MINI REVIEW

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Drug metabolism and drug transport of the 100 most prescribed oral drugs

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Abstract

Safe and effective use of drugs requires an understanding of metabolism and transport. We identified the 100 most prescribed drugs in six countries and conducted a literature search on in vitro data to assess contribution of Phase I and II enzymes and drug transporters to metabolism and transport.

Eighty-nine of the 100 drugs undergo drug metabolism or are known substrates for drug transporters. Phase I enzymes are involved in metabolism of 67 drugs, while Phase II enzymes mediate metabolism of 18 drugs. CYP3A4/5 is the most important Phase I enzyme involved in metabolism of 43 drugs followed by CYP2D6 (23 drugs), CYP2C9 (23 drugs), CYP2C19 (22 drugs), CYP1A2 (14 drugs) and CYP2C8 (11 drugs). More than half of the drugs (54 drugs) are known substrates for drug transporters. P-glycoprotein (P-gp) is known to be involved in transport of 30 drugs, while breast cancer resistance protein (BCRP) facilitates transport of 11 drugs. A considerable proportion of drugs are subject to a combination of Phase I metabolism, Phase II metabolism and/or drug transport.

We conclude that the majority of the most frequently prescribed drugs depend on drug metabolism or drug transport. Thus, understanding variability of drug metabolism and transport remains a priority.

KEYWORDS
ADME, CYP3A4, drug metabolism, drug transport, P-gp

1 | INTRODUCTION

The use of medicines is increasing worldwide.[1] A Danish study found that 51% of individuals ≥75 years are prescribed five or more different medications.[2] Enzymatic drug metabolism and drug transport are important for absorption, disposition, metabolism and elimination of a drug within the body.[3] Drug metabolism and drug transport are known to vary both between and within individuals, and this is a problem as it causes variable treatment efficacy and toxicity. Variation in drug metabolism and drug transport may be caused by drug–drug interactions,[3] epigenetics,[4] genetic polymorphisms in genes that encode drug-metabolizing enzymes or drug transporters [e.g. cytochrome P450 (*CYP*)*2D6*, *CYP2C9* and

CYP2C19],[5] or intrinsic (e.g. sex and inflammation) and extrinsic factors (e.g. diet and chemical exposure from the environment).[6]

A previous literature study described the Phase I enzymes involved in drug metabolism of the 200 most prescribed drugs in the United States.[7] In this paper, we provide an updated mapping of Phase I metabolism but also include Phase II metabolism and drug transporters relevant for the 100 most prescribed drugs in five European countries and Australia. We included data from six countries to make the list more international. Furthermore, we summarized the total enzyme and transporter contribution to understand the number of drugs that will be affected because of variation in metabolism or drug transport. Finally, we reviewed main aspects from the literature of the most important Phase I and II enzymes and drug transporters.

2 | METHODS

We identified the 100 most prescribed drugs in five European countries and Australia and performed a literature search for each drug to understand its metabolism and transport.

2.1 | Identifying the Top 100 most prescribed drugs

We obtained data on prescription drug use from six countries: Denmark, Sweden, Norway, England, Scotland and Australia. Data were available upon specific requests to collaborators in the six countries. For each country, we identified the most prescribed drugs. The ranking of drugs, on the individual lists, was based on different measures. Data from Denmark and Sweden were based on the number of prescriptions per 1000 citizens, data from Norway were based on the number of unique individuals buying a drug, data from England and Scotland were based on the number of dispensed items, and data from Australia were based on the number of prescriptions. Medications that contain two active substances were split into their individual components; for example, the drug combination of codeine and paracetamol was counted as the use of both drugs individually. We only included orally administered drugs for systemic treatment, thus excluding inhalation preparations, intravenous preparations, dermatological preparations, drugs with no absorption from the intestine and dietary supplements. Only prescription data from pharmacies were available, thus

excluding prescription data from hospitals. As the Norwegian data contained the lowest number of individual medications ($n = 179$), we restricted all the remaining datasets to the 179 most used medications as well. For each country, we calculated the percentage the individual 179 drugs on the list constituted. Based on these percentages, we calculated the average ranking across all six countries with the following equation, where X was the percentage of a specific drug in the six countries:

$$Share\ spent\ on\ avarage = \frac{(X_{DK} + X_{SE} + X_{NO} + X_{SC} + X_{UK} + X_{AUS})}{6}.$$

A drug was assigned X = 0 if it was absent from the individual list of a country. Calculation of the Top 100 drug list was carried out using the Stata Statistical Software: Release 16 (StataCorp College Station, TX: StataCorp LLC, USA).

