Innovations, Opportunities and Challenges for Predicting Alteration in Drug Metabolizing Enzymes and Transporters Activity in Specific Populations

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Running Title Page: Altered DMET activity in specific populations.

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Abbreviations

Abstract

Drug metabolizing enzymes and transporters (DMETs) are key regulators of pharmacokinetics (PK), efficacy and toxicity of therapeutics. Over the past two decades, significant advancements in in vitro methodologies, targeted proteomics, in vitro-to-in vivo extrapolation (IVIVE) methods and integrated computational approaches such as physiologically based pharmacokinetic (PBPK) modeling have unequivocally contributed to improving our ability to quantitatively predict the role of DMETs in ADME (absorption, distribution, metabolism, and excretion) and drug-drug interactions (DDIs). However, the paucity of data regarding alterations in DMETs activity in specific populations such as pregnant individuals, lactation, pediatrics, geriatrics, organ impairment and disease states such as, cancer, kidney and liver diseases, and inflammation has restricted our ability to realize the full potential of these recent advancements. We envision that a series of carefully curated articles in a special supplementary issue of Drug Metabolism and Disposition will summarize the latest progress in in silico, in vitro, and in vivo approaches to characterize alteration in DMET activity and quantitatively predict drug disposition in specific populations. In addition, the supplementary issue will underscore the current scientific knowledge gaps which present formidable barriers to fully understand the clinical implications of altered DMET activity in specific populations and highlight opportunities for multistakeholder collaboration to advance our collective understanding of this rapidly emerging area.

Keywords

Drug metabolizing enzymes, IVIVE, PBPK, pharmacokinetics, proteomics, specific populations, transporters
Significance Statement

This commentary highlights current knowledge and identifies gaps and key challenges in understanding the role of DMETs in drug disposition in specific populations. With this commentary for the special issue in Drug Metabolism and Disposition, authors intend to increase interest and invite potential contributors whose research is focused or has aided in expanding the understanding around the role and impact of DMETs in drug disposition in specific populations.
Commentary

Early clinical drug development generally involves evaluation of a new drug in healthy individuals (Karakunnel et al., 2018). In the majority of the cases, other critically important specific populations such as pregnant individuals, pediatrics, and patients with the underlying disease condition are excluded. Although in some instances, late-stage clinical trials enroll a diverse patient population with respect to age, ethnicity, hepatic and kidney dysfunction, pediatrics (primarily adolescents) and varying body mass index, information related to determining a safe and effective dosing regimen in specific populations is mostly derived from data collected in otherwise healthy individuals. Below are a few selected examples to illustrate how altered expression and/or activities of drug metabolizing enzymes and transporters (DMETs), along with ontogeny related changes, can alter the pharmacokinetics (PK) and/or pharmacodynamics (PD) profile of drugs in various specific populations and may potentially result in sub-optimal efficacy and/or unknown risk of adverse effects:

Sex: In recent years, sex related differences in PK of drugs have been widely attributed to differences in body weight, plasma volume, gastric emptying time, plasma protein levels and the activities of key DMETs. Available data suggests that men appear to have higher activities of some Phase I, Phase II enzymes, and efflux drug transporters such as P-glycoprotein compared to women (Schwartz, 2003; Gandhi et al., 2004; Soldin and Mattison, 2009; Yang et al., 2012). Furthermore, sex differences in PK of drugs have been shown to correlate with sex-dependent adverse drug reactions in women (Zucker and Prendergast, 2020). A well-known example is the sedative-hypnotic drug, zolpidem, indicated for the treatment of insomnia. A decade after its approval, post-marketing reports highlighted cognitive deficits in women with this adverse event directly associated with higher systemic exposure of zolpidem in women compared to
men (Zucker and Prendergast, 2020). Subsequently, a drug safety communication issued by the USFDA recommended that the initial dose of zolpidem be reduced in women because of slower elimination relative to men (FDA drug safety communication 2013).

