, p. 316).

[8] A familiar, though controversial example is the use of t-cell counts—rather than death—to evaluate AIDS treatments (Epstein 1996).

the existence of prominent researchers (e.g. Lown, Winkle, etc.) who raised significant doubts over its use.

In 1980, dozens of pharmaceutical companies were developing antiarrhythmic drugs, but were unsure what evidence the FDA would require to substantiate efficacy. In order to gain clarification, pharmaceutical companies developing antiarrhythmic drugs convened a conference that included academic researchers, industry representatives, and members of the FDA cardio-renal division (Morganroth 1981a).

In principle, there is nothing wrong with the FDA demystifying what evidence they will require for approval. However, by organizing the conference, pharmaceutical companies were able to influence who would be in the spotlight and frame debate on their own terms. Crucially, and contrary to the standard account of EBM proponents such as Howick, many researchers were well aware that the arrhythmia suppression hypothesis was not conclusively established. However, this fact was minimized by having Joel Morganroth—an industry darling and rising star in the arrhythmia world—chair the conference and police discussion.

The stated agenda for the conference was to identify "guidelines to determine how to evaluate such new antiarrhythmic drugs for both efficacy and safety in the most expeditious manner. This symposium will not address important issues of whether or not [VEB] suppression is definitely necessary to prevent sudden death" (Morganroth 1981a, p. 2). However, if these drugs were intended to be marketed as a prophylactic for sudden death and VEB suppression was to be used as a surrogate endpoint, then the FDA guidelines for establishing efficacy should have hinged on whether VEB suppression would prevent cardiac death. Instead, the issue was avoided as much as possible.

At the conference, three talks directly addressed the measurement of efficacy. The first speaker argued that using cardiac death was prohibitively expensive and that VEBs should be used as a surrogate endpoint (Hoffman 1981). Next, Morganroth (1981b) echoed the themes from the previous talk and specified how to analyze VEB data as a surrogate endpoint. Finally, the third speaker maintained that the Lown classification system may be a helpful clinical tool, but it was not reliable enough to be used in research (Campbell 1981). All three speakers endorsed industry-friendly positions that were crucial to enabling the arrhythmia disaster.

Moreover, in the ensuing discussion Morganroth repeatedly quashed discussion regarding whether VEBs were an acceptable surrogate endpoint, claiming: "we cannot address the question in this symposium… this means using the definition for drug efficacy as the statistical elimination [of VEBs]," (Morganroth 1981a, p. 123) and

> the real crux of your [Dr. Temple, Director of FDA's Cardio-Renal Division] question I think is, how do we know what the best definition of efficacy should be unless we know whether or not it prevents sudden death. Unfortunately, we can't answer that part of the question, so we have dropped back to try to answer the question how do we know whether the drug is doing something at all [i.e. suppressing VEBs] (128).

The last part of Morganroth's response was inaccurate; whether antiarrhythmic drugs prevented sudden death could be answered, just not by any of the trials currently being planned by industry.[9]

Though Morganroth attempted to shift the topic of discussion, the sufficiency of VEB suppression was raised yet again, this time forcefully by Winkle:

> I don't think that just saying that we have an 83% percent reduction will really help us understand what these drugs are doing to sudden death. We have all fallen into this trap of the numbers game… I think that to just get hung up on some percent reduction of arrhythmias really side steps the true issues, which I know you [presumably Morganroth] don't want to talk about today. We can't deny the fact that we don't know what [VEB] suppression means. (p. 129)

This time Morganroth pivoted, pointed out that every industry trial was designed to assess VEB suppression as a surrogate for sudden death and asked Temple if the FDA would accept this as evidence of efficacy. Temple's response highlights the central importance of industry having presented as unified a front as possible on the sufficiency of VEB suppression: "It is people here who are the experts we have to listen to… obviously people have pointed out and we know ourselves we are not asking the right questions about antiarrhythmics. There is the grossest kind of assumption that drugs that reduce [VEBs] may in cases prevent what is hurting people" (p. 131).

Temple's position was subsequently reaffirmed and expanded upon by Temple's superior, Director of the Bureau of Drugs, Dr. Crout. Crout framed the decision of whether or not to accept VEB suppression as a choice between two kinds of efficacy: *pharmacological effectiveness* in which a manufacturer demonstrates that a drug has some predictable effect on the human body and *therapeutic effectiveness* where the manufacturer shows that the effect benefits the patient. The law required that the FDA have evidence of effectiveness, but not what kind was required:

> What I am saying is that the rules vary depending on the drug class and to some extent depending upon the state of the field. Certainly, if we had taken a position years ago, that an effect on life span had to be shown for antihypertensive drugs, no doubt, medicine and the public at large would have been set back enormously. I don't know where the antiarrhythmic field is at this point, that's for you to decide (p. 177).

Given the state of the field as he understood it, Crout announced that the FDA would accept suppression of arrhythmias as a measure of efficacy rather than require that manufacturers demonstrate that drugs had the capacity "to protect patients or to improve

[9] To be fair, Morganroth's position was that we must first establish that drugs suppress VEBs, then "once antiarrhythmic agents are available which are effective, safe and well-tolerated for long periods of time, we will have the ability to test [the arrhythmia] hypothesis (Morganroth 1983, p. 64). While a reasonable plan for research, it confuses the mandate of the FDA. Drugs are not made available so they can be shown to be effective, they are shown to be effective so they can be made available. As Moore (1995) details, Morganroth was personally brought in by 3M to meetings with FDA director Robert Temple and was successful in convincing him to approve the drug for the wider indication solely on the basis of surrogate endpoint data—a stance Temple had initially regarded as unwarranted and potentially dangerous without further trials (i.e. a trial like CAST).

mortality" (p. 177). As indicated above, though the FDA realized that VEB suppression did not guarantee therapeutic effectiveness, it would rely on expert consensus, as represented at the conference, to determine whether a surrogate end-point should be accepted.

Before moving on, it is worth noting three points that were illustrated by the decision to use VEBs as a surrogate endpoint. The first is that though the standard account is correct in pointing to the use of mechanistic reasoning in this case, it neglects the fact that the potential for negative consequences were acknowledged from the start. Second, the standard account fails to identify the fact that there was a range of opinions regarding the use of VEBs as a surrogate endpoint. Finally, and most crucially, the standard account neglects the role that the pharmaceutical industry had in promoting the use of VEBs as sufficient evidence for FDA approval. Researchers who opposed the use of a surrogate endpoint, though present, were not showcased and were silenced during the group discussions.

3.2 Post-approval: How to win researchers and influence doctors

In the previous section I examined how industry shaped the discussion prior to gaining FDA approval, here I look at how industry shaped both the content of the scientific literature and the visibility of information that supported the wide use of antiarrhythmic drugs. The discussions examined above occurred, if not behind the scenes, at least outside of the purview of average doctors. Yet it is rank and file doctors that prescribed antiarrhythmic drugs. Thus, just as important as understanding how manufacturers secured FDA approval, is understanding how scientific knowledge was disseminated to the portion of the medical community that actually prescribed the drugs.