From the final list, we chose the 100 most prescribed drugs and conducted a literature search.

2.2 | Search strategy

Two authors (DBI and NA) performed a literature search from January to October 2021 using the database PubMed (Medline). We performed separate literature searches for drug-metabolizing enzymes and drug transporters.

The following search strings were applied for the individual drugs:

Drug metabolism: (drug name AND (hepatic OR Liver OR intestinal OR CYP OR cytochrome P450) AND (pharmacokinetic OR ADME OR metabolism OR metabolized) AND in vitro).

Drug transporter: (drug name AND substrate AND (transporter OR transport) AND (elimination OR excretion OR excreted OR efflux OR uptake)).

The search term 'drug name' was defined as the drug name specified on the Top 100 list. Synonyms for the drug name were automatically included by PubMed, for example, a search for paracetamol also included acetaminophen. Additionally, we identified and included relevant references from articles identified via the search string. We included articles regardless of publication year but strived to use the most recently published.

Furthermore, we conducted a literature search for each drug to determine if the drug was categorized as a prodrug. A prodrug was defined as an inactive substance that needs to be converted to a pharmacologically active substance through metabolism or physico-chemical processes.[8]

2.3 | Study selection for Top 100 most prescribed drugs

We created three inclusion criteria before conducting the literature search. The inclusion criteria were that articles included in the analysis had to be specific for the drug in question and had to report (i) original data, (ii) human in vitro studies and (iii) data of Phase I or II metabolism or drug transport.

Documents from Food and Drug Administration (FDA) or European Medicines Agency (EMA) [e.g. Summary of Product Characteristics (SmPCs) or Highlights of Prescribing Information] were included in the analysis if they were found as references to articles in the literature search. Two authors (DBI and NA) were each responsible for the search of 50 drugs from the Top 100 list and independently screened relevant articles found in the literature search. We did not screen all articles obtained in the literature search, but only until the metabolism and transport of a drug was confirmed through an acceptable article that was deemed valid by meeting the inclusion criteria. After completion of the literature search, one author (TBS) double-checked the results to uncover any mistakes or errors concerning the matching of drugs with enzymes and drug transporters known to be involved in drug metabolism or drug transport.

2.4 | Data analysis

For the drug in question, we flagged an enzyme or transporter as major if one of two conditions were achieved, (i) if the article from the literature search stated that the enzyme or transporter were responsible for more than 50% of the fraction metabolized or transported or (ii) if an original paper defined an enzyme or transporter as 'major'. We did not define a lower cut-off to categorize enzymes or transporters as minor based on contribution to drug metabolism or drug transport. Furthermore, the status of the drug (prodrug or not) was recorded. We divided Phase I enzymes into subcategories of isoforms, for example, CYP2C9 and CYP2D6, and calculated the number of the 100 drugs metabolized by each isoform. All isoforms from the Top 100 list were included equally in the calculation regardless of if they were flagged as major enzyme or transporter. Isoforms metabolizing ≤5 of the 100 drugs were categorized as 'Others'. CYP3A4 and CYP3A5 isoforms were grouped as one isoform, CYP3A4/5, as they share 80% structural similarity and have overlapping substrate specificity making it difficult to distinguish the isoforms.[9]

For Phase II enzymes, we only divided the uridine 5′-diphospho-glucuronosyltransferases (UGTs) into isoforms, for example, UGT2B7 and UGT1A9, as UGTs are the largest Phase II superfamily.[10] The remaining Phase II enzymes were grouped to the superfamily sulfotransferases (SULT). For drug transporters, we described P-glycoprotein (P-gp), breast cancer resistance protein (BCRP) and organic anion transporting polypeptide (OATP) in isoforms and grouped organic anion transporter (OAT), organic cation transporter (OCT), multidrug resistance-associated protein 1–4 (MRP1–4) and multidrug and toxic compound extrusion (MATE) into superfamilies. Isoforms and superfamilies, of both Phase II enzymes and drug transporters, were grouped as 'Others' if they metabolized or transported ≤2 of the 100 drugs.

