Pharmacovigilance: An Ethical Issue for Clinical Psychology, Psychiatry, and Pharmacy?

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Pharmacovigilance helps determine when a treatment might cause novel or unintended effects. Patients, clinicians, regulators, and pharmaceutical companies have a stake in determining how the causality of treatment-induced effects should be established and when effects should be noted in settings from the academic literature to a medicine's label. There have been different approaches to this task in different jurisdictions, with reporting to companies more common in the United States and reporting to regulators more common in Europe. Over time, pharmacovigilance has switched from being primarily a clinical enterprise to being a regulatory one, which has led to the elimination of the names of those suffering from an adverse event and the outsourcing of the job of recording the details of events to private companies, which appears likely to reduce the recognition of adverse events. This article calls for a restoration of clinical input on adverse events aimed at increasing reporting and recognition rates for important behavioral events.

Keywords: pharmacovigilance; adverse effects; SSRIs; cause and effect

The first effective medicines appeared in the 1930s. They were made prescription-only in 1951, as pharmaceutical companies argued that they would have to include an entire medical course on the drug's label if these new drugs were made available over the counter. The label of a drug is the information sheet that comes with it. The full label, designed primarily for prescribers, can now run to 40 or more pages of small print.

After a new medicine comes into use, events happen, some predictable, some unexpected. We rarely know as much as the marketing of new drugs pretends. The monitoring of medicines for unintended or adverse events is now called pharmacovigilance. This began to take shape in the 1950s following clinical descriptions of problems like chloramphenicol-induced aplastic anemia. Pharmacovigilance initially sat within a new discipline, clinical pharmacology, also called therapeutics. The first book in the field was *Meyler's Side Effects of Drugs*, published in 1957, and now in its 16th edition (Aronson, 2015).

Chloramphenicol-induced aplastic anemia led to recognition of the need for adverse event reporting systems. In the United States, reporting was primarily to companies. In Europe, reporting was to regulators, with Britain's Yellow Card system set up in 1964 following the thalidomide crisis. The U.S. Food and Drug Administration's (FDA)

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MedWatch system only began in 1993. It opened up to reports from patients in 2004, as did other national reporting systems.

Reporting in Europe to medicine regulators rather than to companies might be thought a good thing, but regulators have a poor track record in establishing links between a drug and an adverse event. Their brief focuses on the wording of drug labels, not clinical practice.

Accepting there is a causal link between a treatment and an adverse event has the potential to create marketing and legal problems for a pharmaceutical company. Not accepting a treatment–adverse event link creates problems for clinical practice. Pharmaceutical companies have an incentive to manage this situation. Their management risks prioritizing company safety over patient safety.

Professional groups, such as doctors, pharmacologists, pharmacists, and within the mental health field, clinical psychologists, have also played a part in establishing adverse events. Up to the early 1990s, many clinical journals carried case reports outlining a specific causal link between a drug and a significant adverse event, such as the triggering of suicidality on selective serotonin reuptake inhibitors (SSRIs; Teicher et al., 1990).

In a 1991 response to Teicher et al.'s article, Eli Lilly argued that while the evident explanation might suggest their SSRI had caused the problem, if their randomized controlled trials (RCTs) showed no evidence their drug can cause this problem, a doctor's guess that it did was human error (Beasley et al., 1991). The claim was the plural of anecdote is not data, when in fact the original phrase was just the opposite and Google would not work otherwise.

This company's response introduced the concept of general causation. Can we say that Drug A causes Problem B in general? Around the same period, a greater appreciation was developing that it might be necessary in cases like birth defects to supplement a clinical evaluation with epidemiological and other methods and take into account that a person might be on multiple drugs rather than just one (Laporte, 2016). This opened up a divide between specific and general causation and widened the divide between therapeutics and regulation. Clinicians deal with specific causation. Drug labels are a matter of average effects, rather than what might happen in individual cases.

In the 1990s, influenced by the emergence of evidence-based medicine, which prioritized RCTs over clinical reports, clinical journals stopped taking clinical reports. There was also more money to be made from reprints of company RCTs demonstrating treatment benefits than from case reports of adverse events.