A first point to be made is that views critical of the position supported by industry faced greater obstacles in the publication process. A case in point is the work of Stanford cardiologist Roger Winkle. During the initial trials, a patient on Enkaid developed a rapid heartbeat that was extremely difficult to reverse and did not respond to standard interventions. Concerned, Winkle reviewed the 140 other cases he had treated and found ten other serious incidents, some of which precipitated death of the patient. Winkle attempted to publish his findings in *Circulation*, but the article was rejected. It was then rejected twice more from other journals.[10] Fortunately, the Stanford cardiologist knew the editor of the *American Heart Journal,* which ultimately published the article, but without such connections, the prospects for publication would have been uncertain. Indeed, it is now known that a number of early trials identifying sudden death in patients treated with antiarrhythmic drugs went unpublished (Cowley et al. 1993). While there is no smoking gun that journal editors consciously refused to

[10] It is difficult to determine the exact causes for rejection and whether bias (conscious or unconscious) plays a role in any individual case. Nevertheless, some of the referee comments that Winkle received were difficult to understand. For example, his article was rejected from *Circulation* "because the literature does not at present contain an overall description of the antiarrhythmic efficacy of Enkaid, it seems somewhat inappropriate to include a separate article about this specific adverse side-effect" (quoted in Moore 1995, p. 66). This explanation is odd given the existence of four separate studies describing the antiarrhythmic efficacy of Enkaid, all cited in Winkle's manuscript (1981).

publish damaging information about one of their advertising clients, the difficulty that Winkle encountered underscores the additional hurdles that commercially damaging evidence must overcome.[11]

Meanwhile, 3M was able to publish abstracts of the same dosing trial three times (Anderson et al. 1981a; Duff et al. 1980; Hodges et al. 1981) and then publish article length treatments of the trial three times (Anderson et al. 1981b; Duff et al. 1981; Hodges et al. 1982). The trial had been designed and analyzed by 3M, but each time the article had different lead authors from academia and netted an appearance in a different top medical journal (*The New England Journal of Medicine, The American Journal of Cardiology, Circulation*). While it is unlikely that journal editors were aware of the multiple publication, it is clear that there were not sufficient safeguards in place to prevent it. 3M then bought and distributed reprints of the articles and used them to begin increasing doctors' awareness of their upcoming product launch.

This effect was amplified by the way that doctors received their information. Winkle was not smeared in public as a result of publishing his concerns. However, 3M broke off talks with him about conducting future trials and despite his influential position at Stanford, he was never contracted to conduct further industry research. In contrast, doctors such as Woosley and Morganroth who were enthusiastic about the prospects for antiarrhythmic drugs continued to get funding and as a result netted numerous publications. In so doing, they became highly influential members of the cardiology community; they were asked to write text books, organize symposia, and sit on the FDA advisory panel. Moreover, one of the primary ways that doctors stay up-to-date is by attending continuing medical educational seminars that describe newly available drugs. When an antiarrhythmic drug gained FDA approval, it was researchers like Morganroth whom 3M sponsored to fly around the country and educate doctors about their merits, even advocating for the use of antiarrhythmic drugs in asymptomatic cases—something 3M was legally prohibited from doing. Critics were not so much silenced as drowned out.

If the NIH had not convened the CAST studies that demonstrated antiarrhythmic drugs increased mortality rates, it is unclear how long it would have taken before such research was conducted. Though companies like Bristol–Meyers Squibb were conducting clinical studies, the vast majority were not addressing pressing unanswered research questions. Instead, most studies were designed to "allow selected cardiologists to obtain premarketing experience" and the ability to "compare the effects of Enkaid to previous antiarrhythmic therapies" (quoted in Moore 1995, p. 179). For example, Bristol–Meyer recruited 191 doctors to participate in such a trial, each paid a few thousand dollars for their participation.[12] While companies spent between $50 million and $80 million in pre-approval clinical trials, "a large fraction of this is spent on the trials of patients with asymptomatic [VEBs] described above and on large

[11] The loss of advertising is a real possibility. In 1992 when the *Annals of Internal Medicine* ran an article that identified false claims made in contemporary medical advertisements, the journal lost $1.5 million from cancelled ad contracts (Altman 1999). Marcia Angell (former editor in chief of *NEJM*) explains that pharmaceutical companies don't even have to be involved explicitly; simply the threat of legal action and potential loss of advertising revenue can lead journal editors to self-censor (Abramson 2004, p. 113).

[12] Precise numbers are not available, but this figure is consistent with industry averages for such arrangements.

'seeding trials' to place the drugs into the hands of selected 'opinion leaders' and 'high prescribers' throughout the United States" (Woosley 1990, p. 556).[13] Without a control group, such studies could not possibly have told the company anything of scientific value. Yet because participation in such trials substantially increased the probability of doctors prescribing the drug, they were of significant financial value.

In sum, from development to product launch, we can see how commercial forces were instrumental in shaping doctors' perceptions about VEBs, subverting regulatory authority, and amplifying the impact of commercially favorable views. Such problems are complex, widespread, and deeply entrenched. Once more, there is nothing particularly unusual about this case; it merely illustrates the pervasive influence of industry funding on the constitution of medical knowledge. Similar factors have been shown to influence prescription habits in a wide variety of cases (Abramson 2004; Bass 2008; Brody 2007; Elliott 2010; Healy 2012; Kassirer 2005; Moynihan and Cassels 2006). On the one hand, no single remedy can address these problems. On the other hand, an account which does not even recognize commercial influences on the constitution of medical knowledge cannot begin to get purchase on them. With a fuller account of antiarrhythmic drugs on the table, I will argue that the philosophers' focus on mechanistic reasoning fails to identify the main threats to epistemically sound treatment decisions.

4 The wrong argument: Why a friction-free account of causation doesn't help in the real world

The case of antiarrhythmic drugs exemplifies some of the main problems that commercial forces present for obtaining reliable knowledge. As these factors are ubiquitous, an account of evidence that fails here, will fail to deal with persistent threats to best practice. In support of this conclusion, I will argue that within the framework of friction-free accounts, where the source of the evidence is neglected, antiarrhythmic therapy was warranted prior to the completion of the CAST-I.

According to Cartwright, warrant has three requirements. The first is reason to believe that the effect observed in the RCT is the product of a capacity that will endure outside the experimental setting. For our purposes, the effect observed is the ability of antiarrhythmic drugs to prevent VEBs.

[13] Woosley wrote this in the sobering year after the CAST-I trial was published in 1989. It should be noted that pre- approval seeding trials were specifically prohibited by the Kefauver–Harris amendments in 1962. Though Woosley was employed by pharmaceutical manufacturers, he was also on the FDA advisory panel and thus—assuming he knew of the seeding trials at the time—had reason to vote against approving antiarrhythmic drugs or in some way censuring the manufacturers when the advisory panel addressed antiarrhythmic drugs in 1984.

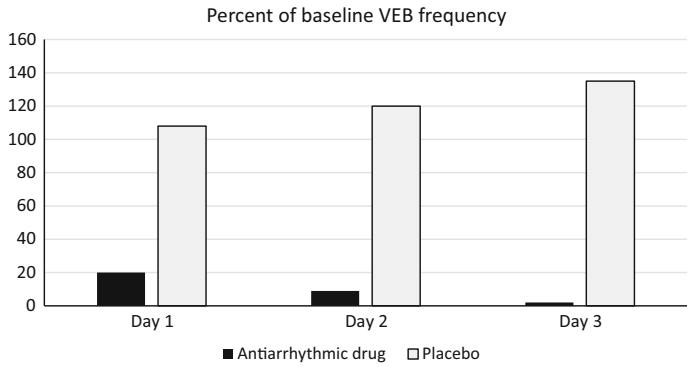

Fig. 2 Early trials demonstrated that administration of antiarrhythmic drugs could extinguish VEBs (for an early example with Encainide (Enkaid) see Roden et al. 1980)

The effect was well attested to (see Fig. 2) and was the basis on which the drugs were approved. Moreover, a diligent cardiologist could confirm the effect with a Holter heart monitor.[14]

The second requirement is reason to believe that the proper causal structure has been identified. On the one hand, we know from our privileged position that the proper structure was not identified and that preventing VEBs would not yield a decrease of cardiac arrests. On the other hand, as discussed in Sect. 3, several epidemiological studies had shown that VEBs are associated with a higher risk of cardiac arrest. Moreover, medical journals available to doctors at the time were flush with articles endorsing the theory. Any cardiologist that attended a continuing medical education event on VEBs would have learned both when to use antiarrhythmic drugs and the supporting causal theory from renowned experts (e.g. Morganroth, Bigger, etc.) and this is sufficient for the general practitioner and even a practicing cardiologist to have reason to believe the correct causal structure has been identified.