For both Phase I and Phase II enzymes and drug transporters, we calculated the substrate overlap within each group (Phase I, Phase II and drug transporters). We grouped substrate overlap in the following groups for Phase I enzymes: 1–5 drugs, 6–10 drugs and more than 10 drugs. For Phase II enzymes and drug transporters, we changed the range of substrate overlap to better reflect substrate overlap within these groups. We grouped substrate overlap as 1–2 drugs, 3–4 drugs and more than 4 drugs. We also calculated the substrate overlap between the drug transporters (P-gp, BCRP and OATP1B1/3) and four CYP enzymes (CYP3A4/5, CYP2D6, CYP2C9 and CYP2C19). We grouped substrate overlap between drug transporters and CYP enzymes as 1–5 drugs, 6–10 drugs and more than 10 drugs. Data visualization was carried out using the statistical software RStudio Team (2021) (RStudio: Integrated Development Environment for R. RStudio, PBC, Boston, MA; http://www.rstudio.com/).

3 | RESULTS

Of the 100 most prescribed drugs (Table S1), 89 drugs are known to be subject to drug metabolism or drug transport, while the remaining 11 drugs are not metabolized or known to be substrates for drug transporters. Phase I enzymes metabolize 67 drugs, 18 drugs are metabolized by Phase II enzymes, and 54 drugs are known to be transported by drug transporters (Figure 1). A total of 27 drugs are known to be substrates for both Phase I metabolism and drug transport, while only seven drugs are known to be substrates for Phase I and Phase II metabolism and drug transport (Figure 1). We included a supplementary table (Table S2) with a ranked list of the 179 drugs from each country combined with the percentage each drug constituted from the list.
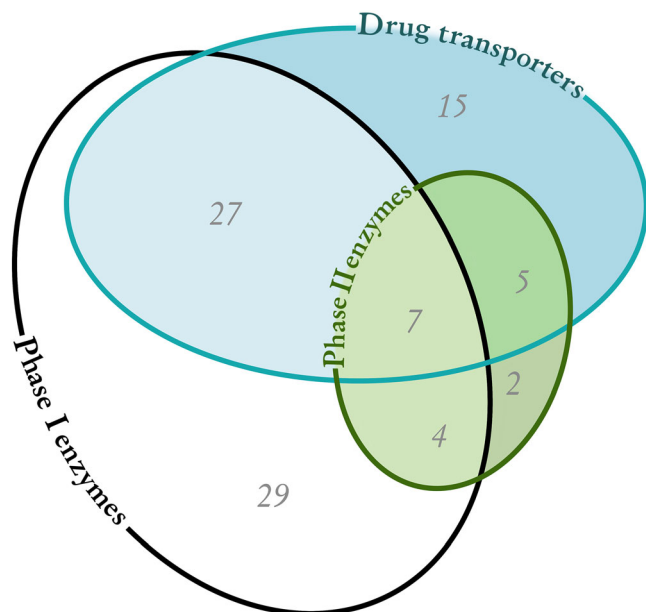
FIGURE 1 Number of the 100 most prescribed drugs metabolized by Phase I enzymes or Phase II enzymes or transported by drug transporters. Overlapping areas reflect a combination of pathways. Of the 100 most prescribed drugs, 11 drugs are not metabolized or transported.

FIGURE 2 Number of drugs metabolized by Phase I enzymes is illustrated with increasing circle size. The size and darkness of the lines between enzymes illustrate the substrate overlap between enzymes. Thin/light-grey line corresponds to 1–5 drugs as substrate overlap. Medium/grey line corresponds to 6–10 drugs as substrate overlap. Thick/black line corresponds to >10 drugs as substrate overlap. Overlap within a group is not illustrated in the figure, but we refer to Table S1 for further information. The group Other includes CYP1A1, CYP2E1, CP2C18, CYP2J2, CYP3A3, CYP3A7, CYP2A6, CYP1B1, AO, FMO and MAO-A + B. AO, aldehyde oxidase; CES, carboxylesterase; CYP, cytochrome P450 enzyme; FMO, flavin-containing monooxygenase; MAO, monoamine oxidase.
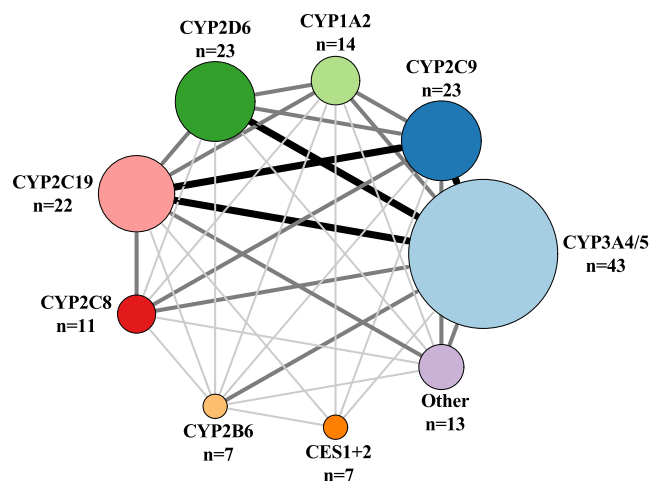
3.1 | Phase I metabolism

