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ORIGINAL ARTICLE

Epistemology of the side effect: anecdote and evidence in the digital age

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Abstract

Through the history of rxisk.org, this article explores some of the Web's effects on the production and circulation of pharmaceutical knowledge. RxISK is an independent website that solicits reports from patients in order to uncover drug-induced harms which clinical trials and national pharmacovigilance schemes fail to identify. The first part of the article locates the origins of the project in the nearly 15-year struggle to obtain recognition and redress for one particular side effect of selective serotonin reuptake inhibitor (SSRI) antidepressants—their ability to trigger violent or suicidal behavior. That struggle, I show, brought to light the ways in which modern evidence-making practices obscure the harms of pharmacological treatment. The second part, based on interviews with the site's creators, examines how RxISK's data collection practices seek to convert the Web from a site for the circulation of misinformation into a usable source of new knowledge about drugs. The project's originality, I argue, lies in its effort to reframe the relation between anecdote and evidence so as to liberate the patient's voice from the burden of representativeness. Within this reframed epistemology, the project is also freed from the imperative of large-scale data extraction that increasingly dominates the economy of digital health.

Keywords Adverse drug reactions · Antidepressants · Clinical trials · Pharmacovigilance · Crowdsourcing

A woman is prescribed a daily estrogen supplement early in menopause. Her bone density shows a slight increase, but shortly after she turns 60 a biopsy reveals a malignancy in one of her ovaries. A healthy middle-aged man receives a third dose of an mRNA COVID vaccine, and within 2 weeks suffers a stroke that leaves him durably disabled. An anxious teenager is put on an antidepressant and, at a follow-up

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visit a month later, reports improvement; her dose is augmented and she commits suicide after a week.

What do stories of this kind tell us about the drugs and disorders they involve? All follow the familiar script of the side-effect story in which 'adverse events' occur after the taking of a drug and are presumed to be related to it. But are they? Often illness or injury merely follows the taking of a drug; only in some cases do they follow *from* it, with no easy way of telling which. What we call evidence-based medicine finds certainties only in large numbers, those of vast controlled trials or (merely a second best) of even vaster observational studies, not in individual cases. In other words, the trials and studies of clinical epidemiology only ever measure a risk. They establish how likely it is that a particular outcome resulted from exposure to a substance; never do they confirm that it actually has in any particular case. As the skills of the statistician replace those of the clinician, the knowledge of the individual gained through the eye and the touch, and through narrative and judgment, yields to the statistically significant findings of controlled studies. When there is truth only in structured aggregates, single clinical cases in which a rare and unexpected effect may come to light are downgraded to the status of anecdotes—of 'mere stories,' often tragic but always stripped of any general truth value. In this way the epistemology of modern medical science has had far-reaching implications for the recognition of so-called 'adverse drug events,' the injuries modern medicine routinely inflicts on those in its care.

This essay is about the fate of side-effect stories after they are dismissed as anecdotes, when they are heard but not listened to, accepted as real but deemed insignificant. Etymologically, 'anecdotal' means 'unpublished.' Nowadays, though, there is a place for stories that fail to appear in authorized publications. Since its beginnings three decades ago, the World Wide Web has provided a kind of universal repository, an expansive, unstructured, but searchable database within which stories stripped of official imprimatur may find a second life. In consequence the Web has grown over time into something like a medical Library of Babel, a beguiling but treacherous trove of information which, like the fictive library in Jorge Luis Borges's famous tale, contains answers to all our questions, but hidden away in stacks upon stacks of misguided, misleading, or merely senseless content (Fig. 1). To reflect on the conditions under which the Web might be converted from a space for the proliferation of misinformation, of dubious stories and unverifiable accounts, into a medium for the production of new knowledge about drugs, I explore the history of a website called rxisk.org. Founded in 2012 by clinicians David Healy and Dee Mangin and medical anthropologist Kalman Applbaum to solicit side-effect reports from those who take (rather than those who prescribe) drugs, RxISK has fashioned itself explicitly as an outlet for stories not heard or accepted elsewhere, while also having to craft its own brand of expertise and devise its own methods to salvage those stories from the epistemic limbo of the Web.

As scholars, we are still working out methods to turn websites into objects of rigorous study. This paper combines two approaches. A first historical part traces the origins of RxISK back to the early 1990s, the same few years that saw the creation of the Web, the advent of the discourse of 'evidence-based medicine,' and also the introduction of a new generation of antidepressants—drugs like Prozac, Zoloft, or

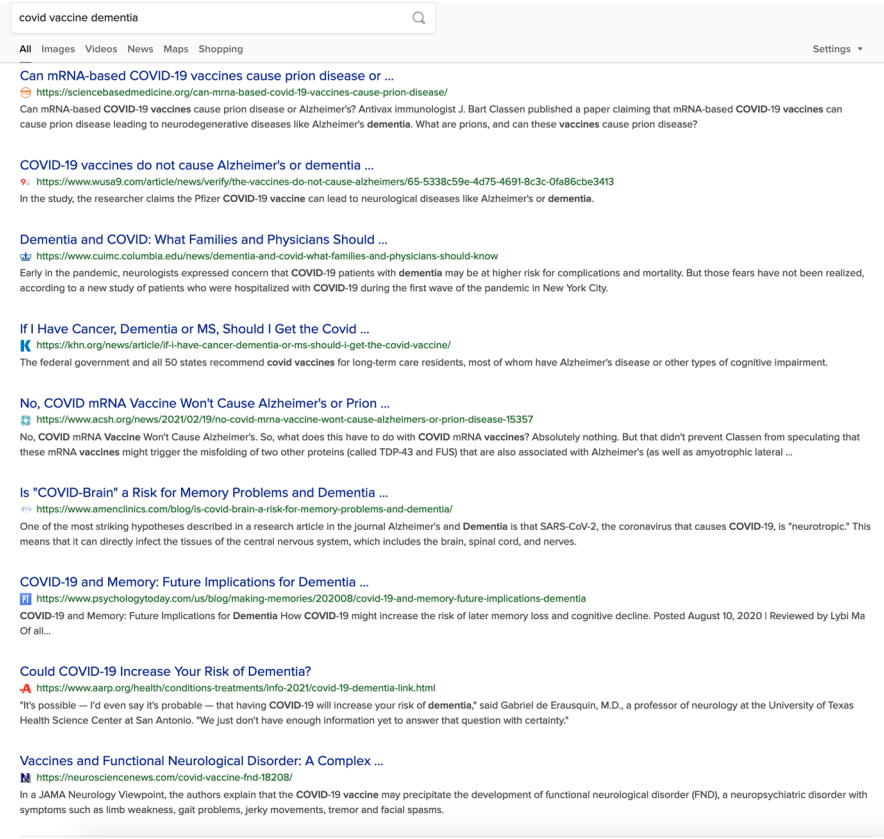


Fig. 1 Side-effect stories on the Web: type the name of a medicine and a side effect you worry about in a search engine, and you are certain to find a confirmation of your worst fears as well as the reassurance you were looking for

Paxil, known collectively as SSRIs (selective serotonin reuptake inhibitors). SSRIs were exemplary of a new kind of 'blockbuster' drugs that were extensively marketed, prescribed to millions of patients for months or years on end, and eventually discovered to cause unsuspected and in some cases lethal harms. As I will show, the nearly 15-year struggle to obtain recognition and redress for one specific side effect of SSRIs—their ability to trigger suicidal or violent behavior—played a key role in crystallizing the rationale for the RxISK project. Much of that struggle played out in the legal arena, and it is an argument of this paper that the forensic origins of RxISK shaped its implicit epistemology in decisive ways.

The latter half of the paper, then, draws on interviews with RxISK's creators and on an analysis of the site's data curation practices to foreground its distinctive place in the landscape of 'eHealth.' RxISK's model is not quite that of the peer-to-peer platform dedicated to the airing and sharing of patient voices. Nor does it rely on the algorithmic mining of large volumes of electronic health data collected from

patients, with or without their consent. As recent work at the intersection of science and media studies made clear, these two seemingly opposite regimes of networked knowledge production are by no means exclusive. The affective economy of airing and sharing increasingly converges with an extractive economy of data collection and commodification, as data brokers exploit the rhetoric of openness, participation, and empowerment to obtain from users the data they subsequently monetize (Lupton 2014; Ostherr 2018; Ruckenstein and Schüll 2017; Van Dijck and Poell 2016). RxISK's originality, I argue, is to seek credibility in a reframing of the relation between anecdote and evidence that, under the right conditions, may liberate the patient's voice from the burden of representativeness. I will describe what RxISK's co-founders understand these conditions to be and how the site works to create them online.

But first, a note about vocabulary. The terms of the art are adverse drug event (ADE) or adverse drug reaction (ADR), and the WHO defines them as any response that is "noxious and unintended and which occurs in doses used in man for prophylaxis, diagnosis, or therapy" (World Health Organization 2002, p. 40).Yet side effect is the better term for my purposes, for the noxious and unintended event, the troublesome perturbation that cannot be predicted and explained away, is not just a pharmacological phenomenon. It is, as Thomas Kuhn theorized in *Structure of Scientific Revolutions*, an inevitable byproduct of any normalized paradigm of knowledge production (Kuhn 1996, pp. 52–53). As such, I hope that the following can be read in two ways: as an argument about an unresolved issue in modern health care, but also as a meditation on the implications of modern evidence-making instruments and institutions, on the relations between narration and truth, and the consequences of shifting media ecologies on the conditions of self-knowledge and self-experience.