Many countries had supported Drug Bulletins, which were often sent free to doctors to alert them to new drugs and possible problems to keep under review. From 2000 on, these bulletins stopped being free and many stopped publishing. Instead, clinicians get notices of the latest guidelines, which only outline the benefits of treatment.

These developments have set up a crisis within pharmacovigilance, which now more than ever uneasily straddles a divide between a clinical need to have rapid and reliable information on the effects of drugs and the brief of regulators to monitor the labels of drugs in a setting where their every proposal will be contested by companies.

This article outlines four not widely noted developments in the management of adverse event causality, asks whether pharmacovigilance still serves the interests of patients, and proposes an approach that might better serve clinical science.

FOUR SCENARIOS ON RESPONSES TO CAUSALITY PROBLEMS

Other Reports

An early company strategy to hide the concession of a causal link between a drug and an adverse event was to place the new event in a section of the drug label headed "Other Reports." Most doctors and patients view "Other Reports" as a section where companies include reports from "Flat Earthers" or conspiracy theorists and dismiss reports accordingly. The company's willingness to include reports from such presumed sources is even viewed as enlightened.

The "Other Reports" section of the label comes after a "Controlled Trial" section, which gives figures for adverse events that arose in clinical trials. These typically show little difference from placebo, often because severity is discounted. Or companies claim there is no statistically significant difference compared with placebo events. Without anything explicit being written, doctors assume these clinical trial figures represent the best estimate of the true rate of events. They do not.

The events in the "Other Reports" section of the label are the most rigorously examined events reported on the drug. Up to 2000, American companies viewed themselves as legally required to assess whether the effect was caused by their drug, and they accepted that to decide cause and effect it was necessary, as a doctor would, to track the event, among other things, to see what happened when treatment is stopped or on reexposure. When the case-specific facts were collected, a company, not infrequently, decided the evident way to explain what had happened was to assign causality to their drug, at which point the event was included in the drug label (Healy, 2004).

Reporting to Regulators

A second company strategy was to encourage American patients and doctors to report directly to regulators, as happens in Europe, rather than to companies. Regulators like the European Medicines Agency (EMA) and the U.S. FDA cannot follow up on events because reports are anonymized on receipt as a matter of procedure. Encouraging reporting to a regulator therefore might sound responsible, but it makes the recognition of an adverse event less likely.

Consider the case of J.T. On May 31, 2001, J.T., an American woman taking GlaxoSmithKline's (GSK) paroxetine (Paxil), emailed a GSK Customer Response Center (Nieman, 2009):

> My name is J.... I was diagnosed with panic disorder about four-and-a-half years ago. Since that time I've been taking Paxil, which is truly a miracle drug. I've been panic-free with this drug and have been able to go on with a normal life.
>
> I was married in October of 2000. My husband and I found out we were pregnant at Christmas time. I was so excited. I love children. The only problem is that I carried the baby to six months gestation and then had to have a termination.
>
> The doctors diagnosed my son with Truncus arteriosus. They said he would not lead a normal childhood and would most likely not make it through the open heart surgery that he would need as soon as he was delivered (if he was able to make it to that time.)

> To say the least, I was distraught by this news. I thought this was something that I did, was because I stayed on Paxil for selfish reasons.
>
> I wanted to know if you could direct me to any information you might have on any woman that has taken Paxil and still had healthy babies.
>
> My husband and I are ready to try again to get pregnant in the next month or two. I am so nervous. I don't want to stop taking my miracle pill. But, then again, if there is a chance that this might hurt or affect the baby I want to know upfront. And I will somehow stop taking it for the time being.
>
> Please contact me as soon as possible. I love everything this drug has done for me. I am so thankful that your company had this available for me. I just want to continue to have a normal life and have the child that I always wanted. Please contact me as soon as possible.

The Customer Response Center responded the same day:

> Thank you for your inquiry. We are attaching a copy of our current product information for Paxil. Please review the section on use during pregnancy. Further questions about your treatment should be directed to the physician, pharmacist, or healthcare provider who has the most complete information about your medical condition. Because patient care is individualized, we encourage patients to direct questions about their medical condition and treatment to their physician. We believe that because your physician knows your medical history, he or she is best suited to answer your questions.