CYP3A4/5 is the most important Phase I enzyme as it is involved in the metabolism of 43 of the 100 drugs, followed by CYP2D6 (23 drugs), CYP2C9 (23 drugs), CYP2C19 (22 drugs), CYP1A2 (14 drugs) and CYP2C8 (11 drugs) (Figure 2).

3.1.1 | CYP3A4/5

We find that CYP3A4/5 metabolizes 43 of the 100 drugs and has substrate overlap with three CYP isoforms, CYP2D6, CYP2C9, and CYP2C19 (>10 drugs for all enzymes; Figure 2).

CYP3A4/5 is predominantly expressed in the liver and intestine and is the most dominant drug-metabolizing enzyme in the body.[11,12] Top 3 drugs from our list with CYP3A4/5 as the major enzyme include bisoprolol, ethinylestradiol and zopiclone.

CYP3A4/5 is transcriptionally regulated by pregnane X receptor (PXR) and constitutive androstane receptor (CAR). PXR and CAR are members of the nuclear receptor (NR) superfamily, and PXR is one of the most important receptors in the regulation of metabolism and drug transport. Flucloxacillin (number 61 of the 100 drugs), dicloxacillin (number 77) and rifampicin (not on the list)

are examples of PXR agonists that cause upregulation of CYP3A4 by PXR.[13,14] Contrary, ciprofloxacin (number 92) is an example of a moderate CYP3A4 inhibitor.[15] The time it takes for induction or inhibition to occur and the time it takes for an enzyme to recover from this is important when optimizing pharmacotherapy. One clinical trial investigated the recovery time for CYP3A4 after use of rifampicin for 7 days and discovered that 8 days was needed to recover from rifampicin-mediated induction.[16] Another clinical trial investigated CYP3A4 induction after 28 days of rifampicin treatment. Discontinuation for 28 days was needed to completely recover from rifampicin-mediated induction.[17] Duration of competitive inhibition depends on the elimination half-life of the inhibitor, whereas duration of non-competitive inhibition and induction depends on different biological factors such as de-induction of PXR-driven transcription (e.g. for CYP3A4), degradation of induced mRNAs and their encoded proteins in the liver and gut, CYP protein synthesis and cell turnover.[17]

Food, drinks, herbal drugs and inflammation can also regulate the expression of CYP3A4/5 and lead to drug concentrations out of the therapeutic range. Both Seville

orange and grapefruit inhibit CYP3A4.[18] St. John's wort, a herbal drug used against depression, is a potent ligand to PXR and an inducer of CYP3A4.[19] CYP3A4/5 can also be downregulated by proinflammatory cytokines during inflammation.[20]

Despite multiple studies on genetic polymorphism in *CYP3A4*, there is currently no evidence of common and clinically relevant polymorphisms in *CYP3A4*. Individuals with *CYP3A5* genetic polymorphism can be characterized as *CYP3A5* expressors or as *CYP3A5* non-expressors. *CYP3A5* non-expressors make up 80%–85% of Caucasians, leading *CYP3A5* expressors to be the minority in Europe.[21] This is in contrast to the Asian and African American population where 60%–73% and 32% are *CYP3A5* non-expressors, respectively.[22] The Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for treatment with tacrolimus (CYP3A4/5 substrate) (not on the list) recommends a standard starting dose for *CYP3A5* non-expressor and a higher starting dose for *CYP3A5* expressors.[21]

3.1.2 | CYP2D6

Our findings show that CYP2D6 metabolizes 23 of the 100 drugs and has the largest substrate overlap with CYP3A4/5 (10 drugs; Figure 2). CYP2D6 is mainly expressed in the liver.[11,12] It is the second most important CYP enzyme in our review, and it accounts for 5% of the total CYP protein content in the human liver.[23] Top 3 drugs from our list with CYP2D6 as the major enzyme include metoprolol, venlafaxine and fluoxetine.

