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Since its launch in 1960, *Clinical Pharmacology & Therapeutics* (*CPT*) has evolved as a cross-disciplinary premier journal in clinical pharmacology. The editorial leadership of *CPT* has set original research articles (ORAs) as a priority to advance innovation in the discipline. As a result, the majority of *CPT*'s content now consists of ORAs, which cover a broad range of topics including clinical trials as well as *post hoc* analyses spanning diverse therapeutic areas, different (e.g., academic, industry, and regulatory) settings, and novel concepts in clinical pharmacology.

In recent years, novel computational methods such as pharmacometrics and machine learning technologies, precision dosing approaches including pharmacogenomics, and pharmacological modalities beyond small molecules have revolutionized clinical pharmacology. Additionally, new developments in clinical trial design and increasingly inclusive patient recruitment have further advanced the field. Recently, real-world evidence, i.e., analyses of observational studies or routinely collected ("real-world") data (RWD; e.g., from electronic health records), has gained increasing interest for hypothesis generation for adverse drug reactions and drug–drug interactions, and has been used to support regulatory decision making. To identify how these new developments in clinical pharmacology have been reflected in *CPT* publications, and how the focus of the journal has shifted, we evaluated key areas and therapeutic modalities studied in ORAs published between 2015 and 2021 (**Figure 1**). This effort was undertaken by *CPT*'s editors-in-training (I.K.M., D.M.S.), which is a role for early career scientists to learn about the editorial process and assist with the manuscript consideration process and other journal activities.[1]

ORAs published in *CPT* in 2015, 2018, and 2021 were manually assigned to associated therapeutic fields, drug modalities, and key areas of interest by two independent authors (I.K.M., D.M.S.). Discordant entries were discussed until consensus was met. Key areas were defined by the editor-in-chief, deputy-editor-in-chief, associate editors, and the editors-in-training, and included pharmacometrics / machine learning (PMx/ML), pharmacogenomics (PGx), transporters/enzymes, RWD, regulatory science, drug–drug interactions (DDIs), and "other."

Categorization was performed based on article content. For example, publications were assigned as PGx if they included genome-wide association studies, candidate gene studies, PGx implementation, or related research. PMx/ML encompassed publications that described, among others, the development and use of population pharmacokinetic/pharmacodynamic models, physiology-based models, machine learning, or related methodology. The category transporters/enzymes was assigned if an article described enzymes (e.g., cytochrome P450) or

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Figure 1 *Clinical Pharmacology & Therapeutics* July 2023 cover image: Trends in Clinical Pharmacology and Therapeutics.

transporters (e.g., organic anion transporters, P-glycoprotein). Publications that focused on the genetic variation of enzymes, transporters, or other entities were classified as PGx. The term "real-world data" emerged over the period of data collection. Articles were thus examined for whether RWD or real-world evidence were explicitly named, or if authors conducted RWD research without explicitly calling it such. Publications were assigned as regulatory science if they described the investigation, evaluation or development of new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of medications. Any articles that assessed drug–drug interactions were classified as such. A category of "other" was used to describe miscellaneous topics beyond the aforementioned areas (e.g., phase I study, diversity, equity and inclusion, pharmacokinetics without methodology mentioned above, dose–response study). Publications were assigned one primary category and, if relevant, a secondary area. For example, an article that focused on the development and application of a novel pharmacometric model that included PGx as one covariate would be classified primarily as a PMx/ML article and secondarily as a PGx article. Lastly, it was documented if the study utilized data from a clinical trial.

Several interesting trends were observed with respect to ORAs published in *CPT* since 2015. Notably, the annual number of ORAs published in 2021 ($n = 186$) increased sixfold compared with 2015 ($n = 33$) (**Table 1**), in line with the journal's strategy explained earlier to prioritize research papers. The absolute number of publications rose across all key areas (PMx/ML, PGx, RWD, regulatory science, enzymes/transporters, DDI) in each progressive year. PMx/ML and PGx were the overall most common primary areas in ORAs (2021: $n = 55/34$, 30%/18%).