The last requirement, that the theoretical description specify how the cause will contribute to the projected consequence, is intended to identify patients for whom the general causal account will not hold, viz. to identify the defeaters. As Cartwright emphasizes, the causal account provides doctors with sub-groups of patients who should not use the drug. For example, some people lack the enzyme that breaks down the antiarrhythmic Enkaid. The Enkaid molecule still had antiarrhythmic properties, but due to a lack of the enzyme, a patient's dose would need to be adjusted to ensure proper plasma levels or another drug substituted. Similarly, use of antiarrhythmic drugs was contraindicated when the patient had second or third degree AV blocks, a bifascicular block, or was known to be hypersensitive to the drug (Anderson et al. 1984). But aside from these exceptions, doctors could give the standard account of blocking VEBs, explain how blocking VEBs would prevent cardiac arrest, and confirm that the antiarrhythmic drug was having the intended effect in the person.

[14] The Holter heart monitor had become a popular way to diagnose VEBs and could be used to ensure the drugs suppressed VEBs as well.

Taken together, these findings satisfy Cartwright's requirements to warrant the usage of what we now know, and could have known then, is a highly toxic and dangerous drug. Moreover, as I have argued above, the reasons that antiarrhythmic drugs came into use are not idiosyncratic, but represent enduring threats to medical epistemology and thus threats to safe and effective clinical decision making. While Cartwright provides a valuable insight into the role of causal powers, her account of causal mechanisms will not address the main threats that face medical epistemology.

Howick has suggested a friendly amendment to Cartwright's position by distinguishing "high- quality" causal mechanistic reasoning and suggests that the antiarrhythmic drug disaster would have been avoided had such a standard been in play. Howick gives two conditions for being "high quality." The knowledge of the causal chain from the intervention to a patient-relevant outcome must not be incomplete and the causal story must take into account the complex nature of human physiology. By his lights, doctors were not warranted in prescribing antiarrhythmic drugs because the causal link between suppressing VEBs and reduced mortality was not high quality. Again, recall that according to Howick's account, if doctors had assessed the effect on mortality with an RCT rather than relying on mechanistic reasoning, the tragedy would have been averted. I shall consider two responses to this. The first is to dispute the factual claim that the available evidence was not high quality. The second is to dispute whether flawed mechanistic reasoning was responsible for doctors' treatment decisions.

Howick (2012) suggests that the reason why mechanistic reasoning was not high quality was that the mechanism that led from VEBs to death was not well supported (127). The only justification he provides is the repetition of Moore's (1995) incorrect assertion that the arrhythmia hypothesis was based solely on large-scale epidemiological studies (see footnote 7). It is supposed that these studies left open the possibility that VEBs were merely a sign of cardiological damage, not a cause of ultimate cardiac arrest. Again, we now know antiarrhythmic drugs increase mortality, but current knowledge cannot be evidence that doctors 30 years ago were unfounded in their beliefs.

To begin with, Howick's suggestion that cardiological damage could be a common cause of VEBs and mortality was examined, but researchers established that the relation between VEBs and mortality held even after controlling for the structural integrity of the heart (Bigger et al. 1984; Lown 1979; Mukharji et al. 1982). Further, the invention of new monitoring devices had provided unparalleled insights into cardiac arrests. As Holter monitors proliferated, some patients happened to be wearing one at the time of death and this allowed doctors to examine the record of the patients' heart activity just before they died and establish the mechanism that led from VEBs to death. The monitors showed that a VEB occasionally precipitated electric instability and caused the heart to begin beating rapidly and erratically (ventricular tachyarrhythmia) eventuating in electrical cardiac death (see Fig. 3). Through an examination of the records of patients that died while wearing a Holter monitor, doctors established "that *the mechanism of this condition* in approximately 80% of patients is an acute ventricular tachyarrhythmia that leads to fatal ventricular fibrillation" (Morganroth 1984, p. 673, italics added).

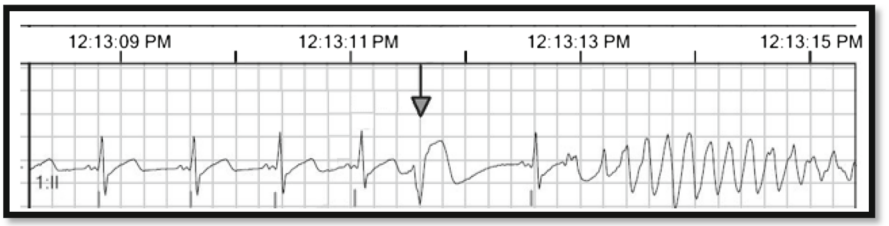

Fig. 3 The strip above shows a normal heartbeat followed by a VEB (arrow), which eventually leads to an onset of ventricular tachyarrhythmia. Records like this gave cardiologists a record of a patient's heart function in the moments leading up to their death. For an example of such images in causal reasoning see Morganroth (1984). Image courtesy of Dawn Altman at ecgguru.com

This would seem to be high-quality evidence that VEBs can precipitate death by causing the heart to become electrically unstable. The last key to the mechanistic causal story is to show that antiarrhythmic drugs could prevent ventricular tachyarrhythmia, the causal intermediary between VEBs and death. Under controlled conditions, ventricular tachyarrhythmia could be electrically induced by programmed ventricular stimulation. In many cases the capacity of direct stimulation to evoke tachyarrhythmia was blocked by antiarrhythmic drugs (Anderson et al. 1983). So, contra Howick, there was high quality evidence regarding the mechanism linking VEBs and cardiac arrests and the ability of antiarrhythmic drugs to prevent cardiac arrest. It is certainly true that the prevention of cardiac arrests had not been shown via randomized clinical trials, but if this is the standard of high quality mechanistic evidence, then mechanistic reasoning isn't a separate source of evidence, it just is the demonstration of an effect via RCTs.

More importantly, the previous discussion in section three shows that the reason that doctors were prescribing antiarrhythmic drugs was not a reliance on faulty mechanistic reasoning. Further evidence that doctors did not rely on mechanistic reasoning is provided by the medical community's reaction to the CAST trial conducted by the NIH. If doctors were relying on mechanistic reasoning, then as the mechanisms of class 1 antiarrhythmic drugs were roughly equivalent, the CAST results should have dramatically reduced the prescription of all Class 1 antiarrhythmic drugs. Indeed, the CAST-I study specifically warned that since the pharmacological properties of all class 1 antiarrhythmic drugs were similar, doctors should not take their patients off of a drug that had been included in the study (Enkaid and Tambacor) simply to put them on a related drug (CAST 1989; c.f. Hine et al. 1989).

In contrast, manufacturers of drugs like Mexatil that were not included in CAST scrambled to claim market share lost by Enkaid and Tambacor. They sent thousands of doctors a letter making them aware of the CAST results and sent them a dosing schedule for their convenience if they wished to switch their patients over to Mexatil. Similarly, Parke-Davis' promotional campaign proclaimed "There is no *conclusive* evidence to indict all I–C arrhythmics" (emphasis in original). Thus, if mechanistic reasoning is driving prescription habits then every drug should decrease in sales after the publication of the CAST results, while if marketing is driving prescription habits, then we might expect a much smaller fallout for drugs not included in the study. In fact,

while the sales of Enkaid and Tambacor did decrease, sales of other arrhythmic drugs did not. For example, sales of Mexatil *rose* 45% in the 12 months after the CAST-I study was published (Moore 1995, p. 239).

