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Pharmacovigilance in the New Millennium: Challenges, Opportunities and New Directions

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It is both a challenge and opportunity to write the first Editor-in-Chief's editorial for a new born journal. The main challenge is to convince the readership that bringing yet another journal in a world already overwhelmed by information overload is justified. Additional challenges include setting up the journal agenda and goals, mindful of the fact that our vision will define the personality and character of our journal.

Why bring a new journal in a world where the journal population is exponentially expanding? This is a question that any first Editor-in-Chief needs to contemplate. In essence this question is no different than the question aspiring parents contemplate before deciding on having a baby: Why bring a new child in a world where the population is exponentially increasing? Quite often deciding to have a baby is a symbol of hope – the hope that that one baby will help make the world a better place. And some parents indeed do end up with children who grow up to be the world's Einsteins, Davincis, and Hegels. Similarly, some journal editors created the NEJM, Nature or Cell journals of the world. It might seem overambitious to aim for a new journal to aspire at the heights of a NEJM; however, I believe that, in a journal's life, it is at the time of its arrival when it is appropriate to not settle for a meager course and objectives. In fact that might be the only time when thinking big might be not only permissible but indeed recommended.

A challenge? For sure. Nevertheless, a great opportunity at the same time. Accordingly, we do have a big vision for the Journal of Pharmacovigilance (JP). In this day and age, data on drug safety is paramount to the practice of good medicine and should represent a public health priority. *Primum non nocere*, first, do no harm, is the foundation of the Hippocratic Oath. When it comes to pharmaceuticals, this principle effectively translates in knowledge about side effects, adverse effects and drug toxicity, which all fall under the umbrella of pharmacovigilance.

Which makes it so much more surprising to see that a PubMed search for "drug safety" [text words](tw) retrieves 3973 publications, with only 140 articles left if the search is further limited to meta-analysis, systematic reviews, or guidelines i.e. the gold standard for clinical practice recommendations. Further, a similar PubMed search for "pharmacovigilance" [tw] retrieves a comparable number of 2462 articles with only 122 articles left is the search is similarly limited to the "gold standard" of meta-analysis, systematic reviews, or guidelines.

To put this in perspective, compare the above numbers with the results of similar PubMed searches for two other key words that are essential to the practice of prescribing pharmaceuticals: "pharmacokinetics" and "pharmacodynamics". Running a search for pharmacokinetics [tw] returns 2631/327286 gold standard/general search papers while searching PubMed for pharmacodynamics returns an overwhelming 44038/5049535. We are literally looking at orders of magnitude differences between types of knowledge that all fall under the umbrella of "drug-body interactions" and thus should not really be as different size-wise. Should we then be surprised when many "safe" medications are taken off the market despite receiving their stamp of approval at the end of a painstaking process emphasizing safety above anything else?

There is a gap between "official" or declared safety and tolerability (SaT) and "real" safety and tolerability. By *official* we mean the SaT profile created by regulatory data required for official approval; by *real* we mean all other SaT data, including premarketing data that is known but remains un-submitted at the time of the submission, as well aspost-marketing data that might be unknown at the time of the submission but uncovers over time in direct relationship with the time since approval and number of patients exposed to the drug. Traditionally, pharmacovigilance research focuses on the latter. How does the Journal of Pharmacovigilance measure against this traditional approach?

Pre Versus Post-Marketing Safety and Tolerability Pharmaceuticals Research

First, to address the pre-post marketing safety dichotomy we will open our journal to any reliable drug safety communication, regardless of when that communication originated in the life cycle of a given pharmaceutical. We consider that *pre-marketing data is at least as important as post-marketing data* when it comes to pharmacovigilance questions. Thus, we encourage clinical researchers and pharmaceutical companies alike to make safety analyses as much a priority as the traditional efficacy analyses and take the opportunity of using the stage offered by our open-access journal to bring this data to the public.