CYP2D6 is not susceptible to enzyme induction by drugs,[24] but CYP2D6 expression is increased during pregnancy.[25] In a clinical trial, the plasma metabolic ratio of the CYP2D6 probe dextromethorphan (not on the list) decreased by 53% during pregnancy compared to after pregnancy.[25,26] The antidepressants sertraline (number 19) and fluoxetine (number 52) are inhibitors of CYP2D6.[27] Inhibition lasts 5 days for sertraline and 42 days for fluoxetine after discontinuation.[27] Clinicians should be cautious when prescribing CYP2D6 substrates following initiation and discontinuation of these antidepressants.[27]

Polymorphism in CYP enzymes plays a critical role, especially in CYP2D6. A meta-analysis showed that the efficacy of metoprolol (number 16) is higher in poor metabolizers compared to non-poor metabolizers.[28] CPIC guideline recommends alternative analgesics to the two prodrugs, codeine (number 7) and tramadol (number 21), in poor metabolizers or ultrarapid metabolizers,[29] as they are more likely to experience poor pain relief or more

adverse effects compared to intermediate metabolizers and extensive metabolizers.[30] The nuclear factor 1B (NFIB) was recently discovered to regulate CYP2D6 gene expression in vitro.[31] The same study showed that *NFIB* rs28379954 T>C carriers that were also *CYP2D6* extensive metabolizers had comparable CYP2D6 activity to ultrarapid metabolizers. This highlights that *NFIB* polymorphisms are important to consider in CYP2D6 drug metabolism.[31]

3.1.3 | CYP2C9

We show that CYP2C9 metabolizes 23 of the 100 drugs and has substrate overlap with CYP3A4/5 and CYP2C19 (>10 drugs for each enzyme; Figure 2). CYP2C9 is predominantly expressed in the liver and gastrointestinal tract.[11,12] The CYP2C family contains CYP2C8, CYP2C9 and CYP2C19, which in total comprise 33% of the total CYP protein content in the liver, with CYP2C9 accounting for 24%.[23] Top 3 drugs from our list with CYP2C9 as the major enzyme include naproxen, diclofenac and warfarin. CYP2C9 is regulated by three nuclear receptors: PXR, CAR and glucocorticoid receptor (GR).[32]

S-warfarin (number 45) is a CYP2C9 substrate with a narrow therapeutic index.[33] Fluconazole (number 87) inhibits CYP2C9, and an epidemiological study found that coadministration of fluconazole with warfarin leads to an increase in mean international normalized ratio (INR) of 0.83.[34] This clinically relevant increase in INR can result in adverse effects.[34] Dicloxacillin (number 77) is an inducer of CYP2C9 through PXR activation.[13] Two epidemiological studies showed that coadministration of dicloxacillin and warfarin leads to a decrease in mean INR at 0.62 after 2–4 weeks of dicloxacillin exposure[35] and an increased risk of ischaemic stroke and systemic embolism (hazard ratio 2.19).[36]

Genetic polymorphisms may affect CYP2C9 activity. *CYP2C9*2* and *CYP2C9*3* are the most studied genotypes and carriers of either have decreased CYP2C9 activity. The plasma clearance of S-warfarin is decreased by 56% (*CYP2C9*1/3*), 70% (*CYP2C9*2/3*) and 75% (*CYP2C9*3/3*) compared to wild type (*CYP2C9*1/1*).[37] Three large randomized clinical trials investigated if genotyping before initiating anticoagulant therapy improves the percentage of time in the therapeutic INR range. The studies reached contradicting conclusions, which complicated implementation of *CYP2C9*-guided treatment with warfarin.[38–40] The CPIC guideline for warfarin therapy only recommends dosing based on genotype if it is known before initiating treatment.[41]