Similarly, CAST-II explicitly concluded that the arrhythmia suppression hypothesis was incorrect (CAST 1992). If doctors were prescribing on the basis of the arrhythmia suppression hypothesis, this would have been the end of the line. The number of deaths would have been astronomically high, but it would have stopped growing, and it is the failure of the latter to obtain that Morganroth, the erstwhile champion of treating VEBs, found so troubling: "Pick any number you want—50,000, 500,000 [deaths]… The issue is, which is much more important, is that despite all these articles… physicians have ignored it because sales of quinidine [the oldest and most dangerous arrhythmic] stayed where it was or went up" (Morganroth, quoted in Moore 1995, p. 246).[15]

The failure of the CAST study shows the power of marketing to overwhelm sound evidence. Clearly the mechanistic reasoning was flawed, and it is clear that patients were treated improperly. But it is just as clear that patients were not treated improperly *because* of flawed mechanistic reasoning, as flawed treatment persisted after the causal story was abandoned. Given that one of the goals of the philosophy of evidence-based medicine is to identify threats to forming reliable and accurate beliefs from the available data, a friction-free epistemology that ignores pervasive commercial forces will inevitably misidentify the causes of medical folly and fail to provide sound recommendations for choosing treatments.

5 Turtles all the way down

To be clear, there is nothing wrong with friction-free epistemology, I would consider some of my previous work to be just such a contribution (Holman 2015). However, it is my contention that the scope of such work is restricted in its implications to investigating the structure and limits of inference. Accordingly, EBM+ makes valuable contribution in exploring the relative strengths and weakness of RCTs and mechanistic reasoning (Illari 2011). What such an approach is not well-equipped to do is make any recommendations about what inferences should be made given the current state of evidence or to make any policy recommendations about how the medical community should reform its institutions or epistemological priorities (e.g. Clarke et al. 2014). As the case study above shows, without careful attention to economic forces at play, a friction-free approach is not in a position to critique the current state of medical research.

In defense of friction-free accounts, it might seem fair to recall that everyone is a fallibilist and so the fact that there exists a case study where the requirements of a friction-free account lead to error is not damning. Defenders may protest that any epistemic standard will get some things wrong. This would be to miss the point. It is simply not the case that all there is to say is that no inferential procedure is perfect. As

[15] It does no good to object that the CAST study happened nearly 40 years ago. The continued use of statins after the ALLHAT study in 2001 is a modern day examples of irrational prescription due to heavy promotion (Lenzer 2003).

argued above, there is plenty to say about how industry funding played an important role in determining what evidence was produced, accepted, and disseminated. Moreover, industry funding is a pervasive and entrenched aspect of medical research and therefore should generally be expected to operate in medical science.

In fairness to Howick (2012), he does briefly address the influence of industry funding and claims that in addition to evidence of a therapeutic effect, there must also be evidence that the size of the effect outweighs possible confounders. Industry funding comes into his account as one possible confounder. One might note that it is not quite clear how exactly one is supposed to assess this. The drop in VEBs was an extremely large effect and just looking at that data (Fig. 2), it is implausible to conclude that the apparent efficacy is the result of biased study design (indeed, it wasn't).

A more promising way to save the applicability of friction-free epistemology would be to show that financial considerations only play a significant role in the evaluation of drugs, whereas the basic science that informs our mechanistic understanding is unaffected. However, even if we only focus on mechanisms, it is clear that financial considerations are at play. As discussed by Robinson (2014) in his anthropological study of translational neuroscience, mechanisms have a blurred economic and epistemological function. For example, in his field study at the Neurotech Investing and Partner conference, he recounts how a tenured professor in neuroscience from Colorado begins her presentation: "Hello my name is Linda Roberts. We have identified a novel mechanism of action and a new class of therapy in a large market place where existing mechanism knowledge has led to an unmet need" (175). As Robinson remarks, in this world "well-done science without a market is almost meaningless" (175).

Prof. Roberts is right to foreground her claim to have discovered a mechanism of action. Especially at the early stages when fledgling products are in need of a cash infusion ($7 million in Prof. Robert's case), mechanistic evidence has a significant commercial value. As the managing partner of a venture capital company explains, "The risk is huge in neuro. You don't have the models. There is a significant [therapeutic] need in psych, in neurology, as well, but pharma has a big interest in neurotechnology [rather than psychiatric treatment]. Psych is very last year" (129). Accordingly, mechanistic evidence is seen as a way of minimizing exposure to risk, the venture capitalist continued "We don't invest if there isn't knowledge about what the mechanism of action is" (131).

Interestingly, in later stages of development, if the prospective treatment is seen as promising enough to be acquired by a pharmaceutical company, mechanistic evidence is of diminished importance. Mary Holburn, head of acquisitions at a major U.S. Pharmaceutical company noted, "we're agnostic to mechanism. Some of our most interesting things are where we don't know it" (136). An attitude, no doubt driven by the fact that it is not required for FDA approval.

Friction-free epistemology elides the fact that mechanisms have a commercial value. I have shown above how commercial interests shaped our mechanistic knowledge in the arrhythmia case and this far from a singular occurrence. For example, Whitaker (2010) has shown how commercial interests significantly shaped both the monoamine theory for depression and the dopamine hypothesis for schizophrenia. Nor is such a phenomenon new, as medical reformers noted over a hundred years

ago, "a false therapeutic notion [mechanism of action] born of speculation soon dies a natural death if exposed unsupported to the cold world of facts, but when nursed by commercial interests it may be kept alive for generations" (CPC 1914, p. 760).

As seen in the arrhythmia case, industry did not merely rig a study or two; they shaped the entire research programme from start to finish. Commercial interests are not an aberration, they are part of the fabric of medical research and I hasten to add, though in the account above the effect was deleterious, industry funding stimulates successes as well as failures. Accordingly, rather than something that is seen as one of many possible confounders, we must have an account of medical epistemology where industry-funding is an integral part of experimentation. Medical epistemology must also account for the fact industry influences which questions get asked and which methods are chosen to answer them. It must account for the fact that science is conducted in a regulated environment and that many experiments are conducted as marketing exercises (e.g. seeding trials). Similarly, it must be an epistemology that concerns itself, not only with the production of knowledge, but with the dissemination of knowledge.

Such an epistemology is not a subjectless system of theories, it is an epistemology populated with doctors, patients, researchers, journal editors, marketers, pharmaceutical executives, and federal regulators. A medical epistemology that aims to be applicable to real-world decisions must consider the circumstances in which medical knowledge is produced and consumed. In short, a medical epistemology capable of answering practical questions must be a social epistemology.

6 Medical knowledge in a social world

In contrast to an epistemological focus on an isolated knower confronting a fixed set of evidence, social epistemology attempts "to come to grips with the social interactions that both brighten and threaten the prospects for knowledge" (Goldman 1999, p. vii). There is, as of yet, no sufficiently robust account of medical epistemology. There are, however, a number of plausible candidate frameworks that may serve as starting points. While a full account of medical epistemology as social epistemology is beyond the scope of this article, I will briefly outline three prominent social epistemologies.

Each of the accounts emerged in the wake of "the science wars" and were attempts to incorporate insights from sociology of scientific knowledge, while maintaining some epistemological virtue (e.g. objectivity, truth, rationality). In each case they do so by showing that the epistemological virtue of the group may obtain, even if the group members are epistemologically sullied. Because these accounts are motivated by an attempt to defend the epistemic status of science and because they see the main threat as social bias, they do not fully capture the way that industry funding systematically affects inquiry. Nevertheless, they each contain tools that will be helpful for future philosophical work.