RWD, which represented 41% of the ORAs published in the journal in 2021, was the area of original research that grew the most from 2015 to 2021 in terms of representation in *CPT* publications (percent content). A search of PubMed for "real-world data" also reflects a sharp growth (1,826 PubMed entries in 2015 vs. 8,336 entries in 2021). In May 2021 and January 2022, *CPT* devoted two special issues to this ever-emerging area with overwhelming response.[2,3] The notation "real-world data" sharply increased (2015: 0%, 2021: 7%). In 2021, 43% of publications on real-world-like data used the terms "real-world data" or "real-world evidence." It can be concluded that in a short period of time *CPT* has become a home for the publication of real-world evidence studies focused on therapeutics development and clinical use, and the editorial leadership is committed to continue to grow this area as one of the journal's priorities. Other areas assessed were largely consistent over the years, except

Table 1 Primary area of original research articles published in *CPT* by year

Area	2015 (*n* = 33)	2018 (*n* = 114)	2021 (*n* = 186)	Total (*n* = 333)
PMx/ML	10 (30%)	37 (33%)	55 (30%)	102 (31%)
PGx	5 (15%)	16 (14%)	34 (18%)	55 (17%)
Regulatory Science	7 (21%)	10 (9%)	15 (8%)	32 (10%)
Drug Interactions	1 (3%)	11 (10%)	14 (8%)	26 (8%)
RWD, unnamed	2 (6%)	7 (6%)	16 (9%)	25 (8%)
RWD, named	0 (0%)	4 (4%)	12 (7%)	16 (5%)
Transporters and enzymes (non-PGx)	1 (3%)	5 (4%)	7 (4%)	13 (4%)
Other	7 (21%)	24 (5%)	33 (18%)	64 (19%)

PGx, pharmacogenomics; PMx/ML, pharmacometrics/machine learning; RWD, real-world data.

for ORAs on "regulatory science," which decreased from 21% in 2015 to 8% in 2021 (Table 1). However, the decrease in ORAs may reflect a shift to other article types focused on regulatory sciences such as perspectives, reviews, and white papers, which are published frequently in the journal.

About one-third of the investigated ORAs were assigned to multiple key areas (see Figure 2). DDI studies were most often associated with other key areas (91%), specifically with transporters/enzymes (28% of all DDI studies with two or more key areas), PMx/ML (28%), but also with PGx (19%) and real-world data (19%). More than half (59%) of the studies that primarily focused on transporters and enzymes were also associated with PGx (40%), PMx/ML (40%), or DDI (20%) as secondary area. In contrast, PGx studies (33.9% with secondary area) were most frequently assigned to the categories real-world data (55%), PMx/ML (30%), and DDI (15%). ORAs on PMx/ML (32% with several key areas) were most closely linked to the fields DDI (31%), transporters and enzymes (25%), PGx (22%), and RWD (17%). RWD analyses focused on regulatory science (36%), PMx/ML (29%), PGx (21%), and DDI (14%) in 33% of respective publications. ORAs on regulatory science were based on RWD as the main secondary area, though in only 15% of their total number. Of the screened publications in regulatory sciences, 44% used data from a clinical trial; among those, 43% involved *post hoc* analyses of clinical trials.

The top three therapeutic fields represented in ORAs of *CPT* from 2015 to 2021 included cardiology, oncology, and infectious diseases, followed by articles on drugs used in "multiple" therapeutic areas, as in DDI studies (pooled years: multiple fields 19%, cardiology 16%, infectious diseases