3.1.4 | CYP2C19

CYP2C19 metabolizes 22 of the 100 drugs and has considerable substrate overlap with CYP2C9 and CYP3A4/5 (>10 drugs for each enzyme Figure 2). CYP2C19 is expressed in the liver and gastrointestinal tract.[11,12] Top 3 drugs from our list with CYP2C19 as the major enzyme include omeprazole, pantoprazole and esomeprazole. CYP2C19 is regulated by the same three nuclear receptors as CYP2C9 (PXR, CAR and GR).[42] Rifampicin (not on the list) is an inducer of this enzyme through both CAR and PXR, and dexamethasone (number 60) induces CYP2C19 through GR.[42]

CYP2C19 polymorphisms have been widely investigated, and some variants might be clinically relevant. Carriers of *CYP2C19*17* are characterized as ultrarapid metabolizers, while carriers of *CYP2C19*2/3* are characterized as poor metabolizers.[43] Patients that carry *CYP2C19*2* who are treated with citalopram (number 30), a substrate of CYP2C19, had lower odds of tolerance to the drug.[44] A clinical study showed that individuals carrying *CYP2C19*2* and *CYP2C19*3* had lower omeprazole (number 4) metabolism compared to individuals carrying *CYP2C9*1*.[45] The same study showed that administration of the CYP2C19 inhibitor fluvoxamine (not on the list) reduced omeprazole metabolism in individuals carrying *CYP2C19*1*, but it had no impact on the metabolism of omeprazole in *CYP2C19*2* and *CYP2C19*3* carriers.[45] CYP2C19 intermediate and poor metabolizers who receive the prodrug clopidogrel (number 36) experience reduced platelet inhibition and increased risk of major adverse cardiovascular and cerebrovascular events.[46] CPIC guideline recommends considering an alternative to clopidogrel in intermediate metabolizers and to avoid clopidogrel in poor metabolizers.[46]

3.1.5 | CYP1A2

Our review shows that CYP1A2 metabolizes 14 of the 100 drugs and has substrate overlap with CYP3A4/5, CYP2C9, CYP2C19 and CYP2D6 (6–10 drugs for each enzyme; Figure 2). CYP1A2 is predominantly expressed in the liver.[11,12] From our list, CYP1A2 is not categorized as the major enzyme in drug metabolism, but the Top 3 CYP1A2 substrates from our list are naproxen, ethinylestradiol and mirtazapine. CYP1A2 is transcriptionally regulated by aryl hydrocarbon receptor (AhR), which is a ligand-activated transcription factor.[47]

Several drugs induce CYP1A2.[48] Omeprazole (number 4) is an inducer of CYP1A2 in vitro.[49] The most potent CYP1A2 inhibitors are planar molecules with a small volume that easily fit into the active site of CYP1A2. They often contain methyl, chloro or fluoro substitutions, for example, ciprofloxacin (number 92).[50] Ciprofloxacin and oral contraceptives containing ethinylestradiol (number 27) and gestodene were investigated for inhibition of tizanidine metabolism (CYP1A2 substrate) (not on the list).[51–53] Ciprofloxacin is a stronger inhibitor than oral contraceptives; however, care should be taken when tizanidine is administered to oral contraceptive users, as tizanidine has a narrow therapeutic range.[51]

The activity of CYP1A2 is subject to individual differences from genetic factors[54] and environmental factors such as smoking.[48] Clozapine (not on the list) is a substrate of CYP1A2 and is an antipsychotic drug where therapeutic drug monitoring is used.[55] A meta-analysis recommended decreasing the dosage of clozapine by 30% for patients who smoke and suddenly stop smoking and to analyse clozapine blood levels.[55]

3.1.6 | CYP2C8

We find that CYP2C8 metabolizes 11 of the 100 drugs and has substrate overlap with CYP3A4/5, CYP2C9 and CYP2C19 (6–10 drugs for each enzyme; Figure 2). CYP2C8 is highly expressed in the liver.[11,12] From our list, CYP2C8 is not categorized as the major enzyme in the metabolism of the 100 most used drugs, but the Top 3 CYP2C8 substrates from our list are ibuprofen, ethinylestradiol and zopiclone. The transcriptional regulation of CYP2C8 is the same as for CYP2C9 and CYP2C19 (PXR, CAR and GR).[56]