Above, I argued that friction-free epistemology does not capture important ways that industry shaped both the debate about methodology and the research agenda (3.1), as well playing a central role in the dissemination of information (3.2), such that by the time drugs were on the market, the medical literature—if taken at face-

value—provided good reason to prescribe antiarrhythmic drugs (4). Below, I will briefly survey the social epistemologies of Helen Longino (2002), Goldman (1999), and Solomon (2001). I will show that each of their views can accommodate at least one crucial aspect that led to the antiarrhythmic drug disaster, but which is neglected by friction-free epistemology.

6.1 Longino's critical contextual empiricism

Helen Longino (2002) takes as her starting point an assumption upheld both by both sides of the science wars, viz., that some line of reasoning is rational if and only if social influences do not play a role. Her first project is to dissolve this false dichotomy and then to provide "an account of scientific knowledge that is responsive to the normative uses of 'knowledge' *and* to the social conditions in which science is produced" (Longino 2002, p. 1, italics in original). Drawing on the work of sociologists of scientific knowledge (e.g. Barnes, Bloor, Latour, Knorr-Cetina), she accepts that science is a social activity. Not only do scientists inherit methods, concepts, and standards from a community, Longino proposes that the very processes that are responsible for the production of scientific knowledge are social processes.

While conceding that it is the individual that is the knower, Longino claims that—for both observation and reasoning—individuals are interdependent, and the production of knowledge is a community achievement. For example, in the arrhythmia case, before potential observations (VEB data) could be brought to bear on establishing pharmacological efficacy, the community first had to resolve which categories were to be used to organize the data (e.g. should the Lown criteria be used to stratify patients into categories according to the severity of their arrhythmias). Likewise, whether demonstrating VEB suppression was sufficient to establish a conclusion about the efficacy of antiarrhythmic drugs was debated within the community of cardiologists (both via journal articles, and in person at conferences). Crucially, Longino sees this process of debate within the community as a cognitive/rational process and interrogates the conditions under which we should consider the deliverances of such debate to be knowledge.

Granting that individual scientists will be affected by various biases, Longino (2002) holds that the processes involved in critical discourse "transform the subjective into the objective, not by canonizing one subjectivity over others, but by assuring that what is ratified as knowledge has survived criticism from multiple different points of view" (2002, p. 129). Meeting such a standard requires: (a) that there are *venues* for critical discourse to discuss methods, findings, assumptions, and evidential standards; (b) that there is *uptake* of criticism by the community when it is warranted; (c) that there are commonly agreed upon goals and publicly available standards of evaluation, such that debate can be adjudicated in a non-capricious manner; and (d) that the distribution of authority in the community respects the condition of *tempered equality*.[16]

[16] Longino (2002) adds "tempered" to her earlier (1990) criterion of equality to ensure that authority is not doled out irrespective of training or track record. A member of the community can lose authority if, for example, they dogmatically adhere to their position in light of cogent criticism. It is also worth noting that in the ideal community, not only must opposing views be given a venue, but the community has a positive

Given its focus on the resolution of scientific disagreement, critical contextual empiricism is especially well-suited to analyze the process that codified the use of VEBs as a surrogate endpoint. As described in 3.1, by its very nature, the conference served as a venue for critical discourse and significant portions of the day were set aside for discussion with appeals to shared standards of evaluation. However, as we saw, Morganroth repeatedly attempted to shut down debate over whether the arrhythmia hypothesis was well-supported. Moreover, depending on how exactly one cashes out the requirement of tempered equality, it seems there is a case to make that Morganroth assumed a disproportionately influential role in the deliberation (explicitly in discussion, but less detectably and perhaps more consequentially in agenda-setting for the conference). By identifying severe violations of the ideal epistemic community, critical contextual empiricism identifies one of the major components that led to the disaster.

6.2 Goldman's V-value

Friction-free epistemology divorces knowledge and evidence from its context and asks what the individual, generic, self-sufficient subject can infer from a body of evidence (Grasswick 2004). From this perspective medical knowledge might be equated with what knowledge was possible given a god's-eye view of the evidence available at a given time. In contrast, Goldman's (1999) account focusses attention on the degree to which community members actually know important facts. Goldman conceives of the *mental infosphere* as the set of all of the beliefs held by a relevant group, and defines human knowledge as the subset of beliefs that are true. Veritistic social epistemology aims to assess practices insofar as they affect the group's veritistic value (V-value), which roughly equates to the extent to which the mental infosphere is populated with true beliefs on questions of interest.[17]

The difference between these two views of knowledge can be stark. In regards to the evidence before the CAST trial, a friction-free approach considers the studies produced by critics like Winkle and advocates like Morganroth in terms of their methodological rigor, and their absolute (or comparative) significance. In Goldman's framework, the central question becomes: What do treating physicians believe? Moving beyond just abstract questions about what evidence existed, the V-value of the cardiology community incorporates considerations of how information circulated.
This epistemological view grants relevance to the fact that positive trials were published in multiple venues, while negative trials met with more resistance. So too, that researchers supporting the broad use of antiarrhythmic drugs gained positions of influence in the community as a result of their ties to industry.On the friction-free account, the millions of dollars that companies spent on seeding trials do not figure into the picture because the methodological design of the trials is such that they do not generate

Footnote 16 continued
duty to "take active steps to ensure that alternative points of view are developed enough to be a source of criticism and new perspectives" (2002, p. 132).

[17] For a full defense of veritistic value see pp. 87–99; for Goldman's development of infospheres see Chapt. 6, esp. pp. 161–165.

reliable evidence. In contrast, because seeding trials are extremely effective at altering practicing physicians' beliefs about treatment decisions, they are an integral part of social epistemology. Similarly, on the friction-free account, the CAST trials are held up as a canonical example of good evidence (Howick 2012; Straus et al. 2005); however, as Morganroth bemoaned, "The issue is, which is much more important, is that despite all these articles… physicians have ignored it." (Morganroth, quoted in Moore 1995, p. 246). This failure is captured in Goldman's conception of knowledge; the community's V-value is only affected when knowledge is successfully disseminated.

Friction-free epistemology focusses its attention on the validity and reliability of evidence, but even in cases where there is valid and reliable evidence against use, selectively highlighting positive information (whether by advertising, or by selectively promoting positive studies) can lead to the widespread use of ineffective treatments (Holman and Bruner 2015). A focus on the technology and economics of communication is crucial because industry funding can corrupt medical decision-making, not just by influencing study design, but also by occupying a central role in the dissemination of information (Sismondo 2007, 2009, 2017).

With its focus on both the creation *and* the transmission of knowledge, Goldman's social epistemology opens up conceptual space to incorporate both. It also makes room for the study of third parties that impact the flow of communication between senders and receivers. In this class, Goldman includes journal editors, media sponsors, and government agencies such as the FCC and the FDA; essentially any party that alters the substance or affects the visibility of messages. Even when these parties are not sending a message themselves, their actions have veritistic consequences by serving as "gatekeepers" of communication channels,

> given the importance of gatekeepers … social epistemology must inquire into the practices available to gatekeepers and the veritistic consequences that might flow from these practices. Casting our net more widely, we should examine not only the practices of individual gatekeepers, but the fundamental institutional arrangements or frameworks that influence the dissemination of thought and idea. (Goldman 1999, p. 189)

As examples of gatekeeping functions, Goldman includes both explicit forms, such as government regulation, and indirect forms, such as when television companies refrain from airing a negative story about one of their advertisers. As discussed above, Winkle faced precisely this issue in trying to publish his research on the dangers of antiarrhythmic drugs. Moreover, the wide-spread use of antiarrhythmic drugs was driven by commercially-funded CME events and extensive publication planning by the pharmaceutical manufacturers' marketing department. Finally, FDA policy influences both the type of evidence produced and various aspects of its dissemination.