On June 1, J.T. wrote again:

> This response is regarding an e-mail that I sent you previously. I was asking to see if you have any or are in the process of any clinical trials for women who are currently on Paxil and pregnant. I wanted to find out information to see how many women were on Paxil during pregnancy and if they were able to successfully have healthy babies.
>
> I am in no way insinuating your product did this to my child. I love the product, and I don't think I could have gotten through my panic attacks without the wonderful help of this miracle drug. I just want to start to try and get pregnant again soon. I do not want to put my unborn child through anything that would hurt him/her. Please, if you do not have this information, where is this information held? Does anyone do studies like this? Please, any information you may give me would be great. Thanks again for your help.

Following a company decision in 2001, the label for Paxil no longer mentioned the number of reports of congenital abnormalities associated with Paxil, where previously it had. J.T.'s obstetrician/gynecologist (OB/GYN) could not have answered her question.

Six days after her second email, the Customer Response Center notified GSK's safety department. On June 13, the safety department sent a letter to an address:

> To follow up on your report, we must have the contact details of your clinical course as it relates to your report. To obtain this we need the name and address of your OB/GYN.

Companies must notify the FDA within 15 days of a serious event. GSK's Dr. Jane Nieman submitted a MedWatch form to the FDA on June 13 noting the events listed

in the email, and the "mother's concurrent medications and medical conditions were not specified." Nieman included J.T.'s phrase "I am in no way insinuating Paxil did this to my child."

The letter that had been sent to J.T. came back on July 5 marked "undeliverable." A later GSK report to the FDA notes the unclaimed letter.

On June 13, 2001, a GSK adverse event division decided this abnormality was "almost certain" to be linked to Paxil. This was not communicated to J.T., her OB/GYN, or the FDA. Later questioned under oath, Nieman offered the view that GSK had kept to the regulations, but that as a mother she would have liked to have been told.

A lay colleague later tracked J.T. down and GSK came to a settlement with her. Encouraging direct reporting to MedWatch avoids possibilities like this.

Creating Misinformation

During the decade after its establishment in 2012, RxISK.org, a website created to record both patient and doctor accounts of adverse events, received over 1,000 reports of enduring sexual dysfunction on selective serotonin reuptake-inhibiting antidepressants, a condition termed post-SSRI sexual dysfunction (PSSD). RxISK's team collaborated on several articles outlining the features of this syndrome (Healy et al., 2018a, 2022).

The team also collaborated on an article outlining the response many patients receive from clinicians when they seek treatment (Healy et al., 2019). Those reporting this problem are often ridiculed. Patients have been detained under the mental health act for crazy ideas (Demasi, 2023). Finding there is no awareness of the problem and no research on treatments has pushed several patients to suicide.

In 2019, hoping to support patients by getting PSSD mentioned in drug labels, RxISK petitioned the FDA, EMA, and Health Canada to add PSSD to the labels of serotonin reuptake-inhibiting drugs (Healy et al., 2018b), sending them copies of all the extant research on PSSD.

Patients with PSSD are reluctant to have their names revealed. This poses a problem for anyone who wishes to establish cause and effect. We contacted all patients in our database, asking for volunteers willing to share their names and contact details with regulators. We also asked volunteers to approach their family doctor and ask for a report from their doctor stating they were not aware of any other factor that could have caused this problem in these patients.

We had more than 80 named reports and reports from more than 30 doctors. We offered to send these to regulators, and EMA accepted our offer. The reports were sent along with a cover letter explaining that the rationale for sending named patient and doctor reports was to enable EMA to contact them to facilitate their efforts to establish cause and effect.

On receipt of the material, EMA wrote back to us explaining that, as a matter of procedure, they had removed all patient and doctor names from the material. This essentially creates misinformation. Regulators can claim there have been thousands of reports and they are still looking for a signal. Journalists and politicians are briefed that in the meantime stating this drug has caused that effect is misinformation.

None of the doctors or patients whose contact details were sent to EMA were ever contacted. But the labels for serotonin reuptake inhibitors were changed, except for the label of the still on-patent vortioxetine. EMA later claimed to have too few reports of PSSD linked to vortioxetine. We could have sent them vortioxetine reports on request.

