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Safety pharmacology in 2022: Taking one small step for cardiovascular safety assay development but one giant leap for regulatory drug safety assessment

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ABSTRACT

The continuing COVID-19 global pandemic. This themed issue of J Pharmacol Toxicol Methods comprises articles arising from the meeting. As in previous years the manuscripts reflect various areas of innovation in SP including a perspective on aging and its impact on drug attrition during safety assessments, an integrated assessment of respiratory, cardiovascular and animal activity of in vivo nonclinical studies, development of a dynamic QT-rate correction method in primates, evaluation of the “comprehensive in vitro proarrhythmia assay” (CiPA) ion channel protocol to the automated patch clamp, and best practices regarding the conduct of hERG electrophysiology studies and an analysis of secondary pharmacology assays by the FDA. The meeting also generated 85 abstracts (reproduced in the current volume of J Pharmacol Toxicol Methods). It appears that the validation of methods remains a challenge in SP. Nevertheless, the continued efforts to mine approaches to detection of proarrhythmia liability remains a baffling obsession given the ability of Industry to completely prevent drugs entering into clinical study only to be found to have proarrhythmic properties, with no reports of such for at least ten years. Perhaps it is time to move on from CiPA and find genuine problems to solve?

1. An overview of content from the 2021 SPS meeting

The Annual meeting of the SP Society (SPS) was held virtually from October 4–8, 2021. In attendance were 364 registrants representing all aspects of drug safety and pharmacology including those from contract research organizations, the pharmaceutical industry, academia, technology providers and global regulatory agencies. Attendees represented multiple countries, delivered 30 scientific talks, 8 rapid fire sessions, poster presentations, and showcased demonstrations from 18 scientific exhibitors. The virtual experience for attendees included plenary keynotes, scientific sessions, a networking lounge and poster ‘room’. As with the previous virtual meeting, additional content was offered to the attendees on-demand that included continuing education (CE) courses, poster discussions, and sponsored sessions. The online CE courses included training presentations on topics such as the use of artificial intelligence and machine learning in drug development and imaging technologies with applications to exploratory pharmacology and drug safety, achieving statistical power in SP studies and an analysis of secondary pharmacology assays by the FDA. The meeting also generated 85 abstracts (reproduced in the current volume of J Pharmacol Toxicol Methods).

The recipient of the Distinguished Service Award was Jean-Pierre Valentin, PhD, HDR, ERT, CBiol, FSBiol, FRCPath, DS from UCB Biopharma SPRL. Dr. Valentin’s presentation ‘Safety & Secondary Pharmacology—Reflecting on the Past to Tackle Challenges Ahead’ was a personal outline derived from 30 years of working within the pharmaceutical industry that reflected the strengths, weaknesses, opportunities and threats that surrounded the evolution of SP.

SPS also provided its inaugural Volunteer Recognition Awards to Frederick Sannajust (Villanova, PA, USA) and Silke Schwengberg (CELLS at WORK Consulting & Services, Dueren, Germany) for their dedicated years of service to the society. SPS provided publication awards for recognition of outstanding scientific research. The technological innovation award was given to Koshman et al. (2021) for the publication ‘Automated blood sampling in canine telemetry studies: Enabling enhanced assessments of cardiovascular liabilities and safety margins’. The Translational SP Award was given to Komatsu et al. (2019) for the publication ‘Japan activity for Improvement of Cardiovascular Evaluation by Telemetry system (J-ICET). Exposure-response
analysis of drug-induced QT interval prolongation in telemetered monkeys for translational prediction to human’. The Most Impactful Publication Award was given to Vargas et al. (2021) for the publication ‘Time for a Fully Integrated Nonclinical–Clinical Risk Assessment to Streamline QT Prolongation Liability Determinations: A Pharma Industry Perspective’.