There are a wide-variety of activities that impact what doctors believe and what drug they ultimately prescribe. The god's-eye view of the available empirical evidence only scratches the surface of these influences. If our concern is what practices the medical community should adopt to form beliefs in the real world, then the purview of medical epistemology must be enlarged. Goldman's account accommodates the issues identified in Sect. 3.2 as a natural and necessary part of medical epistemology.

6.3 Solomon's social empiricism

Rather than focus on institutions, Solomon (2001) is primarily focused on the conclusions reached by scientific communities and when they should be considered rational. Making a sharp break with all but a small handful of philosophers of science before her (e.g. Mill, Feyerabend, and Longino), Solomon claims that dissensus can be the normative state of science and lays out the conditions under which active dissent should be maintained in a scientific community. Specifically, Solomon divides factors into those that incline a scientist to accept an empirically successful theory (empirical decision vectors) and those that do not (non-empirical decision vectors). Preference for a theory with successful novel predictions is an example of the former, whereas alignment with political ideology would be an example of the latter.[18] Scientific consensus is appropriate when only one theory has unique empirical successes (i.e. any empirical success of rival theories can be accommodated in the consensus theory and not vice versa).

By focusing on the scientific community, social empiricism divorces the rationality of a community from the rationality of any of the individual members. Solomon argues that non-empirical decision vectors are always present, but their mere presence does not imply the irrationality of the scientific community. It is only when non-empirical decision vectors are not equally distributed amongst rival theories that debate is being irrationally closed (or prolonged). One might see this as early instantiation of what has recently been called the independence thesis—that the epistemic properties of a group can differ from the properties of the individuals that make them up (Mayo-Wilson et al. 2011). Solomon proposes that the scientific community is in the normatively appropriate state when empirical decision vectors are distributed equitably (in proportion to the empirical success of that theory) and the non-empirical decision vectors are distributed equally among competing theories.

By neutrally highlighting the importance of empirical decision vectors such as egocentrism, Solomon's account can explain why Morganroth and Winkle defended different views without (necessarily) concluding that either of them was operating in bad faith.[19] Likewise, perhaps the greatest strength of social empiricism is that it allows an analysis that doesn't immediately equate pharmaceutical involvement with negative outcomes. Recall that in Sect. 4, I showed that the arrhythmia suppression hypothesis had numerous empirical successes to its credit: that the relation between VEBs and mortality held even after controlling for the structural integrity of the heart (Bigger et al. 1984; Lown 1979; Mukharji et al. 1982); that 80% sudden deaths were precipitated by an arrhythmia (Morganroth 1984, p. 673); that antiarrhythmic drugs had the capacity to prevent direct stimulation from evoking tachyarrhythmia (Anderson et al. 1983). A full social empirical analysis of this episode may in fact show that the

[18] For a full treatment of decision vectors, see chapter 4 of Solomon (2001).

[19] Solomon classes an egocentric bias towards one's own data as an empirical vector because it is preference for a theory on an empirical basis. In this case, recall that Winkle was one of the first to publish on arrhythmogenic effects and Morganroth was conducting research on using VEBs as a proxy for establishing the efficacy of antiarrhythmic drugs. Accordingly, the salience of their own data would be an empirical decision vector for each of their respective views. Incidentally, contrary to his portrayal by Moore (1995), my reading is that Morganroth was largely operating in good faith.

arrhythmia suppression hypothesis had the majority of empirical decision vectors and thus, cardiologists were rationally devoting most of their efforts towards the theory. The fact that social empiricism can incorporate industry as a source of bias without immediately concluding that such an influence is deleterious is certainly to be counted amongst the virtues of Solomon's views.[20]

7 The limitations of friction-free epistemology

Each of the three views rehearsed in Sect. 6 allows epistemologists some accessibility to a crucial aspect of medical research that is otherwise ignored. Furthermore, social epistemology admits other crucial issues beyond the role of commercial interests such as fraud (Bright 2017), the influence of social categories (e.g. race, gender, etc.) on medical knowledge (Merrick forthcoming) and the local epistemologies of medical subdisciplines (Walker and Rogers 2014).[21] That said, this should not be taken as a full-throated endorsement of any of the accounts reviewed above. For example, in focusing on decisions that individuals make, social empiricism obscures the structural features of medical science discussed in Sect. 3.2.

It should also be said that the discussion of various social epistemologies should not be taken to endorse stitching together these disparate views; I have glossed over deep philosophical differences between them that would make that a tall order.[22] Apart from these differences, recent work has suggested that the presence of industry funding complicates matters in ways that are not incorporated in the original articulation of the views.[23] What I take this paper to have shown is that social epistemology provides purchase on the central threats to reliable medical knowledge and as such, is a promising framework for further development.

In contrast, a friction-free epistemology that abstracts away from "sociological factors" and considers only ideal RCTs is an epistemology that confines itself to inferential errors from a fixed set of evidence and seeks to identify ways of avoiding mistakes. But it was not by chance that researchers who favored an expansive treatment indication became prominent figures in the cardiology community. It was not due to an

[20] Which is not to say that this is what the analysis would in fact show, I mean to highlight here that Solomon's view has the virtue of neither being naïve to the presence of industry funding nor too cynical to think that industry-funded research is never dispositive. Goldman's (1999) view has this virtue as well, whereas the power imbalances created by industry seem to make it impossible to satisfy Longino's (2002) account within the current system (see especially p. 131).

[21] I would like to thank Manuela Fernández Pinto, Phyllis Illari, and an anonymous reviewer for pushing me on this point. While, the general trend within social epistemology has been a movement to examine particular cases which produce narrowly tailored normative suggestions, I believe that there is also philosophical work to be done that will apply to medical epistemology writ large (indeed, even industry-funded science generally). In part, this is because companies are using the same tactics across industrial sectors (White and Bero 2010).

[22] For some of the tensions between social empiricism and critical contextual empiricism see Solomon (2015a, b).

[23] For critiques of Longino with specific reference to commercial pressures in science see Biddle (2007), Jukola (2015), Fernández Pinto (2014). For Solomon's emendation on her own view see Solomon (2015a). Solomon (2015b) has recently written extensively on medicine, but while a work in social epistemology, it does not draw heavily on social empiricism.

error that researchers in influential positions dismissed the possibility that arrhythmic drugs were dangerous. It was not a mistake that rank and file doctors were more likely to encounter research that supported the efficacy and safety of these drugs. A friction-free epistemology simply does not capture our friction-filled world.

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References

Abramson, J. (2004). *Overdosed America*. New York: Harper Collins.

Altman, L. (1999). Inside medical journals, a rising quest for profits. *New York Times*, *24*, F1.

Anderson, J., Lutz, J., & Allison, S. (1983). Electrophysiologic and antiarrhythmic effects of oral flecainide in patients with inducible ventricular tachycardia. *Journal of the American College of Cardiology*, *2*, 105–114.

Anderson, J., Stewart, J., & Crevey, B. (1984). A proposal for the clinical use of Flecainide. *American Journal of Cardiology*, *53*, 112B–119B.

Anderson, J. L., Stewart, J. R., Perry, B. A., Van Hamersveld, D. D., Johnson, T. A., & Pitt, B. (1981a). Oral flecainide acetate for elimination of ventricular arrhythmias in man. *The American Journal of Cardiology*, *47*, 482.

Anderson, J. L., Stewart, J. R., Perry, B. A., Van Hamersveld, D. D., Johnson, T. A., Conard, G. J., et al. (1981b). Oral flecainide acetate for the treatment of ventricular arrhythmias. *New England Journal of Medicine*, *305*(9), 473–477.

Angell, M. (2004). *The truth about drug companies*. New York, NY: Random House Press.