Felodipine (number 76) is an example of a potent inhibitor in vitro,[57] and trimethoprim (number 55) is a weak inhibitor of CYP2C8 both in vitro and in vivo.[58] Clopidogrel (number 36) is a CYP2C8 inhibitor via its metabolite, clopidogrel acyl-β-D-glucuronide.[59] A retrospective study showed that patients treated with paclitaxel (CYP2C8 substrate) (not on the list) had a ∼2-fold increased risk of developing neuropathy Grade 2 or higher when co-treated with clopidogrel.[60] Only a few CYP2C8 inducers have been discovered. Dexamethasone (number 60), a corticosteroid, induces CYP2C8 through binding to GR. Rifampicin (not on the list) induces CYP2C8 and increases the expression of the enzyme through PXR activation.[56]

The genetic polymorphism *CYP2C8*3* is the most investigated polymorphism in *CYP2C8*. The allele is common in Caucasians but rare in African and Asian populations.[61] Many studies have investigated this allele, but data are conflicting regarding the effect on metabolism, and the activity of *CYP2C8*3* might be substrate dependent.[62,63]

3.2 | Phase II metabolism

The UGT superfamily is the most important Phase II superfamily and is involved in the metabolism of 17 of the most used drugs, followed by sulfotransferase (SULT) that metabolizes three of the 100 drugs (Table S1).

3.2.1 | UGTs

UGT superfamily can be divided into four families, UGT1, UGT2, UGT3 and UGT8; however, UGT3 and UGT8 are not significant in drug metabolism.[64] We highlight UGT1A and UGT2B as the most important family members for drug metabolism. We show that UGT2B7 is responsible for metabolism of nine of the 100 drugs (Figure 3). UGT1A3 and UGT1A9 are the second most important Phase II enzymes, and they metabolize eight of the 100 drugs (Figure 3). UGT2B7 and UGT1A9 share the largest substrate overlap with five drugs. UGTs are mainly expressed in the liver and intestine.[64]

UGTs are marked as the major enzyme for two of the top 100 drugs; this includes diclofenac and
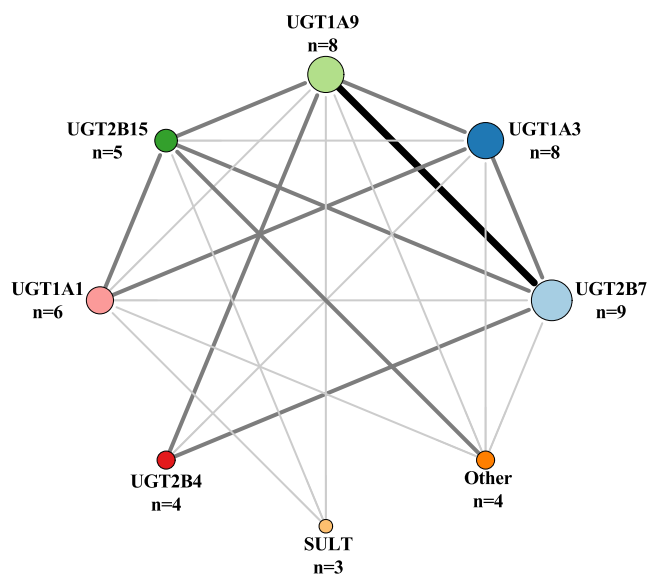
FIGURE 3 Number of drugs metabolized by Phase II enzymes is illustrated with increasing circle size. The size and darkness of the lines between enzymes illustrate the substrate overlap. Thin/light-grey line corresponds to 1–2 drugs as substrate overlap. Medium/grey line corresponds to 3–4 drugs as substrate overlap. Thick/black line corresponds to >4 drugs as substrate overlap. Overlap within a group is not illustrated in the figure, but we refer to Table S1 for further information. The group Other contains UGT1A4, UGT1A6 and UGT2B10. SULT, sulfotransferases; UGT, uridine 5′-diphospho-glucuronosyltransferases.