After the meeting, presentations and/or posters were developed into manuscripts and submitted for this themed issue, and these are described below. As in preceding years articles continue to reflect the diversity of SP and the innovation that persists in all aspects of assay methodology including modifications to drug assessment on multiple cardiac ionic currents, albeit hERG remains the focus, and development of innovative experimental endpoints that are scientifically valid and robust for use in drug safety studies. Thus, the pursuit of validation remains a pivotal component of the SP milieu 22 years after the inception of SP as a distinct scientific discipline. With 17 published themed issues on SP methods derived from the annual SPS meeting, J Pharmacol Toxicol Methods continues to be a major repository and curator of this important work.

As is common practice, articles included for publication in J Pharmacol Toxicol Methods are primarily ‘original articles’ that describe and characterize a new or modified method, technique, model, apparatus or approach to acquire and analyze data directly applicable to the conduct of SP studies. These manuscripts accord with, and reiterate, appropriate study design, experimental conduct, data recording methods and reporting practices, and serve as a primary resource aid to individuals in academia, industry, clinical pharmacology and regulatory that are interested in expanding their appreciation of SP. For further detail on the history and rational of development of methods in SP, overview publications are available (Pugsley, Authier, & Curtis, 2008; Pugsley & Curtis, 2015).

2. Cardiovascular SP principles and practice updates from the SPS community

2.1. Addressing drug safety challenges in elderly populations

Fermin and Bell (2022) provide a valuable perspective on the challenges and regulatory considerations facing development and cardiovascular preclinical safety evaluation of pharmaceuticals for the elderly, a rapidly growing segment of the adult population. The authors highlight the increased risk of adverse drug reactions (ADRs) that may develop in elderly patients due to age-related alterations in pharmacodynamics (PK) and pharmacokinetics (PD) of many drugs. Fermin and Bell (2022) also outline potential approaches to address cardiovascular drug safety issues in older adults. Importantly, from 2010 to 2020, the 65-and-older population has increased by 34% in the United States (U.S. Census Bureau, 2020), and the number of Americans that are 65-and-older is expected to double to 95 million by 2060 (Vespa, Armstrong, & Medina, 2020). The use of pharmaceuticals in older adults needs careful consideration because of a host of potential risks. Due to higher rates of underlying health conditions, elderly patients are more likely to take multiple medications simultaneously, termed ‘polypharmacy’. The term has no precise definition so we will adopt the most conservative version for the purposes of this article: administration of two or more different medicines to a single patient in a single treatment cycle. Polypharmacy increases the potential for drug-drug interactions (DDIs), a particularly concerning problem in older adults (Mangoni & Jackson, 2004; Hajjar, Cañiero, & Hanlon, 2007; Maher, Hanlon, & Hajjar, 2014; Cannon, Choi, & Zuniga, 2006) owing to the increased likelihood that multiple drugs are taken at different times during the day, with the DDI risk consequently dynamic and additionally exacerbated by possible compliance and overdosage risk associated with increasing age. In one study, Björkman et al. (2002) found approximately 46% of elderly adult outpatients were receiving at least one combination of medications with a risk of a DDI, while a prospective cohort study conducted in 275 elderly hospitalized patients found the prevalence of potential cytochrome p450-mediated DDIs at 80% (Doan, Zakrzewski-Jakubiak, Roy, Turgeon, & Tannenbaum, 2013). Fermin and Bell (2022) also examined the drug safety impacts of PK differences in the elderly population. Elderly patients generally weigh less than younger counterparts and have a larger percentage of body fat than younger adults, which can lead to relatively higher plasma concentrations for water soluble drugs. Additionally, older adults likely tend to have reduced first pass liver metabolism, resulting in an altered bioavailability of oral drugs (Mangoni & Jackson, 2004). An age-dependent decline in renal function can also affect drug safety in elderly adults. Glomerular filtration rates may decrease by up to 50% from age 20 to 90 (Turnheim, 2003). These factors resonate with the findings of Davies et al. (2020), who found that twice as many elderly patients were hospitalized for ADRs versus younger groups.