Blinding the clinician

Evidence is an equivocal concept. In Latin, where the word comes from, it denotes that which is "obvious to the eye or mind" (per the *Oxford English Dictionary*), or which does not require proof because, in its transparent obviousness, it is proof in and of itself. *Evidentia*, in other words, names those truths which stand on their own and do not need to be supported. In English usage, by contrast, evidence is always evidence *of* something else; it refers to facts or propositions inasmuch as they support other facts or propositions which are not in themselves obvious. Hence the meaning of *evidentia* in Latin is rendered in English as self-evidence, when the something else which the evidence ascertains turns out to be none other than itself. Both meanings fall on opposite sides of a basic epistemological divide between immediate truths and mediated ones, admissible solely on the basis of other admitted or self-evident facts.

Evidence-as-immediacy grounds the classic epistemology of the clinic. In Michel Foucault's description, the clinic as it emerged around 1800 was not a place, a practice, or a discourse, but a "fundamental experience" (Foucault 1994, p. x) in which space, gaze, and language redeployed their relations in radically new and productive ways. By opening up bodies, literally and figuratively, the clinic of the early

nineteenth century linked seeing and knowing in one and the same operation, displacing a "metaphysics of illness" in which bodies were read through texts rather than cut open with the hand and the eye. The clinic, too, understood itself as evidence-based. The evidence it relied on was the self-evidence of the body marked in its flesh by disease, offered without obstacle to the knowing senses of the clinician and captured in a discourse whose inner structure mirrored that of its object.

Likewise, at least for the first two thirds of the nineteenth century, the visible effects of drugs provided the measure of their efficacy. Drugs were embraced for their powers to alter the bodily economy in immediately discernable ways. Digitalis strengthened the pulse; opium weakened it and induced somnolence; quinine lowered fever; emetics or purgatives evacuated the digestive tract. Evidently these drugs *worked* for they affected the body in ways that could be seen or sensed by both physician and patient (Warner 1986). Later in the century the microbiological laboratory broadened the field of what could be visualized, but it did not fundamentally alter an epistemology that linked evidence to visibility. Writing in the early 1960s, Foucault could still describe the era which the birth of the clinic opened around 1800 as "an era from which we have not yet emerged" (Foucault 1994, p. x).

Yet as Foucault captured its logic on paper, the epistemology of the clinic was beginning to unravel. In 1961, the year he drafted *Birth of the Clinic*, the effects of thalidomide came to global attention. Thousands of expecting mothers to whom that drug had been sold as a safe alternative to older sleeping aids gave birth to babies with severely atrophied limbs. The effect was unusual, visually striking, and widely covered in the media, making the thalidomide catastrophe arguably the most consequential event in the recent history of how drugs are researched and regulated. In its wake drug agencies across the western world stopped approving new drugs unless their producers were able to show proof of safety and efficacy in controlled clinical trials. The so-called randomized controlled trial (RCT), still a new and rather marginal methodology in the early 1960s, remade within a decade the entire process of pharmaceutical research and development (Carpenter 2010; Hauray and Urfalino 2007).

The embrace of the RCT in therapeutic research marked a gradual loss of faith in the reliability of clinical judgment, a growing sense that, in clinical matters, self-evidence and self-deception look too much alike. The random assignment of trial participants to a treatment group (where they receive the therapy under investigation) or a control group (where they receive a placebo or comparator drug instead) prevents clinicians' preconceptions as to who is most likely to benefit from the experimental drug from playing a role in the allocation, ensuring that research subjects do not end up in the treatment arm of a trial because they share hidden characteristics that might bias a comparison with those enrolled in the control arm. Whenever possible, random assignment proceeds under a 'double blind,' so that neither the patients-cum-test-subjects nor the clinicians who track their progress throughout the trial know who is treated with the experimental drug and who isn't. In this way the architecture of the RCT deliberately severs the link between seeing and knowing on which the epistemology of the clinic was founded. In modern clinical trials, clinicians give up their role as subjects of knowledge to become mere links in a vast recording and reporting apparatus.

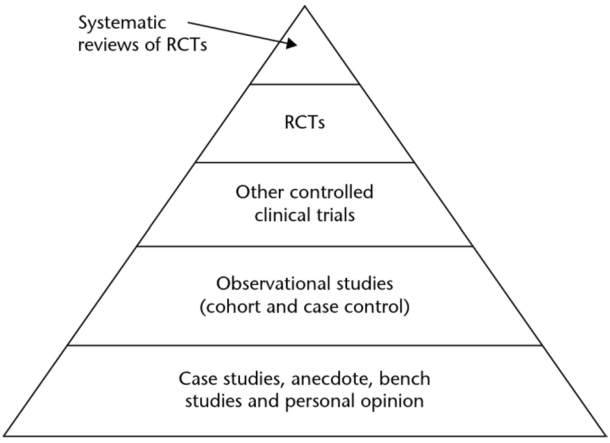


Fig. 2 The hierarchy of evidence. From Trisha Greenhalgh, *How to Read a Paper: The Basics of Evidence-Based Medicine* (Chichester, UK: Wiley-Blackwell, 2010), p. 18. The diagram follows a discussion of the pitfalls of "decision-making by anecdote" (pp 4–5)

The clinical data they log into patients' case report forms do not become knowledge until the trial ends, the 'blind is broken,' and the outcomes of both treatment and control groups can be compared. This is the preserve of the statistician, who reveals the meaning of the data by computing them and calculating their significance.

As data-intensive practices, RCTs evolved in step with electronic information technologies. Like the first electronic computers, they date back to World War II and entered the realm of large corporate and governmental organizations in the 1960s, the age of the mainframe and the punch card. When computers arrived in workplaces, including sites of care, clinical trials began reshaping the practice of medicine as well as the regulation of drugs. The 1992 paper that brought the term 'evidence-based medicine' into circulation just as the Web opened to the public described the transformation in exactly those ways. It opened with the story of an imaginary medical resident who, faced with a difficult case, eschews the guidance of more seasoned clinicians on the ward and instead "proceeds to the library and … conducts a computerized literature search" (Guyatt et al. 1992, p. 2420). Whereas the clinic rested on oral transmission and on the paper chart that documents a single clinical case, the electronic database is the privileged medium of a medical epistemology that locates truth in large data sets. Ease of access to the findings of formal studies (now even the trip to the library can be spared) rendered experience and 'instinct' unnecessary and even suspect. Compared with data produced in experimental settings such as RCTs—the new 'gold standard' of clinical evidence (Jones and Podolsky 2015; Timmermans and Berg 2003)—single clinical cases dropped to the bottom of 'evidence hierarchies.' 'Anecdotal' became a way to lump together the textured case history, once the building block of medical knowledge, with other varieties of biased, speculative, second-hand, or otherwise tainted evidence which clinicians were enjoined to disregard (Fig. 2).

Thus evidence-as-immediacy, gained through the gaze and the touch, gave way in the new medical epistemology to evidence of a mediated kind, one produced away from the day-to-day clinic and channeled back to clinicians expected to adhere to it in their practice. How or how much the new paradigm transformed practice in real clinical settings is a complex empirical question, which sociologists have attempted to answer by querying physicians or observing them at work. Their investigations have yielded a somewhat ambivalent picture, highlighting the growing place of 'evidence-based' clinical guidelines in healthcare governance while also documenting the inertia, skepticism, or resistance of doctors toward developments perceived as undermining their professional autonomy (Dopson et al. 2003; Timmermans and Oh 2010). By considering the implications of EBM through the lens of side effects, I seek to move the analytical focus more fully onto harms suffered by patients. Evidence of such harms is, for reasons outlined in this paper, indirect, elusive, and contested. But its contested nature also makes it valuable in examining the stakes of shifting constructions of the visible and the invisible in medicine.

This is not a side effect

The original exponents of evidence-based medicine saw in randomized trials a means to keep drug companies in check. Findings from controlled trials would empower clinicians to see through the industry's marketing claims and to prescribe the safest and most effective drugs rather than the newest and most expensive (Marks 1997; Podolsky 2010). The vast expansion of the pharmaceutical business in the last three decades, however, suggests a more complex picture. Commissioned and funded by drug manufacturers, RCTs have granted the industry unprecedented influence over the science that is meant to hold it accountable. The trajectory of SSRIs brought this paradox into sharp relief.

Much like thalidomide, SSRI antidepressants were marketed on the basis of their allegedly favorable side-effect profile. Older antidepressants came with notoriously burdensome side effects, so the motto that the new molecules were no less effective yet better tolerated and safer in overdose than older alternatives struck a chord among physicians in primary care as well as in psychiatry. A vast and previously unsuspected market for milder mood disorders opened up, turning Prozac within a few years of its 1988 launch into psychiatry's first "blockbuster" drug. Other companies followed in Eli Lilly's footsteps. By the time Pfizer and SmithKline Beecham launched their SSRIs in the early 1990s, however, the first doubts about the safety of the new drugs had surfaced. Reports about patients who seemed to develop intense suicidal preoccupations on them appeared in the literature. The FDA received several hundred spontaneous adverse event reports from prescribers—880 by July 1991 (FDA 1991, p. 167)—that seemed to confirm the published case reports, calling into question the main selling point on which the industry had staked its marketing of the new molecules.

SSRIs, however, belonged squarely to the post-thalidomide era of drug development. They had undergone extensive clinical trial programs prior to their marketing. The findings from these trials were analyzed and meta-analyzed, peer reviewed, and

published in leading medical journals, and did not appear to show that suicides or suicide attempts were any more frequent on the drug than on placebo (Beasley et al. 1991). Faced on the one hand with a stack of concerning but anecdotal reports, on the other with controlled trial data it had vetted and vouched for, the FDA chose to side with manufacturers. Since self-harm is a familiar complication of clinical depression, regulators in the US and abroad agreed with the companies that any suicides occurring early in a course of treatment were likely due to a worsening of the underlying illness, not to the drug designed to treat it (Healy 1999).