Outsourcing

From around 2000, companies argued against getting patient medical records, as no matter how compelling the case only RCTs can establish if a drug causes an adverse event (Healy, 1999; Hudson, 2000).

This strategy has led companies to log reports as received. They forward received reports to regulators without attempting to follow up with patients on a drug or vaccine or add details to a label. Additions to a label are only likely if public/professional medical opinion forces a change—as in myocarditis linked to COVID-19 vaccines.

However, it still seems necessary to maintain an appearance of pharmacovigilance follow-up, as the publication of two cases brings home; these involved Romain Schmitt, a 16-year-old on paroxetine, and Samuel Morgan, a 25-year-old on citalopram, both of whom committed suicide on treatment, with the treatment being the best explanation for what happened in each case (Healy, 2023).

In Romain's case, GSK made clear that, while conceding paroxetine carried suicide warnings for this age group, the company could not decide if it had done so in this case. They had not contacted the family or requested the medical records.

In Samuel's case, a coroner at his inquest reported the death as a matter of concern to the British Medicines and Healthcare products Regulatory Agency. The regulator said that in the absence of the prescribing doctor attributing causality to the drug, they could not offer a view or change the warnings. The prescribing doctor had been advised by his medical insurer not to take a position on the causal effect of the drug. All doctors are advised this way by medical insurers (Healy, 2023).

Regulators such as EMA, nevertheless, scan the published literature and wrote to the author of the article.

> Dear Dr. David Healy,
>
> I am writing to you on behalf of the European Medicines Agency's Medical Literature Monitoring service, regarding the following article which you recently published: Healy D. Diagnosis, Verdict Conclusion, and Causality. Ethical Human Psychology and Psychiatry. 2023; 25: 29–37.
>
> The European Medicines Agency is the agency of the European Union (EU) responsible for the scientific evaluation, supervision, and safety monitoring of medicines in the EU, working with the regulatory agencies in all EU Member States and the World Health Organization.
>
> We monitor the medical literature for reports of adverse drug reactions (ADRs), turn these into ADR reports, and transmit them to regulatory authorities and pharmaceutical companies in the EU and to the World Health Organization. These are used in detecting possible signals that could lead to a change in the understanding of the risk-benefit balance of the medicines.
>
> In your article, you describe patient who experienced SSRI-induced suicidality and suicide associated with citalopram and more disorganized, aggressive, trouble sleeping, irritability, violent attacks, mood disorders, thought disorders, emotional instability, disinhibition, impaired discernment, suicidality, steady decline in his mental state, and committed suicide associated with usage of unapproved paroxetine.

To aid our pharmacovigilance assessors in their understanding of the reactions caused by these medicines, we would be grateful if you could provide a little more information regarding the [patient, drug, and the reaction(s)].

Any information that you can give us would help. Even approximate information is useful, so, for example, if you only know that the patient was overweight, rather than their exact weight, then that would still be helpful.

Question:	Answer
For scenario 1 and 2 Please provide the patient information: Height and weight of the patient. If you don't have exact information, was the patient underweight or overweight? For scenario 1 Please provide the following information for paroxetine • Posology (form and route of administration)? • Time of onset of reaction from initiation of suspect drug? For scenario 2 Please provide the following information for citalopram • Posology (dose, form, and route of administration)? For scenario 1 and 2 Please provide: Patients history of recreational drugs or alcohol use or smoking history.	

We would be grateful if you could send your response by return email to MLM@kinapse.com.

Thank you in advance for your contribution to the ongoing safety surveillance activities of this product.

With best regards, Ankitha Gongalla, EMA Medical Literature Monitoring service

Kinapse and Syneos

Ankitha works for Kinapse, a medical-writing company. Her email to me was copied to two employees from Syneos.

A now-hidden website says: Kinapse is a global leader in post-approval clinical trial transparency services for both EMA and pharmaceutical companies. For companies, Kinapse offers "Marketing authorization holders' monitoring and reporting requirements" (Phogat & Vashist, 2018).

EMA selected Kinapse in 2010 to provide EudraVigilance data management services (Pharmafile, 2010). They also fill EMA's demands for plain-language summaries of clinical trial results that can be understood by anyone, which as Pharmafile outlines could create new challenges for sponsors.