Evaluating polypharmacy-related ADR risk, especially in the elderly, is not routinely part of the existing non-clinical SP approach which typically involves use of healthy young animals (or healthy young men in clinical trials). Moreover, older animals may not be appropriate for evaluating drug safety because older animals are still young in years compared with older humans and do not readily express diseases that manifest in older humans (unless the animal is modified by some type of gene knock out or put on a pathogenic diet or manipulated in some other way to manifest a disease of the elderly). Therefore, there is a clear need for new approaches to predicting drug safety in the aging population. Existing models relevant to cardiovascular disease include renal stenosis-induced kidney injury, and atherosclerotic lesion development (such as the cholesterol-fed rabbits or Watanabe heritable hyperlipidemic rabbit). Fermin and Bell (2022), focusing on drugs targeted on the cardiovascular system, proposed approaches to account for alterations in statistical power caused by co-morbidity, and the effect of age on pharmacokinetics and pharmacodynamics. They also considered the use of stem cells isolated from older adults for in vitro studies, and the use of human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) for cardiac safety studies. Fermin and Bell (2022) speculate that hiPSC-CMs derived from older adults may be used to predict ADRs in the elderly. Given that in vivo studies in senescent animals are not considered to be adequately predictive of polypharmacy ADR risk in the elderly (see above), it will be an interesting challenge to determine whether predictive accuracy can be improved by using senescent hiPSC-CMs.

2.2. Cardio-respiratory assessments in rats: use of the DECRO jacketed telemetry system

Fares et al. (2022) describe the use of a non-invasive jacketed telemetry recording method that can be used with socially-housed rats to provide a simultaneous assessment of drug effects on the respiratory system, electrocardiogram (ECG) and animal activity (actimetry). Such methodology is widely used for non-rodent safety evaluations. The authors tested a novel DECRO technology system (ETISENSE, Lyon, France) connected to a DECRO telemetry jacket to evaluate quality and reliability of recording parameters as well as tolerability and jacket material integrity in pair-housed rats. The study evaluated the system response to a single 24-h session (like a stand-alone SP study design) as well as in three repeat sessions of 24 h each (similar to inclusion of SP endpoints in a 1-month repeat dose toxicology study). Using baclofen (a GABAB receptor agonist reference compound) to reduce respiration and animal activity, the authors show that the system records the changes in study parameters with the magnitude of responses in agreement with values derived from validated gold standard methods. Importantly, baseline respiratory rate, tidal volume and minute volume as well as heart rate values recorded in jacketed rats were within the physiological ranges reported in literature. In addition, animals can remain group-housed during recording sessions in accordance with current best practice animal housing recommendations.
2.3. QT interval correction for heart rate: simple or not so simple?

As is well known, the QT interval has long served as a surrogate indicator to predict risk of drug-induced TdP. However, estimation of a direct effect of a drug on the QT interval can be complicated by drug-induced changes in heart rate (HR). Therefore, for an accurate interpretation of drug effects, the QT interval is commonly subjected to a rate correction (e.g., QTc) (Tattersall, Dymond, Hammond, & Valentín, 2006; Vandenberk et al., 2016). These correction methods (and there are several) vary in complexity with some being generic and others individualized to the QT/HR relationship of an individual animal. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) has published recommended guidelines using HR-corrected QT prolongation as a TdP risk biomarker pre-clinically (S7B) and clinically (E14) (Anonymous., 2005a, 2005b). However, no specific rate correction method is stipulated. This has led to the generation of numerous data sets for exploring the utility of various QT correction methods (Anonymous., 2022).