Similar arguments shielded companies against lawsuits brought in US courts by families who had lost members to a suicide or act of violence involving a suspected reaction to an SSRI. The first such case to advance to trial was a suit filed in 1990 by the surviving victims of Joseph Wesbecker, a Louisville pressman who a month into a course of treatment with Prozac embarked on a shooting spree at his workplace that left 8 dead, injured a further 12, and ended with his suicide. Added in evidence in that case were the records of Wesbecker's psychiatrist, who had last seen his troubled patient 3 days before the shooting in September 1989. Dr. Lee Coleman had noted his patient's unusual agitation that day and, suspecting his medication might be the cause, recommended to no avail that Wesbecker discontinue the drug and check himself into a hospital. When Coleman's notes were presented during the 1994 trial to Lilly's chief scientific officer, Dr. Leigh Thompson, a one-sided insistence on the reliability of Lilly's voluminous, FDA-reviewed data supplied the defense (Fentress 1994: 14 October, pp. 46–47):

> Paul Smith (plaintiffs counsel): So when the physicians have … said, "I think it's related to Prozac," your opinion is that they're wrong?
> Leigh Thompson: They are wrong because I now have the benefit from a great deal of data and they were looking at a single patient.
> Q. They were looking at the patient, weren't they?
> A. They were looking at the patient; that's correct.
> Q. They knew the patient, didn't they?
> A. Yes, sir. They knew the patient. …
> Q. They could have been a general practitioner that might have delivered that patient at birth and followed that patient's general medical care for 30 or 40 years; correct?
> A. And maybe delivered the patient's parents. Absolutely. They knew the patient very well.
> Q. And it was their opinion that Prozac was causing the suicidality, but you as the chief scientific officer, because you have more data, dispute that that physician is right?
> A. That's exactly what I said.

Here the uncoupling of the visible and the knowable that defined the new medical epistemology was invoked quite deliberately to rule out the sort of first-hand evidence—the eyewitness account by a person with direct knowledge of the facts—on which the law and the clinic both depend to probe the causes of actual injuries. Whenever trial data are brought to bear on the interpretation of a clinical case, the truth that is hidden away in the single suffering body becomes decipherable solely

through the computed experience of multiple other bodies. This detour has a potent de-realizing effect that voids the single case of its significance, foreclosing the possibility of recognition and redress for harms or injuries not documented in companies' own research about their drugs. In the Wesbecker case, the effort to import EBM's rules of evidence—or at least a certain rigid interpretation thereof—into court had the intended effect. The notion that the clinical trial should somehow preempt the legal one did not go uncontested, but it helped Lilly avert a loss that could have had drastic effects on the future prospects of its bestselling drug (Cornwell 1996; Menzies 2005).

Bearing witness

When he finished medical school in Dublin in the late 1970s, David Healy opted to pursue research training and became involved in experimental work on serotonin reuptake, years before the commercial success of SSRIs made the serotonergic system a topic of widespread scientific interest. In Ireland and then at Cambridge in the UK, Healy became part of a tight research network that linked academic and industry scientists in the booming psychopharmacology field. When he eventually took up a position teaching and practicing psychiatry in Northern Wales in 1990, he was ready to embrace the new generation of antidepressants. "In the place in the UK where I was then, I was the kind of person who would be using these drugs earlier than most of my colleagues … I was keen to use them when they came on the market," he told me, "and pretty early on I had two people who became suicidal on them" (2018, personal communication).[1] In 1991 he published a report in *Human Psychopharmacology* describing these two cases involving Prozac/fluoxetine, one of the first pieces in the medical literature to outline a possible link between the new molecule and the induction of suicidal ideation.

A few years later and many thousands of miles away, Cindy Hall, a junior paralegal at the Los Angeles-based law firm of Baum Hedlund, was at work on the second Prozac case to advance to trial, *Forsyth v. Eli Lilly*. Pharmaceutical litigation was new to the firm and required a considerable investment in time and resources from litigators uninitiated in the arcana of drug research and regulation. But the beginnings of the open Web made the mid-1990s an "exciting time," in Hall's words (2018, personal communication). Much of the biomedical literature was becoming available online through the NIH's new PubMed database. In scouring it, Hall stumbled on Healy's name in a 1994 *Lancet* editorial. Approached by Baum Hedlund in the spring of 1997, Healy agreed to draft a report outlining his expert opinion on the evidence in the *Forsyth* case, and a few weeks later flew to New York to be deposed in a hotel room by the JFK airport (Healy 2004, pp. 87–96).

Given the centrality of clinical trials to the industry's defense, plaintiffs faced a twofold challenge. First came the need to deconstruct clinical trial data. If indeed the

[1] When not otherwise referenced, subsequent quotes from David Healy are drawn from personal communications with the author.

alleged link between antidepressants and suicide was real, why did it fail to register in the extensive clinical studies undertaken on Prozac and other SSRIs? In search for answers, their attorneys reviewed millions of pages of industry records obtained in discovery and relied on hired experts to learn how to read trial data against the grain and reveal their hidden meanings for lay jurors. The documents lifted the veil on industry tactics such as the screening out of research subjects with a prior history of suicide or other risk factors for troublesome side effects, loose coding of adverse reactions, selective publication of trial data, or placement of ghostwritten trial reports in medical journals, all of which had the effect of complicating the retrospective identification of side effects in published studies. As one of the plaintiffs' expert witnesses, Healy had privileged access to these documents. His role in the litigation gave him a unique vantage point on the myriad ways in which the drug industry shapes what we know and do not know about drugs, years before the economy of pharmaceutical knowledge—and particularly the funding, design, conduct, and publication of clinical trials—became the object of sustained scholarly investigation (e.g., Epstein 2007; Jain 2010; Lakoff 2009; Petryna 2009; Sismondo 2009).

Second, tort law requires plaintiffs to provide evidence of what it calls "specific causation." Exposing the manipulation of clinical trials that appeared to exonerate a drug goes to general causation only; it shows that the injury for which plaintiffs seek recovery is of a type that could have been caused by the drug in question. To prove that a plaintiff's specific injury—*their* own case of cancer, *their* child's birth defect or *their* parent's suicide—was actually caused by it, attorneys and their experts must make a case for, and out of, carefully textured medical and personal histories. As the first Prozac trial (the 1994 Wesbecker case in Kentucky) had shown, companies appealed to clinical trials not merely to say something of their drugs' particular merits; rather, they invoked them in a quasi-ritual manner to sanction one kind of evidence and stigmatize another. In the way evidence-based medicine constructed this distinction, the hallowed kind happened to be the evidence produced and owned by the industry, the tainted kind the evidence supplied by patients and their physicians, or plaintiffs and their attorneys when they decided to challenge the industry's claims in court.

The relation of medical histories to medical science was at the heart of Healy's testimony in *Forsyth v. Lilly* and in *Tobin v. SmithKline Beecham*, the first two trials in which he appeared on the stand. The two cases were remarkably similar. They were about married men in their sixties, both with children and grandchildren, who had led tranquil middle-class existences until they were prescribed SSRIs for rather mild depressive syndromes. A mere 2 days after beginning treatment, William Forsyth felt so wretched that he checked himself into a hospital where he remained under observation for 10 days. The day after he was discharged with instructions to stay on his Prozac, he stabbed his wife to death, then threw himself against a large kitchen knife tied up to a chair. In similarly grim fashion, Donald Schell fatally shot his wife, daughter, and infant granddaughter before killing himself on February 14, 1998, 48 hours after starting a course of treatment with Paxil (SmithKline's SSRI). The circumstances of these two cases had little in common with those of Wesbecker's, who had had a complicated history of serious mental illness and had threatened several of the co-workers

he eventually shot well before he first took Prozac. In that latter case, blaming the disease instead of the drug was plausible enough; in the former two, it was implausible at best.

During both trials Healy strove to elucidate the conditions under which case histories may provide better evidence of causation than controlled trial data. His testimony in *Forsyth* took the court back to the origins of the randomized trial and the views of Austin Bradford Hill, the English epidemiologist who introduced the method into drug research in the 1940s. Hill, according to Healy, never viewed RCTs as the sole answer to the question of causality. As RCTs were made mandatory in the aftermath of thalidomide, he outlined in an influential paper a set of 9 factors to consider when making determinations of causality, several of which were relevant to the issue of specific causation (Hill 1965; Howick et al. 2009). These included (1) 'Temporality': the effect must occur within a stable timeframe after consumption of the drug; (2) 'Plausibility': the assumed cause-and-effect connection should be biologically plausible, ideally more so than alternative explanations; and (3) 'Consistency': the effect is analogous to outcomes observed in other patients, by other clinicians, or with other drugs (Forsyth 1999, pp. 900–929). At the *Tobin* trial 2 years later, Healy testified to the ways in which individual cases too can be subject to rigorous experiments. In challenge–rechallenge protocols, for instance, a patient who exhibits an adverse reaction on a drug is taken off the drug, then put back on it after the reaction clears up in order to determine if the same reaction reoccurs within the same approximate time frame. Evidence produced in this manner goes to replicability, another one of Hill's causation criteria, though the replication here is staggered across time in the same individual rather than across a pool of different individuals randomly assigned to a same trial arm (Tobin 1999, p. 41). Tests of this nature show how the elaboration of a single clinical case in the form of a structured case history has the ability, as Paul Ricœur wrote of the narrative form in general, to "configure and refigure" an unarticulated succession of events into a meaningful and "followable" totality that represents with different degrees of plausibility the "one after the other" as a "one because of the other" (Ricœur 1984, pp. xi, 65–66, 182). Causality, in other words, can be located also in the synthetic unities of narratology, not solely in the analyzed data of clinical epidemiology.