Further, while we are interested in publishing traditional post-marketing pharmacovigilance research, we feel there is more to the post-marketing drug safety and tolerability story than incidence and prevalence of a certain toxicity based on *official* case reports, case series or retrospective case control studies. To understand how our Journal approach is different with regards to post-marketing safety data, let us have a look at a few defining elements of the current drug safety approval process. At this time, an FDA approval is seen as an iron-clad guaranty that the approved drugs are safe. As part of the process an FDA approved package insert lists a seemingly infinite of possible side or adverse effects. Safety information is presented indiscriminately, without qualifying value judgments clearly informing the patient about likelihood and severity of possible side effect; further, the safety paragraphs appear to be written in a lawyer-ish, liability aversive medical newspeak. The majority of the patients briefly glance at the *ad nauseam* prolonged laundry list of AEs, realize that is mainly a species

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of non-committal, anti-liability, lawyer advised, "safe" language, which is really not that informative when it comes to safety issues that count, and make the only sensible decision under the circumstances: glance over it (if so), maybe ask the doctor about it, or, in this day and age, choose to do an internet check for the "real scoop", which leads us to the first question.

Are the FDA Approved Package Insert Safety Disclosures (Including Toxicity and Adverse Effects) Informative?

Based on our patients' reports, unprepared readers, when faced with the seemingly impossible task of mastering a body of data that is both massive and written in complex medical jargon, such as a phonebook-like lists of "anything possible that might occur while taking drug X", are intimidated and tend to skip the safety section of the package insert. The result? Lacking the motivation to read the safety section of a package insert, patients end up being less informed with regards to medications safety and adverse effects. At this time, this is only a non-systematic and non-controlled observation. Empirical research that will address this or similar questions is sorely needed and will be welcome by our journal. Along these lines, we are keenly interested in research that will quantify safety outcomes of different types of safety communications, in addition to the traditional FDA approved package inserts.

Internet-Searching for Pharmaceuticals Safety Information

Those who give up on package inserts look at the Internet as an alternative source of information. Unfortunately, Internet-based searching for adverse effects and tolerability questions cannot fix the shortcoming of confusing package inserts. The World Wide Web does contain a worldwide wealth of information, including about medication side effects. Typically, this information is posted by patients who had the misfortune of experiencing difficulties while taking a specific medication. There is an advantage in reading information posted by other patients, most times, people whose goal is to share with the hope of getting some advice in return. When it comes to adverse effects, patients' writing is the opposite of the package insert lawyer-inspired disclaimers or squeamishness. The patients prose tends to be straightforward and to the point:

For example, in a patients' forum, a comment on Prozac-induced drowsiness reads:

"It seems that fatigue and drowsiness are not likely to go away once they start." [1]

Straight forward and to the point, yes, but informative? To a certain extent. The main weakness of any self-selected consumer-based database such as the World Wide Web -is that one cannot rule out (self) selection bias. In other words, from one thousand people taking drug X, the one who experienced some adverse effect is more likely to talk about drug safety and tolerability that the 999 who tolerated it without any difficulties. As a result, incidence rates cannot be determined.

In addition, patients' self-reports present a number of limitations that need to be taken into account. A non-exhaustive list of potential issues related to self-report includes:

- Commonly, patients are not skilled in medical diagnosis and associated terminology (e.g. cough, sneezing and feeling warm are reported instead of common cold).
- Self-reported signs or symptoms are often non-specific (e.g. "felt bad" after medication use).
- Patients tend to describe a range of health issues, not just events related specifically to the pharmaceutical in question.
- Duplicate reporting can occur.
- Self-reported signs and/or symptoms often lack detail and specificity, usually available only if a trained professional further investigates the event (e.g. for prescribed medications-details of an AE are often obtained after a physician's medical examination).

So, while straightforward and to the point, the value of Internet derived information is similar to that based on a case report. Web-based reports could not be relied on for understanding the frequency or likelihood of a problem in a specific population, however, web-based information can reliably expand the overall tolerability picture of a pharmaceutical with regards to both granularity and range. Granularity, such as different time courses, degrees of severity or associated issues for a specific AE; range, meaning the listing of an AE that has never been reported before. What is the take home point of all the above for the Journal?