Correction formulae can be categorized as universal or as individual subject corrections. Universal correction methods rely on mathematical formulae containing constant values and assume that the QT/rate relationship does not significantly deviate between subjects or over time. Universal correction formulae have been generally shown to either over-correct or under-correct the QT interval when HR deviates greatly from the average resting rate (Extramiana, Masion-Blanche, Badilini, Beaufls, & Leenhardt, 2005; Malik, 2001). Individual correction methods use regression analysis of data from a single subject (the training data) to determine a subject-specific QT/rate relationship. Using individual correction is not, however, straightforward because it is not intuitive how individualized readout maps to a group mean solution, and in fact the assumption that the individual is the primary source of variation in QT correction means that group mean data cannot be generated simply by taking an average of QT values, individually corrected, from a group of individuals. Ether, Leishman, Bailie, and Lauver (2022) demonstrated a new approach, the Ratio method, an individual correction method that provides greater simplicity (no regression is necessary) over the currently-used rate correction methods and accounts for minute-to-minute changes in the rate relationship and also demonstrate that the method improves QT correction compared to Bazett’s formula in NHP.

2.4. Kinetics of drug block: implementation of the CiPA protocol using an automated patch clamp

The CiPA initiative was set up to find a way of accurately detecting TdP liability without generation of false positives (“throwing the baby out with the bathwater”). This has morphed into a looser collaboration to explore different strategies for assessing TdP liability, with self-sustaining workstreams focused on improving the accuracy of measurement of various TdP surrogates, and this change in focus has had consequences (Authier et al., 2017). The CiPA initiative has attempted to integrate data from in vitro assays using human PSC-derived cardiomyocytes with in silico reconstructions of cellular cardiac electrophysiology. The initial in silico model, designated CiPAORdv1.0, that was developed was a modified version of the O’Hara-Rudy model (O’Hara, Virag, Varro, & Rudy, 2011). CiPAORdv1.0 incorporates hERG gating and drug binding kinetics as well as potency against hERG and other ion channels into risk prediction models (Li et al., 2017, 2019). Subsequently, the CiPA Ion Channel Working group identified a step depolarization protocol with which to evaluate the kinetics of drug binding that is referred to as the Milnes or CiPA dynamic protocol (Milnes, Witchel, Leaney, Leishman, & Hancox, 2010). However, this protocol has been only used for data derived with the manual patch clamp (MPC) system. However, Kramer et al. (2020) conducted a multi-platform/multi-site study that compared of results from 5 APC platforms across 17 sites to evaluate the effects of 12 drugs on 4 human cardiac currents (hERG, peak hNav1.5, hCav1.2 and late hNav1.5) using heterologous expression systems (HEK-293 and CHO cells). Standard voltage clamp pulse protocols were used to measure drug effects on peak hNav1.5, hCav1.2 and late hNav1.5 while the CiPA dynamic protocol was used for hERG. None of the sites were able to record suitable kinetic data using the CiPA dynamic protocol and were only able to use the protocol to determine the IC_{50} values for hERG block because long stable recordings of ≥40 min were required to generate each data from a single cell at a single concentration. Kramer et al. (2020) found that for automated platforms, the IC_{50} values for hERG block with dofetilide ranged from 12 to 103 nM (a 10.4-fold range) but from 0.77 to 1.08 μM (a 1.4-fold range) with quinidine.

To apply an APC approach to drug screening, where a multitude of drugs are evaluated daily, Windley, Farr, TeBay, Vandenberk, and Hill (2022) adapted the Milnes or CiPA protocol for use on the SyncroPatch 384PE automated patch clamp (APC) system. Windley et al. (2022) selected four drugs (bepridil, cisapride, terfenadine and verapamil) from the CiPA testing panel and evaluated single concentration to optimize the Milnes/CiPA protocol for APC. The authors undertook an analysis of study quality control (QC) measures that included establishing thresholds for ease of interpretation, series resistance, cell capacitance, baseline current, leak correction, peak current size, current stability as well as percentage block and noise minimization. The authors also implemented automated offline QC analysis parameters and thresholds for onset of drug block curves and curve fit applied that were subsequently incorporated into the software developed for use in the study. From this they identified optimal voltage protocol parameters including protocol duration and leak correction parameters. The authors subsequently compared their potency and kinetics data to MPC data previously generated (Windley et al., 2017). Significant potency and kinetic differences were found for most drugs, and bepridil data were incorrect due to non-specific binding to the glass bottom patch plates used. The datasets were also compared to data obtained from another APC platform, the CytoPatch System, previously published (Windley, Lee, Vandenberk, & Hill, 2018). Substantial differences were detected in terms of drug potency and kinetic values; thus, quantitative estimates of drug potency (IC_{50}) and efficacy (maximum effect) differed between each of the APC platforms for most drugs tested. In totality, these current and previously published findings suggest that the technical ability of individuals or their equipment are highly site-specific does not map in any way with the idea of data sets ‘generally correlating’.