In both cases, therefore, Healy's testimony made new room for a forensic approach to drug harms, a dedication to fact-finding practices focused on the particulars of a single case (Edwards et al. 2011). The strategy did not succeed in *Forsyth*, which ended with another narrow win for Lilly, but it did in *Tobin*. Though SmithKline defended Paxil in much the same way as Lilly had Prozac, Don Schell's story differed in one crucial respect from Bill Forsyth's: he had taken Prozac during an earlier depressive episode and suffered a sharp surge in his anxiety despite the anxiolytic medication he was taking as well. Unaware of Schell's prior reaction to an SSRI, the internist who saw him in 1998 handed him a Paxil sample without warnings and without a prescription for anti-anxiety pills. The violent paroxysm that ensued 2 days later effectively turned Schell's longer medical history into an unintended challenge–rechallenge experiment that provided more compelling evidence of causation than anything company-sponsored RCTs, whose limitations were slowly coming to light, could have done. On June 6, 2001 a unanimous jury decided

against SKB and awarded Tim Tobin, Schell's son-in-law, millions in damages, making SmithKline the first drug company to be held liable for a psychiatric side effect of one of its products.

"If you think you have a problem, you are probably right"

In the 10 years that separated the verdict in *Tobin* from the creation of rxisk.org, the effects of corporate control over the production and dissemination of pharmaceutical knowledge came into fuller view. The outcome of the *Tobin* trial first captured the attention of a broader public in Britain in October 2002, as the BBC dedicated an episode of its popular public affairs program, *Panorama*, to the hidden side effects of SmithKline's antidepressant. *Secrets of Seroxat* (after Paxil's trade name in the UK) featured scenes of the trial, interviews with Healy, and a reenactment of his forays into SmithKline's archives ahead of his testimony in the case. Seen by an estimated 4 million people, the documentary tapped into a reservoir of hidden suffering whose dimensions few were suspecting. More than 60,000 viewers called the station's hotline or emailed in to tell of their own experiences with the drug, a record response in the channel's history. In the meantime, SmithKline Beecham had merged with Glaxo Wellcome to form GlaxoSmithKline (GSK), then the largest pharmaceutical company in the world. The new company, determined to resolve the crisis building around its bestselling antidepressant, turned over its own internal analyses of the safety data from Paxil/Seroxat trials in depressed children and adolescents to the UK's drug agency, the Medicines and Healthcare Products Regulatory Agency (MHRA). The unpublished data, which pointed to a doubling of the risk of self-harm in patients under 18, were plainly at odds with the published findings of SmithKline's pediatric antidepressant trials, which had declared the drugs safe and effective in that age group. So in May 2003, a full fifteen years after Prozac came onto the market, the MHRA became the first drug agency to acknowledge the reality of SSRI-induced suicides (Bass 2008; Healy et al. 2020; McGoey and Jackson 2009).

In the US the FDA temporized for more than a year after the MHRA's announcement that SSRIs were putting children at risk of self-harm. When it eventually issued warnings of its own in the fall of 2004, the announcement collided with another major prescription drug scandal: the withdrawal of Merck's arthritis drug Vioxx over concerns that it might have caused as many as 150,000 excess heart attacks in its 5 years on the US market. Like SSRIs, Vioxx was typical of modern "blockbuster" drugs: heavily promoted, prescribed to millions of patients for indefinite periods of time because of its alleged safety, and generating billions of dollars in sales. The simultaneous revelations about the hidden harms of such mainstays of our modern pharmaceutical regimen triggered a broad public reckoning about the ways drugs are researched and regulated, the broadest certainly since thalidomide. Drug company practices came under intense scrutiny in congressional hearings (US House of Representatives 2004; US Senate 2004), popular books (Abramson 2004; Angell 2005; Cassels and Moynihan 2005; Whitaker 2010), and in a wave of judicial and journalistic investigations that exposed similar failings with other widely sold

drugs such as Neurontin, Zyprexa, or opioid painkillers (Applbaum 2010; Avorn and Kesselheim 2007; Gottstein 2020; Landefeld and Steinman 2009; Lentacker 2021). So too did the actions of regulatory agencies, which showed a reluctance to admit that medications they had endorsed were causing unforeseen harms (Fontanarosa et al. 2004; McGoey 2007).

In parallel, a new body of scholarship emerged to interrogate the pharmaceuticalization of health care, the redefinition of an ever-broader range of conditions as pathologies to be medicated, and the subtle shifts in cultural understandings of disease, body, and self, which these processes underwrote (Biehl 2007; Dumit 2012; Greene 2007; Hayden 2007; Lakoff 2005; Metzl 2003; Watkins 2007). It was in the course of the global cross-disciplinary conversation that developed on these topics in the mid-2000s that Healy connected with the two other co-founders of rxisk.org, both of whom worked in different fields and on different continents. Kalman Applbaum was an anthropologist at the University of Wisconsin in Milwaukee interested in the mutations of modern marketing, among the first to approach pharmaceutical companies as terrains of ethnographic inquiry. Applbaum and Healy formed a connection at a 2002 Harvard workshop on "Globalization and Pharmaceuticals" in which they both presented work on the marketing of SSRIs (Petryna et al. 2006). Dee Mangin, on the other hand, was a professor of family medicine at the University of Otago in New Zealand whose research explored the determinants of prescription patterns among general practitioners. She had been involved in a campaign to end direct-to-consumer advertising of prescription drugs in her country (then the only one besides the US to authorize the practice) and pursued research on the growing issue of polypharmacy, the concomitant prescription, especially in geriatric patient populations, of high numbers of medications whose adverse effects and interactions are typically underestimated. Mangin and Healy first met at the Inaugural Conference on Disease-Mongering held in Australia in 2006 and began collaborating shortly thereafter.

From various positions, Applbaum, Mangin, and Healy were all first-hand witnesses to the ways in which medicine's information ecology inclined clinicians toward therapeutic activism. Far from projecting a light without shadows on all effects of a drug, the controlled trials on which we rely to deliver the truth about drugs train their lens on one particular effect—typically the benefit that the manufacturer intends to highlight—leaving others, especially infrequent or unforeseen ones, in a statistical penumbra that shields those who make and prescribe drugs from accountability for the harms they may do. Seen from the vantage point of those harms instead of drugs' intended benefits, our regulated regime of pharmaceutical knowledge production emerges in a very different light. RCTs, as Mangin and Healy put it in their "RxISK Manifesto," now appear as the "gold standard to hide side effects" (2019). One result of the uneven evidence base they generate is "an invisible iatrogenic epidemic" responsible for "more morbidity and mortality than most chronic diseases" (Garfinkel and Mangin 2019). RxISK's co-founders, therefore, viewed the need to bring these invisible harms into focus as a task with far-reaching public health implications. Their common work on a new medium and new method for investigating drug harms reflected a sense that the few high-profile side effects to come to light in the mid-2000s were no isolated incidents, but rather symptoms

of a systemic issue that concerned to at least some degree all newer drugs. According to Applbaum, medications for such conditions as "osteoporosis, gastritis, diabetes 2, arthritis, IBS, allergies, etc." loomed as large in the preoccupations of the project's founding team as SSRIs and other psychiatric drugs (2022, personal communication).

The idea of RxISK itself was born when Mangin, Applbaum, and Healy met jointly for the first time in Saint-Louis, MO, in 2010. Following 2 years of drafting and redrafting, the blueprint for rxisk.org emerged around the core conviction that the best evidence on drug-related harms would be obtained from those who experience them. A further hope, Healy told me, was that RxISK could live as a project "powered by people who had lost children or parents or partners to these drugs." To safeguard the endeavor's independence, its creators established RxISK as a limited liability corporation unaffiliated with any university or other institution. Unlike corporate eHealth sites, it generates no revenue by way of advertising, reselling user data, or recruiting for clinical trials (Tempini and Del Savio 2019). Funding for the project, which required approximately half a million dollars in initial layouts, has come from fees Healy continues to receive for his legal work, personal contributions of the founders, and third-party donations. A pathbreaking contribution to the site's creation came from Peter and Julie Wood, a Toronto-based couple whose elder son took his life while treated with an antidepressant. A retired Ernst & Young executive with extensive experience helping start-ups off the ground, Peter Wood offered managerial as well as financial support, taking over the project's business administration in the latter half of 2011 and steering it from a mobile app model to a website, which was registered the following year under the domain name rxisk.org.

The anecdote digitized

The turn of the millennium was a time of rapid change in the economy of the internet. The online landscape became increasingly dominated by social media and other corporate networking sites based on user-generated content. The emergence of "eHealth" fit squarely within this moment, with sites such as PatientsLikeMe driving a shift from the patient-run discussion boards of the early years of the Web to structured data-gathering platforms maintained by for-profit companies (Tempini 2015). Although not specifically dedicated to identifying side effects, PLM prompted its users to write in detail about the medications they took, and about how and why they took or ceased to take them. Side effects' reports from patients, which had always been scarce in the pre-internet era, started proliferating in various online forums. A vague but pervasive sense that the internet was, in Healy's words, "a tool that might break things open, might be a force for consumers to get their voices out," informed conversations on the future of drug safety across government, industry, and activist constituencies (2018, personal communication; Anderson and Herxheimer 2013).

A more immediate influence on the architecture of RxISK, however, was the work of British policy analyst Charles Medawar. Medawar began scrutinizing the dynamics of drug regulation during the 1980s in his role as director of the Public Interest Research Centre, an independent research group established in London as

an offshoot of Ralph Nader's Public Citizen. Equipped with a computer, a "128k modem," and an early "strategic sense" of the internet's potential as a tool to "exchange information and consolidate experiences," as he put it in a 2002 interview with Healy, Medawar scoured discussion boards to which antidepressant users turned in search of community (Medawar 2002). In 1997 he published "the Antidepressant Web," a study that drew in part on material collected from those discussion boards, and set up a website at socialaudit.org.uk to disseminate his research findings and host further conversations about the unacknowledged harms of SSRIs (Medawar 1997). Healy, who became acquainted with Medawar and his work that same year, described him to me as the "prime mover" in the field, "the one who launched that idea, the whole way of thinking that there is both underuse and overuse of drugs, that benefits get hyped a lot and harms are being minimized."