The Kinapse profile on LinkedIn states that Kinapse, a Syneos Health company, is recognized as a leading advisory and operational services provider to the global life sciences industry. Founded by professionals from the biopharmaceutical sector, the company provides its services across the full clinical and commercialization lifecycle, collaborating with its clients to improve the lives of patients, through a unique Advise–Build–Operate Delivery Model. Many of the top 20 global biopharmaceutical companies rely on the breadth of Kinapse's world-class advisory and operational services to analyze, implement, and perform a wide range of projects and programs across global markets, delivering quantifiable business benefits and operational success. Headquartered in the United Kingdom, Kinapse has over 600 staff located in Europe, India, and the United States.

Syneos Health (formerly InVentiv Health Incorporated and INC Research) is a Nasdaq-listed American multinational contract research organization based in Morrisville, North Carolina. It specializes in helping companies with late-stage clinical trials. In January 2018, INC Research acquired inVentiv Health, the parent company of a subsidiary, Syneos, and the resulting company was named Syneos Health. In April of 2021, Syneos partnered with Medable to leverage DCT technology solutions to expand patient access to clinical trials.

On May 10, 2023, an investment consortium comprising Elliott Investment Management, Patient Square Capital, and Veritas Capital, agreed to take Syneos private in a deal worth $4.46 billion, or $7.1 billion including debt. Michelle Keefe, the current CEO of Syneos Health, was previously a Pfizer Vice-President of sales, and regional president.

EFFICIENT OR EFFECTIVE?

Just as pharmaceutical companies have done, regulators now outsource functions. Modern management believes that disarticulating operations into their components can improve overall efficiency if each of the parts is made efficient. The Kinapse scenario illustrates the potential consequences of outsourcing seen as a value in its own right distinct from the purpose of an operation.

The more the operation is disarticulated into parts, the less it is possible to take the overview needed to determine causality, especially if the testimony of the patient or those close to him is eliminated. This testimony is central to the best balance of probabilities judgment.

Cooperation with EMA/Kinapse's requests for such details will lead to reports being filed away, once all boxes are ticked. EMA and other regulators are likely to state years later they are still compiling data about this adverse event on that drug looking for a signal, in the absence of which we must accept the drug has not been proven to cause the problem.

Pharmacovigilance systems working to regulatory requirements to monitor a drug's label are likely becoming increasingly efficient at getting details about a person's weight or prior substance abuse, possibly pertinent to the wording of labels, but delays of decades in adjusting a label, driven by a need to settle on a reasonable general description of the effects of the drug, do not support the clinical need for information on possible specific treatment effects.

AN ETHICAL ISSUE FOR ALL CLINICIANS?

Over 60 years ago, soon after the original serotonin reuptake-inhibiting tricyclic antidepressants were introduced, psychotherapists noticed an effect of these drugs on what they called transference reactions (Mandel, 1998). These effects are noticeable within 48 hours of starting treatment. Noticing does not require clinical expertise; patients can spot it in healthy volunteers (Healy, 2004). Reports like these prompted Arvid Carlsson to make the first SSRI to investigate this effect as a possible therapeutic principle.

Wider SSRI use has characterized this feature as an emotional numbing (Hoehn-Saric et al., 1990; Barnhart et al., 2004). It appears to be the primary therapeutic principle through which SSRIs work when it is produced to the right extent (not too much) and when the patient finds the effect useful rather than ego-alien.

While obvious to some clinicians, for much of the last 60 years psychiatrists and psychologists have been seeing this effect in patients and have been told about it by them, often missing what they see and discounting rather than building on what they hear.

A striking counterexample of listening came from Sandra Leiblum in 2001, who described what is now known as persistent genital arousal disorder (Leiblum & Nathan, 2001). As a psychotherapist, she might have been expected to believe this was caused by psychological factors, but her hunch that it was organic led to a link between persistent genital arousal disorder and SSRI use, which psychologists have done more than anyone else to confirm (Jackowich & Pukall, 2020).

Given increasing company control of the academic literature in medicine, it can be difficult for patients to raise these issues with prescribers. They risk being detained under a mental health act for crazy nonevidence-based ideas (Demasi, 2023). While committed to trauma-informed care, it is rare to hear of a psychologist supporting a patient in dealing with abuse of this kind.