The adapted Milnes or CiPA protocol for use in APC platforms is poor and the findings suggest that data derived from APC methods should be highly scrutinized and that much work needs to be done to improve efficiency rates if such data is to ever be considered applicable to risk assessment determinations. MPC remains the gold standard method.

2.5. hERG assay best practice as outlined in the ICH E14/S7B Q&As guideline

Recently, the ICH E14 and S7B Clinical and Nonclinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential—Questions and Answers (2020) guidance document was issued. It provides revisions to sections 5.1 (that describes how concentration response modelling may be used for regulatory decisions) and 6.1 (that describes certain cases, i.e., oncology indications, where a conventional TQT study may not be feasible and suggests other methods that may be used to evaluate drug-induced QT prolongation).

Alvarez Baron et al. (2022) report hERG assay case studies with relevant positive control drugs including cisapride, dofetilide, terfenadine, sotalol, and E-4031. The authors used manual whole cell patch clamp methods with step-ramp voltage waveforms to determine hERG IC_{50} values. Experimental factors such as recording temperature, voltage protocol, stimulation rate, drug loss during the experiment and carry-over effects affect assay results were assessed. Based on the study the authors provide several key points for drug developers and regulators to consider. These include the fact that recording temperature may affect...
hERG block potency. We have known this for many years (Polonchuk, 2012) and although the authors found that 3 out of the 5 drugs examined had potency shifts of \( < 2 \times \) it is generally recommended to conduct these studies at physiological temperatures. The authors found drug loss during patch clamp studies can occur due to nonspecific binding to the glass and plastic materials used to perform the experiment and suggest that concentration-verification and drug perfusate sample collection directly from the recording chamber provide the most accurate assessment of drug concentration exposed to cells during the conduct of the patch clamp study.

3. Secondary pharmacology: the role of in vitro pharmacology profiling in drug discovery and development

Previously, Bowes et al. (2012) and Jenkinson, Schmidt, Rosenbrier Ribeiro, Delaunois and Valentin (2020) described best practice for the conduct of secondary pharmacological profiling of an NCE. These articles discuss target composition, screening technologies, assay formats and the interpretation of panels. Subsequently, Dodson et al. (2021) from the FDA evaluated 226 secondary pharmacology profiles obtained from industry sponsors using data manually derived from IND applications and the FDA’s Global Substance Registration System (GSRS) and identified improvements that may be made to secondary pharmacology studies. The authors explored methods to extract binding data and targets evaluated from the totality of secondary pharmacology binding screen affinity profiles for different targets submitted to the agency. Data tables defining targets, compound information, and binding data were extracted from each submitted study file associated with each IND using the open source software tool Tabula (Aristaran, Tigas, Merrill, & Das, 2019), checked for accuracy manually and assigned a binary (positive or negative) classification. A target hit similarity analysis was conducted using hit responses across submitted INDs. From submitted data sets, Dodson et al. (2021) found that for those drugs that ‘hit’ a receptor (i.e., if the response is greater than or equal to 50% inhibition of the control specific binding at the target) <50% of ‘hit’ targets were tested in a functional assay by the sponsors of the IND. Thus, currently there is no uniform consensus across the industry regarding what constitutes a sufficient secondary safety binding study profile for a drug in development (i.e., how data is presented, and which targets are selected for testing). However, there is a regulatory effort to remedy this situation by compiling data for those receptors tested most frequently and then link the secondary pharmacology data findings to clinical safety outcomes.