After *Secrets of Seroxat* aired in October 2002, BBC journalist Shelley Jofre and *Panorama* producer Andrew Bell invited Medawar and Oxford pharmacologist Andrew Herxheimer to review the nearly 1400 messages emailed by viewers to the channel in the wake of the broadcast (Medawar et al. 2002; Medawar and Herxheimer 2003/2004).[2] The emails formed from the authors' own admission a "highly skewed" dataset. They came from a self-selecting group of viewers with overwhelmingly negative experiences on GSK's drug. The absence of random sampling and of a control group made it unsuitable for any estimation of ratios and frequencies. Many emails lacked key information such as the user's age, sex, dosage, or diagnosis. They were quintessentially "anecdotal" in the sense of evidence-based medicine. Nonetheless, the goal of the study was not to draw quantitative inferences from a representative sample, but to convey what the authors called in a telling ethnographic metaphor "the value of 'immersion'" in a rich, albeit haphazardly assembled, collection of narrativized accounts (Medawar et al. 2002, pp. 161–162). Apprehended holistically, the first-person accounts cited at length throughout the paper yielded a pregnant picture not only of the reality of these effects, but also of their underappreciated impact on the quality of life of those who experienced them—"what withdrawal problems, weight gain, suicidal behavior, or loss of libido actually mean in the context of personal and social life" (Medawar and Herxheimer 2003/2004, p. 15).

In the UK as in most other countries at the time, drug authorities solicited adverse event reports exclusively from health professionals. Pharmacovigilance relied on physician reporting, not patient reporting, of side effects. "We believe the underlying reason for regulators' disdain," Herxheimer and Medawar wrote, "is their prejudice that what a patient reports is 'anecdotal' and does not constitute 'scientific' evidence, and therefore should not be accepted without confirmation by a professional." To put that prejudice to the test, Herxheimer and Medawar examined the self-narratives emailed by Seroxat users to the BBC alongside reports filed by physicians with the MHRA regarding the same suspected side effects. The side-by-side comparison demonstrated how, under the delegated system favored by drug

[2] The emails and their analysis became the subject of a second *Panorama* episode on Seroxat, "Emails from the Edge," broadcast in May 2003, https://vimeo.com/115681493, last accessed 14 July 2021.

regulators, "the patient's report is filtered through the doctor's own expectations and his or her interpretation of what is credible, serious, relevant, or worth reporting." As "translation[s] in medical shorthand of what the patient says," doctors' reports are terse (40–75 words per report on average) and stripped of any textured description of the lived experience of side effects and of their consequences on relationships, employment, or mobility that figured so saliently in the BBC emails (Medawar et al. 2002, pp. 167–168). In sum, the arrangements regulators typically depend upon to monitor the safety of drugs lead not only to underreporting—a well-known issue, as authoritative estimates generally put the proportion of reported events at somewhere between one and ten percent of all reactions serious enough to result in hospitalization (Hazell and Shakir 2006)—but also to widespread misreporting that yields a flattened and distorted picture of patients' experience with their medications.

These findings provided a foundation for RxISK's design. As Applbaum put it (2021, personal communication):

> Research we trusted observed that patient reporting yields data as good or better for tracking ADEs than what doctors report—provided you know how to analyze it. Patients are more motivated to provide details about their experience in both medical (what other drugs they're taking at what doses, compliance, what conditions they suffer from, what supplements they may be taking, and so on) and experiential (quality of life questions—"what was your life before and after you started taking drug X?") dimensions.

The emphasis on patient reporting sets RxISK apart from official pharmacovigilance schemes. To be sure, the fallout from the SSRI, Vioxx, Zyprexa, and other drug safety failures revealed since the early 2000s forced a rethinking of pharmacovigilance procedures. In a growing number of countries drug agencies took steps to open up adverse event reporting to consumers (Herxheimer et al. 2010). Nevertheless, the main tool of pharmacovigilance remains the computerized mining of large quantities of ADE reports. In this approach stories are useful inasmuch as they generate "data blips" in automated searches, and reports filled out by physicians, whose practice is to abstract recognizable code words from idiosyncratic patient accounts, remain the most easily exploitable. As a result, even those drug agencies which allow consumer reporting of ADEs do little to encourage it. Portals for patient reporting were grafted onto systems designed for professionals. On the FDA's crowded website, for instance, a user needs to click through four successive links, three of them tucked below the fold, to gain access to the agency's reporting tool. Of the reports submitted directly to the FDA in 2020, therefore, only one in five came from consumers.[3] All reports are entered into the same database and processed according to the same methods (Anderson and Herxheimer 2013). Rxisk.org, by contrast, interpellates the patient as a privileged informant about drugs. A link to RxISK's reporting tool features prominently on the site's home page (Fig. 3). Rxisk.org's iconography, "About" page,

[3] That is, 16,411 of 78,559 reports. Data available at https://fis.fda.gov/sense/app/d10be6bb-494e-4cd2-82e4-0135608ddc13/sheet/7a47a261-d58b-4203-a8aa-6d3021737452/state/analysis, last accessed 30 June 2021.

Fig. 3 rxisk.org homepage. The online reporting tool is accessible in a single click through an icon located on the homepage (highlighted area in the lower right corner). So are each one of the site's related functionalities (icons on the middle left side of the page)

and blog convey with various levels of directness or detail the reasons for the systemic misrecognition of drug-related harms. The argument captured in the home page's headline "No one knows a prescription drug's side effects like the person taking it" is reiterated in various forms throughout the site: "If you think there is a problem, you are probably right"; "Make your voice heard," etc. Each one of the site's ancillary functionalities is accessible in a single click through icons located on the home page.

Healy compares the documentary work of RxISK to "picking up the junk." Scraps of information about drugs litter the Web, amounting to little more than debris as long as they remain scattered across multiple social media sites, blogs, comment sections, and the like. To become recyclable the scraps need to be salvaged, sorted, and stored in a single place. On RxISK, users submit their side-effect stories through a structured reporting tool, which, in addition to a free narrative account of the reaction, solicits basic metadata needed for the proper storage, retrieval, and interpretation of the report (e.g., sex, age, country of residence, name of the suspected medication, dose and duration of treatment, treated condition, concomitant medication, etc.). The online reporting form, in other words, informs rather than formats the account, removing none of its texture but ensuring that it is recorded with the data points that make it usable from a forensic-clinical standpoint (Fig. 4). Currently, the website receives about 2000 such reports yearly, about 30% from users in the US, 40% from Europe, and the remaining 30% from other locales. Although the RxISK database, compiled through the unremunerated labor of a handful of scholars, operates on a smaller scale than the databases of national regulators, it is in

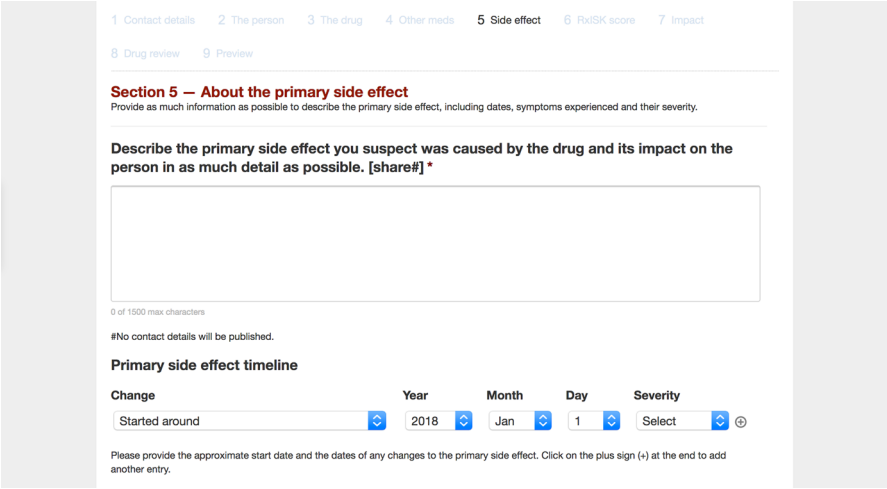


Fig. 4 RxISK's reporting tool

Healy's estimation the world's largest independent repository of patient-generated side-effect reports.

The relative smallness of the project is in keeping with an epistemology that locates the moment of discovery in the intuitive elucidation of patient narratives. RxISK investigates side effects not through computerized mining of vast amounts of standard-issue reports, but through what Herxheimer and Medawar described as immersive close reading practices. One of the first effects to be elucidated through reports submitted on the site came to light as a result of a single patient telling her story in unusually rich detail. The patient, a hospital employee in the south of England named Anne-Marie, was prescribed Seroxat following the sudden passing of her father. While the eating disorder for which she had sought help gradually resolved, friends started remarking on her increased alcohol consumption. In denial at first, she lost many of those friends, often missed work, and suffered repeated car crashes. She was arrested on several occasions for compulsive nuisance calls she made to her local police station when drinking at night. Seeing her life unravel, she turned to the internet in search for answers and started suspecting her drug. Her doctor, "sympathetic but not convinced," agreed to change her prescription but switched her to citalopram, another SSRI, only to see her troubles worsen. She lost her job, spent time in prison and rehab centers, but failed to overcome her self-destructive cravings. Further online research turned up no information on alcohol dependence and SSRIs, though she eventually came across a post on a discussion forum citing a 1994 Yale study concerning the link between alcohol dependence and the serotonin system. Pursuing the lead, she eventually got her doctor to prescribe mirtazapine, a non-SSRI antidepressant, instead, and almost immediately the cravings vanished (Anne-Marie 2012).