Avorn, J. (2004). *Powerful medicines: The benefits, risks, and costs of prescription drugs*. New York, NY: Alfred A. Knopf.

Bass, A. (2008). *Side effects*. Chapel Hill, NC: Algonquin Books.

Biddle, J. (2007). Lessons from the Vioxx debacle: What the privatization of science can teach us about social epistemology. *Social Epistemology*, *21*, 21–39.

Bigger, J, Jr., Fleiss, J., Kleiger, R., Miller, J., & Rolnitzky, L. (1984). The relationship between ventricular arrhythmias, left ventricular dysfunction and mortality in the two years after myocardial infarction. *Circulation*, *69*, 250–258.

Bright, L. K. (2017). On fraud. *Philosophical Studies*, *174*, 291–310.

Broadbent, A. (2011). Inferring causation in epidemiology: Mechanisms, black boxes, and contrasts. In P. Illari McKay, F. Russo, & J. Williamson (Eds.), *Causality in the sciences* (pp. 45–69). Oxford: Oxford University Press.

Brody, H. (2007). *Hooked: Ethics, the medical profession, and the pharmaceutical industry*. Lanham, MD: Rowman and Littlefield.

Campbell, R. W. (1981). Evaluation of antiarrhythmic drugs: Should the Lown classification be used. In E. N. J. Morganroth (Ed.), *The evaluation of new antiarrhythmic drugs* (pp. 113–122). Boston, MA: Martinus Nijhoff Publishers.

Cartwright, N. (2007). Are RCTs the gold standard? *Biosocieties*, *2*, 11–20.

Cartwright, N. (2009). What is this thing called "efficacy"? In C. Mantzavinos (Ed.), *Philosophy of the social sciences. Philosophical theory and scientific practice* (pp. 185–206). Cambridge: Cambridge University Press.

Cartwright, N. (2010). What are randomized controlled trials good for? *Philosophical Studies*, *147*, 59–70.

Cartwright, N. (2011). A philosophers view of the long road from RCTS to effectiveness. *The Lancet*, *377*, 1400–1401.

Cartwright, N., & Hardie, J. (2012). *Evidence-based policy*. Oxford: Oxford University Press.

Cartwright, N., & Stegenga, J. (2011). A theory of evidence for evidence-based policy. In P. Dawid, W. Twinning, & M. Vasilaki (Eds.), *Evidence, inference and enquiry* (pp. 291–322). Oxford: Oxford University Press.

CAST Investigators. (1989). Preliminary report: Effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *New England Journal of Medicine*, *321*, 406–12.

CAST II Investigators. (1992). Effect of the antiarrhythmic agent Moricizine on survival after myocardial infarction. *New England Journal of Medicine*, *327*, 227–233.

Clarke, B., Gillies, D., Illari, P., Russo, F., & Williamson, J. (2014). Mechanisms and the evidence hierarchy. *Topoi*, *33*, 339–360.

CPC (Council on Pharmacy and Chemistry). (1914). The hypophosphite fallacy. *JAMA*, *67*, 760–762.

Cosgrove, L., Vannoy, S., Mintzes, B., & Shaughnessy, A. F. (2016). Under the influence: The interplay among industry, publishing, and drug regulation. *Accountability in Research*, *23*, 257–279.

Cowley, A., Skene, A., Stainer, K., & Hampton, J. (1993). The effect of Lorcainide on arrhythmias and survival in patients with acute myocardial infarction: An example of publication bias. *International Journal of Cardiology*, *40*, 161–166.

Crowley, P. (1981). Corticosteroids in pregnancy: The benefits outweigh the cost. *Journal of Obstetrics and Gynaecology*, *1*, 1147–150.

Dragulinescu, S. (2012). On 'Stabilising' medical mechanisms, truth-makers and epistemic causality: A critique to Williamson and Russo's approach. *Synthese*, *187*, 785–800.

Dragulinescu, S. (2017). Mechanisms and difference-making. *Acta Analytica*, *32*, 29–54.

Duff, H. J., Roden, D. M., Maffucci, R. J., Vesper, B. S., Conard, G. J., Higgins, S. B., et al. (1981). Suppression of resistant ventricular arrhythmias by twice daily dosing with flecainide. *The American Journal of Cardiology*, *48*, 1133–1140.

Duff, H. J., Roden, D. M., & Woosley, R. L. (1980). Abolition of resistant ventricular arrhythmias by twice daily dosing with flecainide. *Circulation*, *62*, 181.

Elliott, C. (2010). *White coat black hat: Adventures on the dark side of medicine*. Boston: Beacon Press.

Epstein, S. (1996). *Impure science. Aids and the politics of knowledge*. Berkeley-Los Angeles: University of California Press.

Fernández Pinto, M. (2014). Philosophy of science for globalized privatization: Uncovering some limitations of critical contextual empiricism. *Studies in History and Philosophy of Science Part A*, *47*, 10–17.

Fink, D., & Howell, I. (2000). How does Cisplatin kill cells? In I. Kelland & N. Farrell (Eds.), *Platinum-based drugs in cancer therapy* (pp. 149–167). Totowa: Humana Press.

Fuller, J. (in press). The confounding question of confounding causes in randomized trials. *British Journal for the Philosophy of Science*.

González-Moreno, M., Saborido, C., & Teira, D. (2015). Disease-mongering through clinical trials. *Studies in History and Philosophy of Science Part C: Studies in History and Philosophy of Biological and Biomedical Sciences*, *51*, 11–18.

Goldman, A. (1999). *Knowledge in a social world*. New York, NY: Oxford University Press.

Graboys, T., Lown, B., Podrid, P. J., & DeSilva, R. (1982). Long-term survival of patients with malignant ventricular arrhythmia treated with antiarrhythmic drugs. *The American Journal of Cardiology*, *50*, 437–443.

Grasswick, H. E. (2004). Individuals-in-communities: The search for a Feminist model of epistemic subjects. *Hypatia*, *19*(3), 85–120.

Healy, D. (2012). *Pharmageddon*. Berkeley: University of California Press.

Hine, L., Laird, N., Hewitt, P., & Chalmers, T. (1989). Meta-analysis of empirical long-term antiarrhythmic therapy after myocardial infarction. *JAMA*, *262*, 3037–3040.

Hodges, M., Haugland, J. M., Granrud, G., Asinger, R. W., Mikell, F. L., & Krejci, J. (1981). Flecainide acetate, a new antiarrhythmic agent: Dose-ranging and efficacy study. *The American Journal of Cardiology*, *47*, 482.

Hodges, M., Haugland, J. M., Granrud, G., Conard, G. J., Asinger, R. W., Mikell, F. L., et al. (1982). Suppression of ventricular ectopic depolarizations by flecainide acetate, a new antiarrhythmic agent. *Circulation*, *65*(5), 879–885.

Hoffman, B. F. (1981). Relationship between effects on cardiac electrophysiology and antiarrhythmic efficacy. In J. Morganroth, E. N. Moore, L. S. Dreifus, & E. L. Michelson (Eds.), *The evaluation of new antiarrhythmic drugs* (pp. 5–16). Boston, MA: Martinus Nijhoff Publishers.

Holman, B. (2015). Why most sugar pills are not placebos. *Philosophy of Science*, *82*, 1330–1343.

Holman, B., & Bruner, J. (2015). The problem of intransigently biased agents. *Philosophy of Science*, *82*, 956–968.

Holman, B., & Bruner, J. P. (2017). Experimentation by industrial selection. *Philosophy of Science*, *84*, 1008–1019.

Howick, J. (2012). *The philosophy of evidenced-based medicine*. West Sussex: British Medical Journal Books.