Scott, Dodson, Saulnier, Snyder, and Racz (2022) expanded on the previous analysis of secondary pharmacology studies by Dodson et al. (2021) by manually curating and analyzing all study results received by the FDA using two internal databases, the Document Archiving, Reporting, and Regulatory Tracking System and the GSR (Pereya et al., 2020) until late 2020. The authors, members of the FDA, outlined a specific set of criteria to include submitted secondary pharmacology studies in their analysis. These criteria include in vitro binding assay data from a small molecule be expressed as percent inhibition of control specific binding at a concentration of 10 μM. Furthermore, the drug identification number and molecular weight must match between the IND and secondary pharmacology report. The authors used the Linguamatics Natural Language Processing (NLP) tool (IQVIA, Cambridge, UK) to extract drug safety data and PharmaPendium (Elsevier, Amsterdam, Netherlands) to identify relevant human concentrations (Cmax) for these same drugs. The analysis examined 1120 secondary pharmacology study reports from various IND applications, more than previously (Dodson et al., 2021) evaluated, and the results were generally consistent. This study demonstrated that the greatest challenge for current secondary pharmacology submissions is the lack of standardization of terminology and file structure as well as target panel profile. If these studies were perhaps conducted better, then the outcomes would be better. Improvements could make research on secondary pharmacology, regulatory review and identification of potential clinical safety liabilities potentially less difficult.

4. Summary

Each year, SP scientists enhance, adapt and validate non-clinical models for use in early research and development and drug safety assessments. The current series of manuscripts described here continues to reflect this effort. For the upcoming year, the ICH E14/S7B Q&A guideline (Anonymous, 2022) will be the focus of the SP membership as it attempts to outline and define best practices involved in the design, conduct, analysis, interpretation and reporting aspects of the hERG and in vivo cardiovascular core nonclinical safety assays. This effort, as described above, addresses the ICH E14/S7B-based “double-negative” nonclinical findings which will place SP studies at the forefront in support of clinical decision-making strategies by the pharmaceutical industry.

SPS annual meeting – live (finally) in 2022

The SP Society (SPS) 2022 Annual Meeting is to be held September 12–14 in Montreal, QC, Canada at the Palais des congrès de Montréal and in partnership with the Canadian Society of Pharmacology & Therapeutics (CSPT). The 2022 Scientific Program features a diverse range of scientific sessions presenting innovative formats and covering topics such as collaborative regulatory topics (i.e., those globally-driven from science vs. those from a regulatory perspective), vaccine development and vigilance, heart rate variability (HRV), investigating cardiac conduction slowing and the impact on drug safety with a characterization of class I antiarrhythmic properties, ‘thinking beyond plethysmography’ – a bridge with clinical functional investigations of respiration and testing of respiratory drugs in clinical trials and the use of iPS cells - moving from mechanistic studies to creating translational value.

Disclaimer

The opinions presented here are those of the authors. No official support or endorsement by participating companies is intended or should be inferred.

Conflicts of interest

None of the authors have any conflicts of interest, other than employment at either a contract research organization (SA), a biotech company (TdeK) or a pharmaceutical company (YEK, MKP, BRW).

Data availability

No data was used for the research described in the article.

References

Alvarez Baron, C. P., Thiebaud, N., Ren, M., Viatchenko-Karpinski, S., Indapukar, A., King, T., et al. (2022). hERG block potencies for 5 positive control drugs obtained per ICH E14/S7B QkAs best practices: Impact of recording temperature and drug loss. Journal of Pharmacological and Toxicological Methods (in press).

Anonymous.. (2005a). ICH S7B: The non-clinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals. In International council for harmonisation of technical requirements for pharmaceuticals for human use. Federal Register (pp. 36791–36799).