Having encountered Healy's name during her online searches, Anne-Marie contacted him just before the launch of rxisk.org. He saw in her story a striking illustration of the new site's purpose:

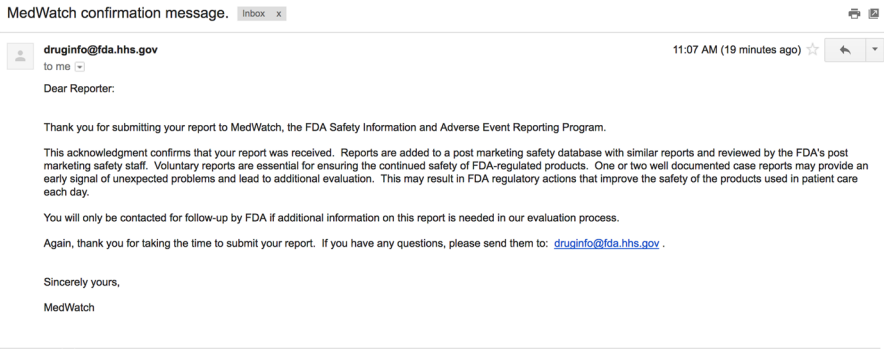
> I know a lot about the serotonin system, and here is a woman who at this stage was telling me things about the serotonin system that I didn't know. You had a woman with access to the internet, and motivation to chase things. And she chased a ton of things. Most of what she chased was worthless, but putting one thing into another, taking her time and working slowly, she was able to piece together a story about how SSRIs could be causing the problem, and drugs like mirtazapine might be the answer to an SSRI-induced problem. There's nothing, no articles out there, that actually supported this; there were no doctors who thought this at that point. The only people who agreed with her—they didn't agree publicly—were pharmaceutical companies who were working on drugs like mirtazapine as treatments for alcoholism, but the world didn't know about this…

In 2013 Healy partnered with Anne-Marie to publish a report about her case in the *International Journal of Risk and Safety in Medicine* (Healy et al. 2013). The following year, 2 years after RxISK's launch, the same journal published a co-authored paper examining 93 further cases of SSRI-induced alcohol dependence drawn from the RxISK database, making these the first two publications to outline this unreported risk of SSRIs in the medical literature (Healy et al. 2014).

Medicine remediated

Every platform dedicated to collecting ADR reports articulates a certain metanarrative about itself, a story about the value of patient stories and the fate of such stories in a broader narrative of vigilance and discovery. In the metanarrative of drug agencies, the normal trajectory of an ADR report is unidirectional and ascending. On the ground level, a patient speaks up, either by submitting a report directly to the regulator or, preferably, by speaking to their physician. The physician is expected to act as a mediator, a trained interpreter of their patient's complaint and diligent informant of the regulatory authorities, by transcribing credible complaints and forwarding them to the regulator. Agency staff are then tasked with screening and encoding the reports and entering them into a national adverse event database. Abstracted and broken down in data bits, the reports are ready to be queried by computers programmed to extract a signal from the noise of patient complaints. For both patient and physician there is a reassuring finality to the process. Once they have spoken up and filed a report, their report is filed away in competent hands. A thank you note is emailed back to the reporter, signaling that their part in the process has already come to an end (Fig. 5).

That metanarrative overlaps in substantial ways with the kind of stories told on commercial eHealth sites. There too the patient voice is celebrated, but becomes a source of knowledge only by being disaggregated as voice and reaggregated as information in signal-generating databases. What is being sourced on "crowdsourcing" platforms is not users' insights but the processable data trail they leave in interacting with the site. As scholars have noted, the extraction imperative that governs data capitalism gives the discourse of eHealth its distinct speculative


MedWatch confirmation message. Inbox x

druginfo@fda.hhs.gov 11:07 AM (19 minutes ago)

to me

Dear Reporter:

Thank you for submitting your report to MedWatch, the FDA Safety Information and Adverse Event Reporting Program.

This acknowledgment confirms that your report was received. Reports are added to a post marketing safety database with similar reports and reviewed by the FDA's post marketing safety staff. Voluntary reports are essential for ensuring the continued safety of FDA-regulated products. One or two well documented case reports may provide an early signal of unexpected problems and lead to additional evaluation. This may result in FDA regulatory actions that improve the safety of the products used in patient care each day.

You will only be contacted for follow-up by FDA if additional information on this report is needed in our evaluation process.

Again, thank you for taking the time to submit your report. If you have any questions, please send them to: druginfo@fda.hhs.gov .

Sincerely yours,

MedWatch

Fig. 5 Email acknowledgment of receipt from the FDA's voluntary adverse event reporting system for consumers

structure. Platforms generate participation by selling visions of a future in which the personalization of health care comes not from a personal encounter with a clinician but from the fine-tuning of artificial intelligence through the exponential accumulation of personal health data. In the rhetoric of big data, scale is another way to arrive at the kind of totalizing data closure which randomization achieves in formal drug trials.

The story RxISK tells on the roles of patient, clinician, and data in spotting side effects is very different. Research on professional ADE reporting systems has demonstrated just how remote the notion of the physician as interpreter of their patients' complaints and informant of regulatory bodies is from the realities of medical practice. Reporting rates are strikingly low, while those reports that do get filed are frequently inadequate—more so in fact than those submitted directly by patients (Anderson and Herxheimer 2013; Avery et al. 2011). In surveys patients routinely note physicians' resistance to contemplating that the medications they prescribe might be causing unanticipated problems. Those who developed suicidal thoughts on an SSRI, for instance, were often advised to stay on their drug or increase its dose because antidepressants were meant to prevent suicide (FDA 1991, pp. 30, 41). Likewise, when Anne-Marie K. told her physician that she suspected paroxetine might have a role in her drinking problem, he dismissed her concern on the grounds that paroxetine was the kind of medication given to recovering alcoholics; the drug could not be causing the problem it was supposed to treat. In consequence, Healy notes,

> most people are very nervous about bringing problems to the doctor. If the doctor puts you on a drug and something is going wrong, even people from the United States who have a reputation for going in and being awkward and bolshie with doctors, in actual fact don't. If there's a particular problem they're having on a drug, they don't tell the doctor.

RxISK's starting point is therefore to acknowledge the dead ends of doctor–patient communication and to look for remedies to the misrecognition of side effects not in better informatic tools for the downstream processing of filed ADE

reports, but in an overhaul of the relational structure in which the side effect is originally meant to be reported and recorded.

A report filed with RxISK is not merely filed away in a database for future review by analysists other than the patient and their clinician. Based on the user's answers to a number of "causality questions" on the site's reporting form, every report is assigned a "RxISK score" that gives a preliminary estimation of the likelihood of a link between the drug and the reported injury. A .pdf copy of the report is emailed back to the reporter along with its assigned RxISK score and a recommendation to print out the report and bring it to their treating physician. Ideally the act of reporting is only the first step in a recursive inquiry that brings the patient back in front of the doctor, and the authentication and adjudication of a report is a process that unfolds both on- and offline:

> We thought that if we could get [patients] to print a RxISK report […] and bring the report to the doctor, it would equalize the power relation a bit. You know if I go in and tell you I'm having a problem and you blow me off and throw me out, then there's no record of it. It's just my word against yours. But if there's a RxISK report brought to the doctor, and they know this has been printed off an expert website and there's a record of it, then the doctor should be less likely to blow you off.

To close the feedback loop, the website also added in 2017 a portal allowing doctors whose patients brought them an RxISK report to log back into the website and, using a unique identifying code generated for each report, to submit their own observations on the likelihood that their patient's complaint is indeed treatment-induced (Fig. 6). Envisioned in this way, the platform's value is not primarily in the content it accumulates; nor are RxISK scores intended to deliver a final verdict on the truth value of any one report. RxISK scores and RxISK reports are better thought of as boundary objects whose circulation facilitates new relational formations across the digital divide (Star 2010).

RxISK's ongoing campaign to bring visibility to the problem of drug-induced sexual dysfunction showcases this use of the Web to document side effects in a set of reconfigured relations. SSRIs' effects on sexual function are known to clinicians, though their toll on patients is typically overshadowed. SSRI labels describe these effects as infrequent, usually mild, and always transitory, while in fact some degree of genital anesthesia occurs in nearly all patients treated with that class of drugs. RxISK received several hundred reports from patients who experienced sexual dysfunction that persisted long after discontinuing treatment with SSRIs, as well as with the hair loss medication finasteride and the acne medication isotretinoin (Healy et al. 2019). Given its deep impact on patients' well-being and relationships, enduring sexual dysfunction is a clear example of a drug-related harm of which patients are acutely aware, but which they are reluctant to disclose to physicians. To push the issue onto the agenda of the FDA, the UK's MHRA, and the European Medicines Agency (EMA), Healy and Mangin submitted in May 2018 a petition signed by 22 specialists of PSSD (post-SSRI sexual dysfunction) and PGAD (persistent genital arousal disorder) requesting a review and redrafting of the drugs' labels. Low reporting rates and a high proportion of anonymous reports, usual obstacles to the

RxISK Report

Your RxISK score is: **14**. The following is a guide to the score.*

0 - 4 — More information required
5 - 8 — Likely link between medicine and side effect.
9 + — Strong possibility of a link between medication and side effect.

A record of your submission follows.

*Your RxISK score is based on Koch's postulates, the Bradford-Hill criteria, and the Naranjo algorithm for cause and effect. This is a better approach than randomized clinical trials, and is something your doctor or pharmacist should take seriously.

If you provided permission to publish some of your comments from the report, the questions marked [share#] are the ones that may be published. Sharing stories and not just numbers of reports is hugely valuable in allowing others to learn from your experience and understand their own. PLEASE NOTE THAT NO CONTACT DETAILS WILL BE PUBLISHED.

Terms of Service

I acknowledge that I have read and fully understand the Terms and Privacy Policy of Data Based Medicine Americas Ltd. and its family of web sites.
Further, I acknowledge that I have read and fully understand the risks, limitations, and conditions of use of e-mail to send me a copy of the RxISK Report.

