DOI: 10.1002/psp4.12804

EDITORIAL

Quantitative approaches to drug safety: The 2022 PSP special issue

As one of three journals within the ASCPT family of publications, *CPT:PSP* is committed to publishing top-quality work that applies quantitative methods to important issues in drug discovery and development. As the full name of the journal suggests, pharmacometrics and systems pharmacology were originally envisioned as the two central approaches;[1] however, recent years have seen the journal's scope expand to include methods beyond those core approaches, including advanced statistical analysis, construction of biological networks, and machine learning (ML)/artificial intelligence.[2] With respect to applications, articles published in *CPT:PSP* cover a wide range of drugs, both approved and in development, and a wide range of disease and treatment modalities. Because the content included in the journal is quite broad, it is useful to occasionally collect articles that share a common theme, in order to gain an appreciation of new developments within a particular field. *CPT:PSP* has long done this through the creation of "virtual issues" that are posted online, and more recently with the publication of special issues related to a particular topic. After 2021's highly successful inaugural special issue on Pharmacometrics and Statistics,[3] we are happy to present the second annual special issue, which addresses "Quantitative Approaches to Drug Safety."

The Drug Safety special issue contains a variety of original research articles that collectively demonstrate how several different quantitative strategies can be applied to understand, predict, and ultimately prevent a wide range of adverse events. These are complemented by a review article that provides useful "big picture" context,[4] and two brief Perspectives that describe somewhat specialized issues that are sometimes overlooked in classical toxicity studies. These Perspectives cover drugs potentially carried in breast milk by nursing mothers[5] and toxicity caused by snake bites.[6] A brief description of the research articles, grouped thematically, is intended to provide a useful overview of the various techniques and applications that are showcased in our special issue.

It has long been appreciated that drugs that cause beneficial effects at the correct doses may cause extremely undesirable effects at excessively high concentrations. After all, it was in the 16th century that Paracelsus, sometimes referred to as the "Father of Toxicology," said, "Solely the dose determines that a thing is not a poison." Accordingly, a substantial amount of work in drug safety is aimed at determining dosing schedules that will maximize efficacy while avoiding potential adverse events. Because population pharmacokinetics and pharmacodynamics (PopPK and PopPD) are explicitly designed to address dosing questions, it should come as no surprise that several articles in the special issue employ such a strategy. For example, Araki et al.[7] used PopPK/PopPD to address the effects of TAS-114, a compound in development that is intended to improve the therapeutic index of capecitabine. The latter drug is a chemotherapeutic that can sometimes cause hand-foot syndrome, a form of dermatitis, and the authors explore how concurrent treatment with TAS-114 may improve tolerance of capecitabine in some patients. Similarly, Keutzer et al.[8] use PopPK modeling to examine bedaquiline, a drug with a long terminal half-life that is used for treatment of drug-resistant tuberculosis. When bedaquiline is reintroduced after dose interruption, concerns exist about the risk of QT-prolongation and potential ventricular arrhythmias, and the results presented by the authors demonstrate a potential strategy for safe reintroduction of the drug. Along similar lines, Marco-Ariño et al.[9] use a PopPD model to address pupillary reflex dilation caused by remifentanil, an opioid used as an analgesic during surgery, and Dosne et al.[10] use PK/PD modeling for individualized dosing of erdafitinib, a drug that can treat urothelial carcinoma but can cause acute hyperphosphatemia in some patients. Together, these articles demonstrate the centrality of pharmacometrics approaches in ensuring that highly useful drugs do not cause adverse events due to improper dosing.

Although PK/PD models remain the gold standard when a drug has been administered to many patients and

target concentration ranges have been established, sometimes, particularly early in the drug development pipeline, investigators are unsure about the potential for a new compound to cause adverse events because biological mechanisms may be incompletely understood. In such cases, quantitative systems pharmacology (QSP) models, which incorporate cellular mechanisms and frequently also consider interactions between organ systems, can be highly useful for suggesting adverse event mechanisms and guiding future work intended to minimize toxicity while maintaining efficacy.[11,12] The special issue also contains strong examples of how models based on mechanism may be used to distinguish between alternative compounds, thereby nudging drug development into a direction that is more likely to be successful. For example, Gadkar et al.[13] present a QSP model that simulates how T-cell proliferation may affect epithelial barrier integrity in the gastrointestinal (GI) tract, potentially leading to adverse events, such as colitis. By using this model to examine PI3-kinase inhibitors that have differential selectivity for various PI3-kinase isoforms, they suggest ways to avoid colitis in patients through targeting of particular isoforms. Similarly, Fu et al.[14] expand on previous research from their group by presenting a QSP model of the cardiovascular system that accounts for interactions among relevant biomarkers, such as heart rate, arterial blood pressure, and cardiac output. Through validating the model with a proof-of-concept drug, the β-blocker atenolol, they establish a platform that can be used to minimize the possibility that developmental compounds may cause adverse cardiac events.

Although the studies mentioned above illustrate the wide range of potential drug toxicities that can be explored, readers of *CPT:PSP* are fortunate that two interesting articles addressed thrombocytopenia, or depletion of blood platelets, which can result from several types of cancer therapeutics. This provides an opportunity to compare and contrast the approaches taken by the authors of the two papers. For example, Krishnatry et al.[15] used PK/PD modeling to address how molibresib, a bromodomain inhibitor, may lead to thrombocytopenia, QT prolongation, and GI events. The strategy taken by Lignet et al.,[16] who were interested in the effects of three pan-proteasome inhibitors, shared significant similarity with respect to the treatment of drug PKs but included somewhat more detail with respect to how the drugs may affect both proliferation of platelet progenitor cells and platelet budding. The comparison between the two studies therefore reveals how the specific mechanisms included within a model depend on the questions being addressed, consistent with the philosophy that a model should be as simple as possible, but no simpler.

Finally, it is worthwhile to highlight a couple of publications that discuss and use methods that are not typically encountered in *CPT:PSP*. The review article by Soldatos et al.[4] advocates for the construction of biological networks through the integration of molecular data (such as target lists or drug-induced changes in gene expression) with adverse event reports, often obtained through sophisticated text mining strategies. Along similar lines, in the paper by Jeong et al.,[17] the authors use mechanistic simulation results to build a classifier using a convolutional neural network. This strategy of combining mechanistic and ML approaches is currently receiving considerable attention,[18,19] and the Jeong et al. study provides a nice example of the potential benefits. Both approaches—network analysis and ML classifiers—are currently active areas of research that are likely to become increasingly important in the coming years as our understanding improves.

When considered collectively, therefore, the articles in the Drug Safety special issue demonstrate a wide range of approaches to a variety of adverse events caused by several different drugs. Together the research studies, along with the review and the two perspectives,[5,6] show how creative quantitative approaches are becoming increasingly important in all phases of drug development, not only for preclinical and clinical predictions of absorption, distribution, metabolism, and excretion and efficacy, but also for questions related to drug safety.

CONFLICT OF INTEREST

The author declares that no conflicts of interest exist.

FUNDING INFORMATION

Research in Dr. Sobie's laboratory is funded by the National Heart Lung and Blood Institute (U01 HL 136297 and R44HL139248) and the US Food and Drug Administration (75F40119C10021).

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