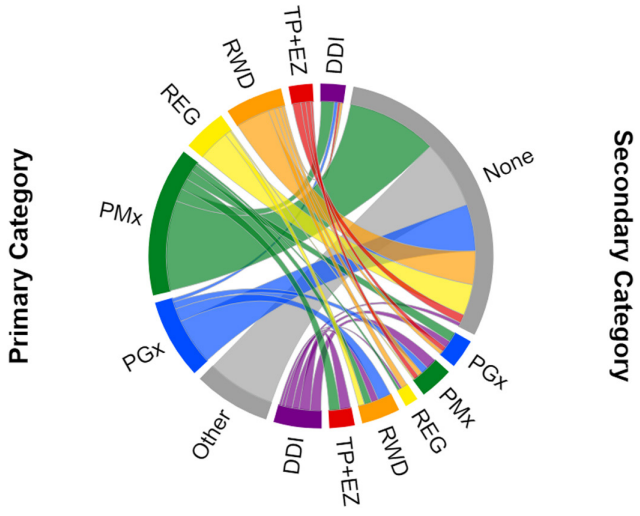

Figure 2 Intersection of key areas in clinical pharmacology research. DDI, drug–drug interaction; PMx, pharmacometrics (including machine learning), PGx, pharmacogenomics; REG, regulatory science; RWD, real-world data; TP+EZ, transporters/enzymes (non-PGx).

14%, and oncology 14%). Articles spanning multiple therapeutic fields were most common in 2018 (multiple fields 20%, cardiology 19%, oncology 15%, and infectious diseases 11%) and 2021 (multiple fields 19%, infectious diseases 16%, cardiology 14%, and oncology 14%). As expected owing to the COVID-19 pandemic, infectious diseases was the most well-represented single therapeutic field in 2021. Consistent with this trend, ORAs on small molecules focused on infectious diseases more commonly than on other areas in 2015–2021.

Treatment modalities studied in ORAs of *CPT* have become considerably more diverse in the past years. While the proportion of original research on small molecules (only) remained comparably high (2015: 72%, 2018: 78%, 2021: 70%), the number of other therapeutic modalities increased (2015: $n = 4$ types, 2018: $n = 7$, 2021: $n = 13$). In 2021, monoclonal antibodies (10%) represented the most prominent pharmacological modality other than small molecules. Further novel modalities studied in ORAs ranged from biomarkers (2021: 2%), antibody–drug conjugates (<2%), diverse biologics (<2%), gene therapy (<1%), RNA, and small interfering RNA, to T cells, herbs, (fusion) proteins, probodies, and peptibodies. In line with this trend, *CPT* will publish a special themed issue dedicated to Novel Modalities in September this year. Roughly 10% of ORAs (2021: 8%, 2018: 6%, 2015: 13%) presented research on multiple diverse modalities.

Recently, *CPT* has emphasized Diversity, Equity, and Inclusion (DEI) in the study populations included in its publications. The journal has taken a broad definition of DEI, which includes diversity in disease, sex, gender, geographical location, and race and ethnicity. A closer look at ORAs on pharmacogenomics revealed that 49% of the PGx studies (i.e., with PGx as the primary category) published in 2015, 2018, or 2021 investigated study populations with diverse ethnic backgrounds, i.e. beyond studies solely focusing on patients classified as White or of European ancestry (29%). In most ethnically diverse study populations of PGx articles in *CPT*, White or European participants were predominant, followed by African American, African, or Black participants. Twenty-two percent of PGx studies did not include explicit descriptions of ethnic diversity in the study populations, suggesting that both editors and authors need to be more careful in their documentation and review of this important information. A recent special themed issue in March 2023 and a mini-theme in October 2021 have spotlighted the crucial topic of DEI and gained wide acclaim from our readers, authors, and editors.[4,5] *CPT* aims to further enhance DEI, adhere to relevant guidelines, and promote research among minority populations to better understand the frequently vast variability in drug response and to ultimately achieve effective and safe use of therapeutics in all patients.

Clinical Pharmacology & Therapeutics continues to serve as a home for cross-disciplinary and diverse original research with respect to therapeutic fields, methodologies, treatment modalities, and study types. The integration of multifarious technological and scientific advances is vital to accelerate the understanding of clinical pharmacology aspects in drug development and to overcome limitations for therapeutic innovation and the ultimate benefit for patients.

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CONFLICT OF INTEREST
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