Web-based Quantitative and Qualitative Pharmacovigilance Research

While keeping in perspective the limitations of web-based research, we will consider for publication quantitative pharmacovigilance research focused on or using web-based pharmaceuticals SaT data – including data collected via horizontal, general search, as well as data collected via specialized, vertical search on patient forums, use net groups, providers and patients' maintained websites, third parties disease and drug collection data sites (e.g. Patients like Me).

In addition, JP's interest in post-marketing data includes understanding the quality and safety consequences of communication about medications safety and tolerability (SaT). JP welcomes qualitative research on traditional, pharma-generated SaT communications – such as medications package inserts, as well as on the modern, web-based, patient-generated SaT communications – including user or peer-groups such as patient forums, use net groups, providers and patients' maintained websites, third parties disease and drug collection data sites (e.g. Patients like Me).

Expanding the Definition of Pharmacovigilance

Publication bias and selective outcome reporting in the medical literature have been found across types of interventions (pharmacological, surgical, diagnostic and preventive) and diagnoses(including metabolic disorders, neurological and psychiatric disorders, cardiovascular disease, GI disorders, various types of cancer, infections, and acute trauma, among others) [2].

In this biased literature context, one of the most important functions for our Journal is to be an open forum for scientific communications that will address reporting bias and thus improve our understanding of pharmaceuticals real risk-benefit profiles. One of the implicit assumptions of *primum non nocere* is that a medical intervention should have a favorable risk-benefit ratio in order to be deemed safe. An intervention with no benefit is essentially unsafe regardless of the magnitude of the risk as without benefits, the risk is implicitly greater than the benefit. Thus, when there are no clear benefits, even interventions with trivial or minimal risks should be deemed unsafe.

Consistent with this view, we see studies that change a pharmaceutical risk-benefit ratio by demonstrating a sizeable decrease in the effect size as belonging under the umbrella of pharmacovigilance research.

In this spirit, JP will consider for publication negative findings, systematic reviews or meta-analyses that found that drugs deemed safe and effective either do not separate or only minimally separate from placebo* [3-7]. Further, we would like to open the doors of our Journal for debates on the pros and cons of medication prescriptions, informed by up-to- date risk-benefit analysis, such as we have seen recently on the subject of antidepressants efficacy [6-12].

Safety Data for OTC and Complementary/traditional Medicines

Last but not least, there is a dearth of data regarding the safety of over the counter medications (OTCs), including complementary medicines or traditional remedies. The OTC situation is, in our opinion, a disaster in the making. While most OTC products have a biological action and adverse effects, there is an endemic lack of professional supervision of the entire process that culminates in the consumption of any OTC product by a patient. Starting with a lack of labeling with detailed safety information (i.e., package insert) and ending with no requirement for a physician prescription-meaning no opportunity for the patient to review the drug's safety profile with a qualified health care professional or pharmacist prior to intake, the overall relaxation of the OTC regulatory process greatly increase the safety concerns with OTC pharmaceuticals. In addition, OTC use is rarely reported by patients or recorded in the medical record, which drastically limits the ability to ascertain and report potential adverse effect or toxic drug-drug interactions.

In this context, in addition to traditional pharmaceutical pharmacovigilance research, we see as part of JP's mission is to showcase research about the potential risks and toxicities associated with OTC pharmaceutical, nutriments, supplements, and traditional medicines.

Conclusions

The Journal of Pharmacovigilance aims to use an array of strategies with the common goal of correcting a number of deficits characterizing the current pharmaceutical SaT knowledge.

In addition to being a showcase for traditional pharmacovigilance research, JP is an open-access forum for pre and post-marketing safety and tolerability pharmaceuticals research, research on the efficacy of current safety practices (e.g. package inserts), internet-based quantitative and qualitative pharmacovigilance research, studies that might change a pharmaceutical risk/benefit profile (such as negative studies, publication bias studies, etc.), or SaT research for OTC and complementary/traditional medicines.

We aim to make JP an essential player in developing story of pharmacovigilance research. And it is now, in these beginning stages of our journal when your expert readership contribution will help position JP to help us achieve the goal of helping pharmacovigilance research grow and flourish. We look forward to your contributions and to our journey together.

*The quoted studies are examples of studies that could be submitted to the Journal without any implications for our endorsing the cited evidence.

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