**Pregnancy:** Several studies have reported significant changes in PK of drugs during pregnancy due to physiological changes that lead to altered activities of DMETs (Hebert et al., 2008; Zhang et al., 2020). For example, the systemic exposure of metoprolol and lamotrigine is decreased by up to 5-fold due to increased metabolic clearance during pregnancy (Hogstedt et al., 1985; Pennell et al., 2004). Another study by Mlugu EM et al. demonstrated that the 4β-hydroxycholesterol/cholesterol ratio was significantly higher in pregnant women compared to non-pregnant women. Further, in pregnant women, the authors reported a significant increase in 4β-hydroxycholesterol/cholesterol ratio from the second trimester to the third trimester of pregnancy (Mlugu et al., 2022). The increased CYP3A4 activity is also evident in the study by Hebert MF et al. In this study, systemic exposure of midazolam (CYP3A4 substrate) was significantly decreased (1.9-fold) during pregnancy (28-32 weeks gestation) compared to that during postpartum (6-10 weeks). In the same study, increased renal P-glycoprotein activity was also evident as digoxin (P-gp substrate) renal secretion was 2-fold higher during pregnancy compared to that during postpartum (Hebert et al., 2008).

**Age:** Most clinically relevant DMETs show unique developmental pattern (Shi and Klotz, 2011; Brouwer et al., 2015; Elmorsi et al., 2016; Chapron et al., 2022) thus presenting uncertainties in quantitative PK predictions, especially in pediatric population for whom understanding of DMET abundance across the age continuum is inadequate. For example, Liu et al proposed a physiologically based pharmacokinetic (PBPK) modeling framework to predict neonatal PK. The sensitivity analysis conducted by the authors showed that the OCT2 activity in term newborns is
25-50% of the value implemented in the model and highlighted the need for additional evaluation to investigate OCT2 ontogeny in the newborns (Liu et al., 2021). Further, changes in key physiological processes in the elderly population can also significantly alter drug disposition (McLachlan and Pont, 2012). For example, reduced phase I and II metabolism and reduced renal clearance is reported in elderly population, which may have a substantial effect on drug disposition. Recently published data have indicated a 2.3-fold increase in systemic exposure of midazolam in healthy elderly population compared to healthy adults and this was attributed to reduced activity of CYP3A4 (Rattanacheeworn et al., 2021).

**Disease state:** Disease associated changes in the activity of DMETs can have a significant impact on the PK and/or toxicity of drugs (Staudinger, 2013; Cheng et al., 2016; Evers et al., 2018). The effect of liver diseases such as alcoholic liver disease (ALD) and nonalcoholic fatty liver disease (NAFLD) such as nonalcoholic steatohepatitis (NASH) on DMET activity has been widely evaluated and it has been demonstrated that the severity of the disease state is directly linked to its impact on activities of various DMETs that are implicated in the ADME of drugs (Vildhede et al., 2020; Ladumor et al., 2023; Lin et al., 2023). In chronic liver diseases, the abundance of hepatic CYP3A4 and OATP transporters is substantially reduced, which can lead to drug accumulation and thus requiring dose adjustment (Verbeeck, 2008; Lin et al., 2023). To this end, a study by Weersink et al. systematically evaluated the safety of 209 drugs in liver cirrhosis patients. Based on their analysis, the authors recommended avoiding all nonsteroidal anti-inflammatory drugs (NSAIDs) in the setting of liver cirrhosis (due to altered PD) as these patients are at higher risk of renal insufficiency with NSAIDs use compared to the healthy population. Further, the authors also indicated that several calcium channel blockers are also deemed either unsafe or require dose adjustment in liver cirrhosis patients due to altered
pharmacokinetics as most calcium channel blockers are primarily cleared by the liver (Weersink et al., 2018).

Severe liver diseases may also alter kidney function and renal transporter activity. A recent study by Frost KL et. al. indicated a significant decrease in the abundance of organic anion transporter (OAT)-3 in NASH, ALD and viral hepatitis C (HCV), decrease in the abundance of OAT4 in NASH and that of urate transporter 1 (URAT1) in ALD and HCV (Frost et al., 2023). Therefore, it is important to consider renal transporter changes in addition to hepatic DMETs for potential dose adjustment in chronic liver disease patient population. Like liver diseases, chronic kidney diseases (CKD) have also been shown to significantly alter PK of a drug or its metabolites due to decreased renal excretion. Changes in expression/activity of DMETs in the liver and gut of patients with CKD can further impact disposition of drugs (Sun et al., 2006; Nolin et al., 2008; Yeung et al., 2014).