✔ **I agree to the Terms of Service**

Terms | Privacy Policy

Share
Yes, please share my comments to help others

Section 1 — Contact details

Email
antoine.lentacker@gmail.com

May we contact you?
Yes

RxISK Report 1 / 7 18/05/2018

Fig. 6 RxISK report cover page. A RxISK report is emailed back to anyone who reports a side effect on rxisk.org with the following note: "This report is designed to be used in conversation with your doctor or pharmacist on the possible linkage between the suspect drug and the primary side effect. You can also invite them to add to your RxISK report to indicate whether they agree that there is a linkage: http://rxisk.org/hcp-comment/." As noted, the RxISK score is calculated based on questions that evaluate the strength of a link along axes laid out in Austin Bradford Hill's criteria

collection of credible evidence on drug-related harms, were further heightened by the sensitive and stigmatized nature of the condition. As a way around those obstacles, Healy and Mangin contacted over 300 individuals who had submitted relevant reports on rxisk.org to invite them to request supporting documentation from their treating physician and to resubmit their reports with name and email address to the EMA, indicating in the event their willingness to be contacted. In the brief window given them by the EMA, they were able to submit 82 named reports in support of their petition, 32 of which contained additional documentation from health professionals. In May 2019 the Agency completed its review and ordered labeling changes to reference reports on sexual dysfunction enduring after discontinuation of the treatment (RxISK 2019).

Achieving this triangulation between patient, physician, and website is undoubtedly the most elusive of RxISK's goals. As Healy and Applbaum concede, the site has had considerably more success in engaging users than prescribers of drugs (personal communication 2018, 2021). Participation of physicians in the PSSD/PGAD campaign could be secured only by means of a hands-on outreach effort conducted via patients. That campaign, in other words, enacted on an experimental scale what remains at this point a mostly aspirational model for a different way of treating patients and protecting them from harm. So RxISK too shares with other eHealth sites a certain promissory logic, inviting participation from users by conjuring up a vision of a medical future that has yet to come. Its distinctive identity lies in the kind of medical future that is being envisioned, one in which digital tools would be used not to bypass the clinical relation but to reconfigure it in an effort to render physician and patient more present to each other.

*

In the end, the broader meaning of RxISK—of its achievements as well as its limits—is perhaps that there is no single method or single locus for the discovery of side effects. Side effects are, by definition, unintended and unsought; they occur out of focus and out of order, in the blind spots of what Kuhn called normal science. As such, every one of the major side effects uncovered in the past three decades has its own unique revelation story, involving some serendipitous deviation from the straight path of drug development and some subversive use of evidence collected for other purposes.

There is no question that certain categories of side effects—particularly those with long latencies and no intuitive connection to a drug's indication or immediately perceptible effects—will only be detected in epidemiological investigations, either randomized or observational. Vioxx's cardiotoxic effects, for instance, were revealed in the course of a post-approval trial commissioned by Merck to license the drug for the prevention of colorectal polyps, although the pre-launch trials done to get the drug on the market as an arthritis medication already contained much overlooked evidence of its toxicity (Jüni et al. 2004). In the case of estrogen supplements, the hazards of long-term hormone replacement therapy came to light in

large, NIH-funded trials undertaken in response to advocacy from women's health organizations (Avorn 2005). The main challenge in cases like these is to ensure that adequate safety studies be conducted and disclosed in a timely manner, since manufacturers have no incentive to fund research designed to expose the liabilities of their products.

Yet, as RxISK demonstrates, other varieties of side effects may require other methods to come into focus. Self-reports by medicine takers have proven critical in documenting adverse reactions that are felt by patients but produce no unambiguous signs in common diagnostic tests. The various neuro-psychiatric disturbances caused by SSRIs are typical of those effects, which tend to be described (and dismissed) as (merely) subjective. This circumstance helps explain why SSRIs and other psychiatric medications continue to loom so large on rxisk.org, even as the site welcomes reports about the suspected harms of any prescription drug. Another explanation of their continued prominence on the site lies in Healy's own trajectory. His long-time involvement in the struggle to bring SSRIs' hazards to light and the influential critique of the pharmaceutical industry he articulated in the process put him at the center of an activist network that was poised to engage with a project like RxISK. In that regard, the hidden dynamics behind rxisk.org may be compared to those animating a website like erowid.org, the online information exchange on psychedelic and other mind-altering black- or gray-market drugs (Langlitz 2009). Both are undertakings seeded and supported by a virtual community of users mobilized in some way against official drug policy and normalized regimes of pharmaceutical knowledge production.

It is precisely because the discovery of side effects must often happen against or outside the normal paradigm of drug research that the Web can be a uniquely generative medium in matters of pharmacovigilance. What renders the Web suspect as a source of evidence—the uncredentialed nature of its users and unsystematic manner of data accumulation—is also what makes it the forum of choice to voice experiences not reflected or recognized in constituted bodies of knowledge. As such, the generativity of projects like RxISK will hinge on the Web's continued ability to catalyze not only genuine activist sensibilities and their specific forms of expertise against the encroaching logic of data capitalism, the spread of evidence-free conspiratorial thinking, but also the removal of unsanctioned knowledge which an ill-defined concept of misinformation may seem to justify.

Declarations

Conflict of interest The author states that there is no conflict of interest. I have no competing interests, financial or intellectual, in the research.

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References

Abramson, J. 2004. *Overdosed America: The Broken Promise of American Medicine*. New York: HarperCollins.

Anderson, C., and A. Herxheimer. 2013. Harnessing Patients' Awareness of Adverse Reactions to the Drugs They Take. In *Understanding and Using Health Experiences: Improving Patient Care*, ed. S. Ziebland, 116–126. Oxford: Oxford University Press.

Angell, M. 2005. *The Truth About Drug Companies: How They Deceive Us and What to Do About It*. New York: Random House.

Anne-Marie. 2012. Out of My Mind. Driven to Drink, 15 March 2012. https://ssristories.org/out-of-my-mind-driven-to-drink-davidhealy-org/. Accessed 4 Aug 2021.

Applbaum, K. 2010. Shadow Science: Zyprexa, Eli Lilly and the Globalization of Pharmaceutical Damage Control. *BioSocieties* 5 (2): 236–255.

Avery, A., C. Anderson, C. Bond, H. Fortnum, et al. 2011. Evaluation of Patient Reporting of Adverse Drug Reactions to the UK 'Yellow Card Scheme': Literature Review, Descriptive and Qualitative Analysis, and Questionnaire Surveys. *Health Technology Assessment* 15 (20): 1–227.

Avorn, J. 2005. *Powerful Medicines: The Benefits, Risks, and Costs of Prescription Drugs. Revised and Updated*. New York: Vintage Books.

Avorn, J., and A.S. Kesselheim. 2007. The Role of Litigation in Defining Drug Risks. *Journal of the American Medical Association* 297 (3): 308–311.

Bass, A. 2008. *Side Effects: A Prosecutor, a Whistleblower, and a Best-Selling Antidepressant on Trial*. Chapel Hill: Algonquin Books.

Beasley, C.M., et al. 1991. Fluoxetine and Suicide: A Meta-analysis of Controlled Trials of Treatment for Depression. *British Medical Journal* 303: 685–692.

Biehl, J.G. 2007. The Pharmaceuticalization of Health Care: AIDS Treatment and Global Health Politics. *Anthropological Quarterly* 80 (4): 1083–1126.

Carpenter, D. 2010. *Reputation and Power: Organizational Image and Pharmaceutical Regulation at the FDA*. Princeton: Princeton University Press.

Cassels, A., and R. Moynihan. 2005. *Selling Sickness: How the World's Biggest Pharmaceutical Companies are Turning Us All into Patients*. Sydney: Allen and Unwin.

Cornwell, J. 1996. *The Power to Harm: Mind, Medicine, and Murder on Trial*. New York: Vintage.

Dopson, S., L. Locock, J. Gabbay, E. Ferlie, and L. Fitzgerald. 2003. Evidence-Based Medicine and the Implementation Gap. *Health* 7 (3): 311–330.

Dumit, J. 2012. *Drugs for Life: How Pharmaceutical Companies Define Our Health*. Durham: Duke University Press.

Edwards, I.R., B. David, K. Hartigan Go, D. Healy, A. Herxheimer, and J. Labadie. 2011. Is There a Need for Forensic Pharmacovigilance as a Speciality? *International Journal of Risk and Safety in Medicine* 23: 31–42.

Epstein, S. 2007. *Inclusion: The Politics of Difference in Clinical Research*. Chicago: The University of Chicago Press.

FDA. 1991. *Psychopharmacological Drugs Advisory Committee Hearing Transcript*, 20 September 1991. FDA. https://commons.wikimedia.org/wiki/File:1991_FDA_Psychopharmacological_Drugs_Advisory_Committee.pdf. Accessed 12 July 2021.

Fentress et al. v. Shea Communications et al. 1994. Transcript of the Proceedings, Case No. 90-CI-06033 (Jefferson Circ. Crt., Ky.).

Fontanarosa, P.B., R. Drummond, and C.D. DeAngelis. 2004. Postmarketing Surveillance—Lack of Vigilance, Lack of Trust. *Journal of the American Medical Association* 292 (21): 2647–2650.

Forsyth v. Eli Lilly & Co. 1999. Transcript of Proceedings, Case No. 95-CV-00185ACK (D. Haw.).

Foucault, M. 1994. *Birth of the Clinic: An Archeology of Medical Perception*. New York: Vintage.

Garfinkel, D., and D. Mangin. 2019. Addressing the Invisible Iatrogenic Epidemic: The Role of Deprescribing in Polypharmacy and Inappropriate Medication Use. *Therapeutic Advances in Drug Safety* 10: 1–5.