Illari, P. M. (2011). Mechanistic evidence: Disambiguating the Russo–Williamson thesis. *International Studies in the Philosophy of Science*, *25*, 139–157.

Illari, P. (2017). Mechanisms in medicine. In M. Solomon, J. Simon, & H. Kincaid (Eds.), *Routledge companion to philosophy of medicine* (pp. 48–57). New York, NY: Routledge.

Jukola, S. (2015). Longino's theory of objectivity and commercialized research. In S. Wagenknecht, N. Nersessian, & H. Andersen (Eds.), *Empirical philosophy of science: Introducing qualitative methods into philosophy of science* (pp. 127–143). Berlin: Springer.

Jureidini, J. N., Amsterdam, J. D., & McHenry, L. B. (2016). The citalopram CIT-MD-18 pediatric depression trial: Deconstruction of medical ghostwriting, data mischaracterisation and academic malfeasance. *International Journal of Risk and Safety in Medicine*, *28*(1), 33–43.

Kassirer, J. (2005). *On the take*. Oxford: Oxford University Press.

Krimsky, S. (2003). *Science in the private interest: Has the lure of profits corrupted medical research?*. Landham, MD: Rowman and Littlefield.

Lenzer, J. (2003). Marketing: Spin doctors soft pedal data on antihypertensives. *British Medical Journal*, *326*, 170.

Longino, H. E. (1990). *Science as social knowledge: Values and objectivity in scientific inquiry*. Princeton, NJ: Princeton University Press.

Longino, H. E. (2002). *The fate of knowledge*. Princeton, NJ: Princeton University Press.

Lown, B. (1979). Sudden cardiac death: The major challenge confronting contemporary cardiology. *The American Journal of Cardiology*, *43*, 313–328.

Mayo, D., & Spanos, A. (2010). *Error and inference: Recent exchanges on experimental reasoning, reliability, and the objectivity and rationality of science*. New York, NY: Cambridge University Press.

Mayo-Wilson, Connor, Zollman, Kevin J., & Danks, David. (2011). The independence thesis: When individual and social epistemology diverge. *Philosophy of Science*, *78*, 653–677.

Merrick, T. (forthcoming). From 'Intersex' to 'DSD': A case of epistemic injustice. *Synthese*. http://doi.org.ssl.access.yonsei.ac.kr:8080/10.1007/s11229-017-1327-x

Moore, T. (1995). *Deadly medicines: Why tens of thousands of heart patients died in America's worst drug disaster*. New York, NY: Simon and Schuster.

Morganroth, J. (1981a). *The evaluation of new antiarrhythmic drugs*. Boston, MA: Martinus Nijhoff Publishers.

Morganroth, J. (1981b). Long-term ambulatory electrocardiographic recording in the determination of efficacy of new antiarrhythmic drugs. In E. N. J. Morganroth (Ed.), *The evaluation of new antiarrhythmic drugs* (pp. 103–112). Boston, MA: Martinus Nijhoff Publishers.

Morganroth, J. (1983). Study design for patients with chronic ventricular ectopy: Determination of efficacy and tolerance. In J. Morganroth & E. Moore (Eds.), *Sudden cardiac death and congestive heart failure: Diagnosis and treatment* (pp. 64–73). Boston, MA: Martinus Nijhoff Publishers.

Morganroth, J. (1984). Premature ventricular complex. *JAMA*, *252*, 673–676.

Moynihan, R., & Cassels, A. (2006). *Selling sickness: How the world's biggest pharmaceutical companies are turning us all into patients*. New York, NY: Nation Books.

Mukharji, J., Rude, R., Poole, K., Croft, C., Thomas, L., Braunwald, E., & Cooperating Investigators . (1982). Late sudden death following acute myocardial infarction: Importance of combined presence of repetitive ventricular ectopy and left ventricular dysfunction. *Clinical Research*, *30*, 108A.

Popper, K. (1970). Normal science and its dangers. In Imre Lakatos & Alan Musgrave (Eds.), *Criticism and the growth knowledge*. Cambridge: Cambridge University Press.

Robinson, M. (2014). *Neuro-innovation: Translational science, ethics and the financialization of health* (Doctoral Dissertation, Princeton University).
Roden, D., Reele, S., Higgins, S., Mayol, R., Gammans, R., Oates, J., et al. (1980). Total suppression of ventricular arrhythmias by encainide: Pharmacokinetic and electrocardiographic characteristics. *New England Journal of Medicine*, *302*, 877–882.
Russo, F., & Williamson, J. (2007). Interpreting causality in the health sciences. *International Studies in the Philosophy of Science*, *21*, 157–170.
Russo, F., & Williamson, J. (2011). Epistemic causality and evidence-based medicine. *History and Philosophy of the Life Sciences*, *33*, 563–581.
Sismondo, S. (2007). Ghost management: How much of the medical literature is shaped behind the scenes by the pharmaceutical industry? *PLoS Medicine*, *4*(9), e286.
Sismondo, S. (2009). Ghosts in the machine: Publication planning in the medical sciences. *Social Studies of Science*, *39*, 171–198.
Sismondo, S. (2017). Hegemony of knowledge and pharmaceutical industry strategy. In D. Ho (Ed.), *Philosophical issues in pharmaceutics* (pp. 47–63). Dordrecht: Springer.
Solomon, M. (2001). *Social empiricism*. Cambridge, MA: MIT Press.
Solomon, M. (2015a). Expert disagreement and medical authority. In Kenneth S. Kendler & Josef Parnas (Eds.), *Philosophical issues in psychiatry III: The nature and sources of historical change* (pp. 60–72). Oxford: Oxford University Press.
Solomon, M. (2015b). *Making medical knowledge*. Oxford: Oxford University Press.
Stegenga, J. (2014). Down with the hierarchies. *Topoi*, *33*, 313–322.
Straus, S., Richardson, W., Glasziou, P., & Haynes, R. (2005). *Evidence-based medicine: How to practice and teach EBM* (3rd ed.). Edinburgh: Churchill Livingstone.
Vedula, S. S., Goldman, P. S., Rona, I. J., Greene, T. M., & Dickersin, K. (2012). Implementation of a publication strategy in the context of reporting biases: A case study based on new documents from Neurontin® litigation. *Trials*, *13*, 136.
Velebit, V., Podrid, P., Lown, B., Cohen, B., & Graboys, T. (1982). Aggravation and provocation of ventricular arrhythmias by antiarrhythmic drugs. *Circulation*, *65*, 886–894.
Walker, M. J., & Rogers, W. (2014). What can feminist epistemology do for surgery? *Hypatia*, *29*, 404–421.
Whitaker, R. (2010). *Anatomy of an epidemic: Magic bullets, psychiatric drugs, and the astonishing rise of mental illness in America*. New York, NY: Crown Publishers.
White, J., & Bero, L. A. (2010). Corporate manipulation of research: Strategies are similar across five industries. *Stanford Law and Policy Review*, *21*, 105.
Winkle, R., Mason, J., Griffin, J., & Ross, D. (1981). Malignant ventricular tachyarrhythmias associated with the use of encainide. *American Heart Journal, 102*, 857–864.
Woosley, R. (1990). CAST: Implications for drug development. *Clinical Pharmacology and Therapeutics*, *47*, 553–556.
Worrall, J. (2002). What evidence in evidence-based medicine? *Proceedings of the Philosophy of Science Association*, *69*, S316–S330.
Worrall, J. (2007a). Evidence in medicine and evidence-based medicine. *Philosophy Compass*, *2*, 981–1022.
Worrall, J. (2007b). Why there's no cause to randomize. *British Journal for the Philosophy of Science*, *58*, 451–488.
Worrall, J. (2010). Evidence: Philosophy of science meets medicine. *Journal of Evaluation in Clinical Practice*, *16*, 356–362.