If nondoctors are asked why they do not support their patients' perceptions, a common response is that prescribing has been outsourced to doctors, and health service operational systems expect their operatives to keep to specified domains of expertise. This has some truth to it, but misses the fact we all operate now in a climate in which drugs can only do good and doctors find it as difficult to notice and speak up about problems as others do, perhaps even more so. Their patients find it even harder to voice their concerns to the prescriber, whose goodwill they now think they need more than ever as their problems worsen than they would to anyone else.

In being able to tweak the dose of a drug, doctors have some advantages when it comes to linking a drug to harm. Patients with skin in the game and access to Google, however, can educate doctors on aspects of their treatment like never before. Motivation is now worth as much as expertise, and safety in clinical settings has to be more cooperative than hitherto but may need support from another professional.

Besides, noticing many adverse events is not a specialist domain of expertise. Hairdressers were among the first to note a change in hair texture on contraceptives along with a failure of hair color to take on antidepressants. Journalists, like Morton Mintz in the case of thalidomide and Shelley Jofre with SSRIs, made adverse events impossible for regulators to ignore.

While regulatory reporting systems have been opened up to everyone and proportional reporting ratios for cumulated side effects on different drugs can point toward what regulators call signals, a definitive view of links between a treatment and a problem needs an assembling of the evidence that named patients and clinicians can provide. This has never been part of the brief of regulators.

Up to 30 years ago, a doctor in a court case hinging on whether Drug A had caused Problem B would have offered a balance of probabilities view based on a review of a patient's medical history, an interview with them or surviving family and others, along with some familiarity with other causes and ruling them out. This is specific causation, which means deciding on an evident explanation in an individual case.

It is not enough for a psychologist, family doctor, or psychiatrist to claim they cannot offer a view as they have not been trained in the finer details of psychopharmacology. Drugs can bring pharmacokinetic, pharmacodynamic, and perhaps epigenetic factors soon into play, and these may play a part in establishing how a drug might produce a specific effect in this specific person, such as their hair color not taking—but not that it has produced the effect. Establishing that it has produced an effect is a matter of clinical science.

Our histories of science stress that science deals with questions that can be "settled by data" rather than questions about the meaning of life. The emphasis is usually on the word *data*, as though the data speak, are guarantors of objectivity, and considering anything else other than data is to introduce values, a word from which many step back.

Scientific data never speak in this way, even when processed through statistical tests. The keyword in this history of science is "settled." Objectivity comes from the experiment of testing hypotheses in public aiming at a consensus view, as a legal trial does in front of a jury, or as a scientific experiment does when carried out in public. Objectivity does not fall out of statistical tests or algorithms. It stems from two or more people attempting to establish the meaning of events in front of them, which is what should happen in clinical settings, but is at risk because of the presence in the clinic of others—guideline makers, ghostwriters, managers, and regulators—who increasingly inhibit all clinicians from engaging with their patients.

In a proper clinical encounter, all of the data are available, and the patient is the experimental apparatus. As the task has been in scientific experiments for centuries, the clinical task is to come to a best-on-the-balance-of-probabilities consensus view on the experiment before adjusting the controls to add further details, such as increasing the dose of the drug, which may kill the patient, or stopping it, which may alleviate the problem.

Considering whether a drug might be linked to an effect is not a matter of how such effects are produced, but rather one of coming to a consensus judgment with a patient, and perhaps other clinicians and patients, as to whether a behavioral or another effect that has become apparent since treatment began is best explained in terms of a link to the treatment.

There is a strong case for saying that all clinicians should report the adverse effects they notice in their patients taking a drug to a clinical journal, with both clinician and patient names in place. Reports with names attached count as legal and scientific evidence in a way that anonymous reports do not. Reports like this would inform clinical practice in a way that pharmacovigilance once did but no longer does.

Adherence to an operational protocol distinguishes bureaucratic from professional roles. Professionals are supposed to take responsibility and lead even at the risk of personal consequences. Few settings better illustrate the importance of leadership than the safety issues linked to the prescribing of a psychotropic drug, where treatment can injure innocent third parties by inducing homicide (Healy et al., 2007) or wreck marriages by inducing emotional numbing or a change of personality.

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