Anonymous.. (2005b). ICH E14: The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. In International council for harmonisation of technical requirements for pharmaceuticals for human use. Federal Register (pp. 36791–36799).

Aristaran, M., Tugas, M., & Das, J. (2019). Tabula (1.2.1). Retrieved from https://tabula.technology/.

Author, S., Pugsley, M. K., Koerner, J. E., Ferrini, B., Redfern, W. S., Valenin, J.-P., … Curtis, M. J. (2017). Proarrhythmia liability assessment and the comprehensive in vitro proarrhythmia assay (GIPA): An industry survey on current practice. Journal of Pharmacological and Toxicological Methods, 86, 34–45.
Kramer, J., Himmel, H. M., Lindqvist, A., Stoelzle-Feix, S., Chaudhary, K. W., Li, D., et al. (2007). Polypharmacy in elderly patients. Hajjar, E. R., Cafiero, A. C., & Hanlon, J. T. (2007). Polypharmacy in elderly patients: Systematic review of reviews. Journal of the American Medical Directors Association, 8, 181–187. Doan, J., Zakrzewski-Jakubiak, H., Roy, J., Turgeon, J., & Tannenbaum, C. (2013). Prevalence and risk of potential cytochrome P450-mediated drug-drug interactions in older hospitalized patients with polypharmacy. Annals of Pharmacotherapy, 47(3), 324–332. doi:10.1177/1521166213478685 Dodson, A., Li, M., Russo, D. P., Scott, C., Saulnier, M., Snyder, K., & Racz, R. (2021). Adverse outcomes of polypharmacy in older people: Systematic review of reviews. Journal of the American Medical Directors Association, 21, 181–187. Cannon, K. T., Choi, M. M., & Zuniga, M. A. (2006). Potentially inappropriate medication use in elderly patients receiving home health care: A retrospective data analysis. The American Journal of Geriatric Pharmacotherapy, 4, 134–143. Davies, L. E., Spiers, G., Kingston, A., Todd, A., Adamson, J., & Hannatty, B. (2020). Time for a fully integrated nonclinical-clinical risk assessment to streamline QT prolongation liability determinations: A pharma industry perspective. Clinical Pharmacology & Therapeutics, 109, 310–318. doi:10.1002/cpt.2029 Varga, H. M., Rolf, M. G., Wisialowski, T. A., Achanzar, W., Bahinski, A., Bass, A., et al. (2021). Improving the in silico assessment of proarrhythmia risk by combining hERG (human ether-a-go-go-related gene) channel drug-binding kinetics and multichannel pharmacology. Circulation. Arrhythmia and Electrophysiology, 10, Article e004268. Li, Z., Ridder, B. J., Han, K., Wu, W. W., Sheng, J., Tran, P. N., ... Strauss, D. G. (2019). Analysis of an in silico mechanistic model for proarrhythmia risk prediction under the GIPA initiative. Clinical Pharmacology & Therapeutics, 105, 466–475. Mahler, R. L., Hanlon, J., & Hajjar, E. R. (2014). Clinical consequences of polypharmacy in elderly. Expert Opinion on Drug Safety, 13, 57–65. Malik, M. (2001). Problems of heart rate correction in assessment of drug-induced QT interval prolongation. Journal of Cardiovascular Electrophysiology, 12(4), 411–420. doi:10.1046/j.1540-8167.2001.00411.x Mbangui, I. K., Fastbom, J., Schmidt, I. K., Bernsten, C. B., & Pharmaceutical Care of the Elderly in Europe Research (PEER) Group. (2002). Drug–Drug interactions in the elderly. Annals of Pharmacotherapy, 36, 1675–1681. Bowes, J., Brown, A. J., Hamon, J., Jarolimek, W., Sridhar, A., Waldron, G., et al. (2001). Problems of heart rate correction in assessment of drug-induced QT prolongation. Journal of the American Heart Association, 5, 107206.