Greene, J.A. 2007. *Prescribing by Numbers: Drugs and the Definition of Disease*. Baltimore: The Johns Hopkins University Press.

Gottstein, J. 2020. *The Zyprexa Papers*. Anchorage, AL.

Guyatt, G., et al. 1992. Evidence-Based Medicine: A New Approach to Teaching the Practice of Medicine. *Journal of the American Medical Association* 268 (17): 2420–2425.

Hauray, B., and P. Urfalino. 2007. Expertise scientifique et intérêts nationaux: L'évaluation européenne des médicaments 1965–2000. *Annales. Histoire, Sciences Sociales* 62 (2): 273–298.

Hayden, C. 2007. A Generic Solution? Pharmaceuticals and the Politics of the Similar in Mexico. *Current Anthropology* 44 (4): 475–495.

Hazell, L., and S. Shakir. 2006. Under-reporting of Adverse Drug Reactions: A Systematic Review. *Drug Safety* 29 (5): 385–396.

Healy, D. 1999. A Failure to Warn. *International Journal of Risk and Safety in Medicine* 12: 151–156.

Healy, D. 2004. *Let Them Eat Prozac: The Unhealthy Relationship Between the Pharmaceutical Industry and Depression*. New York: New York University Press.

Healy, D., and D. Mangin. 2019. Clinical Judgements, Not Algorithms, Are Key to Patient Safety. *British Medical Journal* 367 (l5777): 1–3.

Healy, D., O.V. Atigari, A.M. Kelly, and Q. Jabeen. 2013. New Onset Alcohol Dependence Linked to Treatment with Selective Serotonin Reuptake Inhibitors. *International Journal of Risk and Safety in Medicine* 25: 105–109.

Healy, D., L. Brookwell, C. Hogan, and D. Mangin. 2014. Ninety-Three Cases of Alcohol Dependence Following SSRI Treatment. *International Journal of Risk and Safety in Medicine* 26: 99–107.

Healy, D., J. Le Noury, and D. Mangin. 2019. Enduring Sexual Dysfunction After Treatment with Antidepressants, 5α-Reductase Inhibitors and Isotretinoin: 300 Cases. *International Journal of Risk and Safety in Medicine* 30: 167–178.

Healy, D., J. Le Noury, and J. Wood. 2020. *Children of the Cure: Missing Data, Lost Lives, and Antidepressants*. Toronto: Samizdat Health.

Herxheimer, A., R. Comburg, and T. Alves. 2010. *Direct Patient Reporting of Adverse Drug Events. Briefing Paper*. Amsterdam: Health Action International.

Hill, A.B. 1965. The Environment and Disease: Association or Causation? *Proceedings of the Royal Society of Medicine* 58 (5): 295–300.

Howick, J., P. Glasziou, and J.K. Aronson. 2009. The Evolution of Evidence Hierarchies: What Can Bradford Hill's 'Guidelines for Causation' Contribute? *Journal of the Royal Society of Medicine* 102: 186–194.

Jain, L.S. 2010. The Mortality Effect: Counting the Dead in the Cancer Trial. *Public Culture* 22 (1): 89–117.

Jones, D.S., and S.H. Podolsky. 2015. The History and Fate of the Gold Standard. *The Lancet* 385: 1502–1503.

Jüni, P., et al. 2004. Risk of Cardiovascular Events and Rofecoxib: A Meta-analysis. *The Lancet* 364: 2021–2029.

Kuhn, T.S. 1996. *The Structure of Scientific Revolutions*, 3rd ed. Chicago: The University of Chicago Press.

Lakoff, A. 2005. *Pharmaceutical Reason: Knowledge and Value in Global Psychiatry*. New York: Cambridge University Press.

Lakoff, A. 2007. The Right Patients for the Drug: Managing the Placebo Effect in Antidepressant Trials. *BioSocieties* 2: 57–71.

Langlitz, N. 2009. Pharmacovigilance and Post-Black Market Surveillance. S*ocial Studies of Science* 39 (3): 395–420.

Landefeld, C.S., and M.A. Steinman. 2009. The Neurontin Legacy—Marketing Through Misinformation and Manipulation. *New England Journal of Medicine* 360 (2): 103–106.

Lentacker, A. 2021. The Opioid Documents: A Report on the Politics of the Public Record. *Social History of Alcohol and Drugs* 35 (1): 137–165.

Lupton, D. 2014. The Commodification of Patient Opinion: The Digital Patient Experience Economy in the Age of Big Data. *Sociology of Health and Illness* 36 (6): 856–869.

Marks, H. 1997. *The Progress of Experiment: Science and Therapeutic Reform in the United States, 1900–1990*. New York: Cambridge University Press.

McGoey, L. 2007. On the Will to Ignorance in Bureaucracy. *Economy and Society* 36 (2): 212–235.
McGoey, L., and E. Jackson. 2009. Seroxat and the Suppression of Clinical Trial Data: Regulatory Failure and the Uses of Legal Ambiguity. *Journal of Medical Ethics* 35 (2): 107–112.
Medawar, C. 1997. The Antidepressant Web: Marketing Depression and Making Medicines Work. *International Journal of Risk and Safety in Medicine* 10: 75–126.
Medawar, C. 2002. The Bidet View of Psychopharmacology. Interview by David Healy. https://samizdathealth.org/wp-content/uploads/2020/12/Medawar.pdf. Accessed 21 July 2021.
Medawar, C., and A. Herxheimer. 2003/2004. A Comparison of Adverse Drug Reaction Reports from Professionals and Users, Relating to Risk of Dependence and Suicidal Behaviour with Paroxetine. *International Journal of Risk and Safety in Medicine* 16: 5–19.
Medawar, C., A. Herxheimer, A. Bell, and S. Jofre. 2002. Paroxetine, *Panorama* and User Reporting of ADRs: Consumer Intelligence Matters in Clinical Practice and Post-marketing Drug Surveillance. *International Journal of Risk and Safety in Medicine* 15: 161–169.
Menzies, K.B. 2005. A Curse Worse than the Disease. *Trial* 14 (3): 20–29.
Metzl, J. 2003. *Prozac on the Couch: Prescribing Gender in the Era of Wonder Drugs*. Durham: Duke University Press.
Ostherr, K. 2018. Privacy Data Mining, and Digital Profiling in Online Patient Narratives. Catalyst: Feminism, Theory. *Technoscience* 4 (1): 1–24.
Petryna, A. 2009. *When Experiments Travel: Clinical Trials and the Global Search for Human Subjects*. Princeton: Princeton University Press.
Petryna, A., A. Lakoff, and A. Kleinman, eds. 2006. *Global Pharmaceuticals: Ethics, Markets, Practices*. Durham: Duke University Press.
Podolsky, S.H. 2010. Antibiotics and the Social History of the Controlled Clinical Trial. *Journal of the History of Medicine and Allied Sciences* 65 (3): 327–367.
Ricœur, P. 1984. *Time and Narrative*, vol. 1. Chicago: The University of Chicago Press.
Ruckenstein, M., and N.D. Schüll. 2017. The Datafication of Health. *Annual Review of Anthropology* 46: 261–278.
RxISK. 2019. EMA Acknowledges Persistent Sexual Dysfunction After SSRIs and SNRIs. RxISK Blog, 11 June 2019. https://rxisk.org/ema-acknowledges-persistent-sexual-dysfunction-after-ssris-snris/. Accessed 15 July 2021.
Sismondo, S. 2009. Ghosts in the Machine: Publication Planning in the Medical Sciences. *Social Studies of Science* 39 (2): 171–198.
Star, S.L. 2010. This is Not a Boundary Object: Reflections on the Origin of a Concept. *Science, Technology, and Human Values* 35 (5): 601–617.
Tempini, N. 2015. Governing PatientsLikeMe: Information Production and Research Through an Open, Distributed, and Data-Based Social Media Network. *The Information Society* 31: 193–211.
Tempini, N., and L. Del Savio. 2019. Digital Orphans: Data Closure and Openness in Patient-Powered Networks. *BioSocieties* 14: 205–227.
Timmermans, S., and M. Berg. 2003. *The Gold Standard: The Challenge of Evidence-Based Medicine and Standardization in Health Care*. Philadelphia: Temple University Press.
Timmermans, S., and H. Oh. 2010. The Continued Social Transformation of Medicine. *Journal of Health and Social Behavior* 51 (S): S94–S106.
Tobin v. SmithKline Beecham. 2001. Transcript of Trial Proceedings, Case No. 00-CV-0025BEA (D. Wyo.).
US House of Representatives. 2004. *FDA's Role in Protecting the Public Health: Examining FDA's Review of Safety and Efficacy Concerns in Anti-depressant Use by Children*. Hearing Before the Subcommittee on Oversight and Investigations of the Committee on Energy and Commerce, 108th Congress, 23 September 2004.
US Senate. 2004. *FDA, Merck, and Vioxx: Putting Patient Safety First? Hearing Before the Senate Committee on Finance*, 108th Congress, 18 November 2004.
Van Dijck, J., and T. Poell. 2016. Understanding the Promises and Premises of Online Health Platforms. *Big Data and Society* 3 (1): 1–11.
Warner, J.H. 1986. *The Therapeutic Perspective: Medical Practice, Knowledge, and Identity in America, 1820–1885*. Cambridge: Harvard University Press.
Watkins, E.S. 2007. *The Estrogen Elixir: A History of Hormone Replacement Therapy in America*. Baltimore: The Johns Hopkins University Press.
Whitaker, R. 2010. *Anatomy of an Epidemic: Magic Bullets, Psychiatric Drugs, and the Astonishing Rise of Mental Illness in America*. New York: Crown Publishers.

World Health Organization. 2002. *The Importance of Pharmacovigilance*, 1 January 2002. World Health Organization. https://www.who.int/publications/i/item/10665-42493. Accessed 31 Aug 2022.

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