Altered expression and/or activities of clinically relevant DMETs have also been identified as a key driver in PK variability across diverse populations (Yang et al., 2013) (Figure 1). Over the last few years, biomarkers, exosome analysis and targeted proteomics have emerged as powerful tools to quantitatively evaluate or measure the protein levels or activity of DMETs in key organs involved in drug disposition (liver, intestine, kidney, and brain) and have led to improvements in IVIVE and prediction of inter-individual variability in PK of drugs through coupling with PBPK modeling (Prasad et al., 2019; Ahire et al., 2023). However, there are still considerable knowledge gaps in our understanding of the modulation of abundance and activity of DMETs in specific populations and subsequent impact on drug disposition (Table 1).
To shine light on the recent advancements in our understanding of changes in DMETs expression and/or activity in various specific populations and stimulate discussions for future research to address the current knowledge gaps, the overarching goals of this special supplementary issue in *Drug Metabolism andDisposition* are:

1) Summarize the latest advancements in *in silico*, *in vitro*, and *in vivo* approaches to characterize alteration in DMET activity and quantitatively predict drug disposition in specific populations,

2) Underscore the current scientific knowledge gaps which present formidable barriers to fully understanding the clinical implications of altered DMET activity in specific populations,

3) Highlight opportunities for multistakeholder collaboration to advance our collective understanding of this rapidly emerging area.
Data Availability Statement

The authors declare that all the data supporting the findings of this study are contained within the paper.

Authorship Contributions.

Participated in research design: not applicable.

Conducted experiments: not applicable.

Contributed new reagents or analytic tools: not applicable.

Performed data analysis: not applicable.

Wrote or contributed to the writing of the manuscript: Paresh P. Chothe, Vikram Arya, Bhagwat Prasad, Diane Ramsden, Kunal Taskar.
References


Financial Disclosure

Paresh P. Chothe and Diane Ramsden hold common stocks in AstraZeneca.

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Figure legends

Figure 1: Illustration of challenges (top part of the figure) with predicting PK, PD and DDIs due to alteration in DMETs in various specific populations. Newer approaches and advanced methodologies including *in vitro* tools, IVIVE methods and PBPK modeling will enable us in improved understanding of DMETs in specific populations to achieve clinical success of therapeutic drugs (bottom part of the figure).

*External factors including diet, concomitant medication use, smoking.*
Table 1. Key Challenges, Innovation and Opportunities in Various Areas Important for Understanding the Role of DMETs in Drug Disposition in Specific Populations

<table>
<thead>
<tr>
<th>Area</th>
<th>Challenges</th>
<th>Innovation and Opportunities</th>
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<tbody>
<tr>
<td>In vitro methods</td>
<td>• lack of <em>in vitro</em> assays representing specific populations</td>
<td>• novel 3D or microphysiological systems (MPS) models representing special population (Freag et al., 2021; Teng et al., 2021)</td>
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<td>• limited access to human reagent from specific populations (e.g., hepatocytes, microsomes)</td>
<td>• cross industry, academia, and research effort to source primary tissue from patient populations.</td>
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<td>• poor viability of primary cells from specific populations (e.g., hepatocytes)</td>
<td>• integration of iPS cells from patients and healthy volunteers</td>
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<td>• technologies (i.e., CRISPR) to recapitulate or model disease progression (Ramakrishna et al., 2021)</td>
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<td><strong>In vivo non-clinical models</strong></td>
<td><strong>In Vitro In Vivo Extrapolation</strong></td>
<td><strong>PBPK modeling</strong></td>
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<td>• species differences in the abundance, zonation, and activity of DMETs</td>
<td>• appropriate selection of animal models that closely mimic target human population in relation to abundance and activity of DMETs (Zhu et al., 2023)</td>
<td>• unknown physiological and genetic differences (systems parameters) that can modulate activity of DMETs.</td>
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<td>• lack of knowledge on age special maturation of DMETs in different organs,</td>
<td>• building disease special animal models (Hayashi et al., 2023)</td>
<td>• lack of understanding in ontogeny of DMETs.</td>
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<td>• scarcity of appropriate disease models</td>
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<td>• tissue procurement and large-scale targeted proteomics in special populations</td>
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<td>• poor translation of drug PK to humans</td>
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<td>• tissue special exosome analysis</td>
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<td>• biomarker incorporation</td>
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<td>• technology development</td>
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<td>• bigger efforts for collaboration among scientific communities in obtaining and sharing information.</td>
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<td>Lack of Tissue-Specific Data in PK Studies</td>
<td>Development of Open Databases and Promotion of Professional Training</td>
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<td>Lack of Clinical Data for Reverse Translation and Model Verification</td>
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Figure 1