telmisartan. Different nuclear receptors are involved in regulation of different isoforms in the UGT superfamily. This includes AhR, CAR, PXR, farnesoid X receptor (FXR), liver X receptor (LXR) and peroxisome proliferator-activated receptor (PPAR).[65] Studies investigating the regulation of UGTs are sparse compared to CYP enzymes. However, some drugs have been identified as inhibitors of UGTs in vitro though few are confirmed in in vivo studies. UGT1A1 is involved in glucuronidation of bilirubin, and a study found that tyrosine kinase inhibitors inhibit UGT1A1, which increases the risk of hyperbilirubinaemia in patients.[66] Atazanavir (not on the list) is used to treat HIV and inhibits UGT1A1. If *UGT1A1* genotype is known before treatment start, CPIC guideline recommends considering an alternative agent to atazanavir in poor metabolizers as there is an increased risk of jaundice.[67] In vitro studies have also shown that UGTs are subject to induction. Many UGT inducers also induce other enzymes such as CYP enzymes and include rifampicin (not on the list), phenobarbital (not on the list) and carbamazepine (not on the list).[68] In vivo studies investigating induction or inhibition are difficult to conduct since there are few good and specific probe drugs for UGT isoforms.[69]
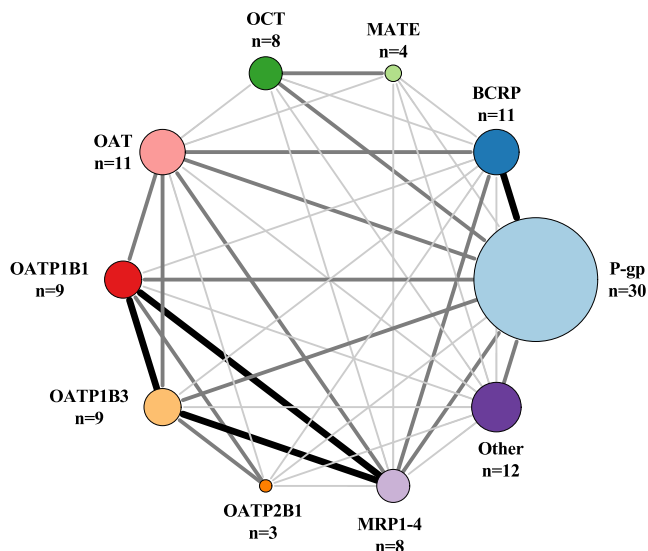
3.3 | Drug transporters

P-gp is the most important drug transporter and known to transport 30 of the 100 drugs. Breast cancer resistance protein (BCRP) is known to transport 11 drugs, and organic anion transporting polypeptide 1B1 (OATP1B1) and OATP1B3 are both known to transport nine drugs (Figure 4).

3.3.1 | P-gp

We find that P-gp is known to transports 30 drugs and has the largest substrate overlap with BCRP (five drugs; Figure 4). Substrate overlap of 3-4 drugs is shared with OATP1B1 and OATP1B3, organic cation transporter (OCT), organic anion transporter (OAT) and multi-drug resistance protein 1–4 (MRP1–4) (Figure 4). The overall largest substrate overlap for P-gp is with CYP3A4/5 (>10 drugs; Figure 5A), and a minor substrate overlap is seen with CYP2D6, CYP2C9 and CYP2C19 (6–10 drugs; Figure 5A).

P-gp has wide tissues distribution, for example, brain, endocrine tissues, gastrointestinal tract, liver and kidney.[11,12] It belongs to the ATP binding cassette (ABC) transporter superfamily, and the function of P-gp is to

FIGURE 4 Number of drugs transported by drug transporters is illustrated with increasing circle size. The size and darkness of the lines between enzymes illustrate the substrate overlap. Thin/light-grey line corresponds to 1–2 drugs as substrate overlap. Medium/grey line corresponds to 3–4 drugs as substrate overlap. Thick/black line corresponds to >4 drugs as substrate overlap. Overlap within a group is not illustrated in the figure, but we refer to Table S1 for further information. The group Other contains MCT, OATP1A2, OATP4C1, OCTN, LAT, SERT, PMAT, THTR, CHT, NTCP, PePT and AE. AE, anion exchange protein; BCRP, breast cancer resistance protein; CHT, choline transporter; LAT, L-amino acid transporter; MATE, multidrug and toxic compound extrusion; MCT, monocarboxylate transporter; MRP, multidrug resistance-associated protein; NTC, sodium-taurocholate co-transporting polypeptide; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OCT, organic cation transporter; OCTN, organic cation transporter novel; PePT, peptide transporter; PMAT, plasma membrane monoamine transporter; P-gp, P-glycoprotein; SERT, serotonin transporter; THTR, thiamine transporter protein.

limit cellular accumulation of endogenous metabolites and xenobiotics.[70]

From our list, P-gp is not categorized as the major transporter in drug transport of the 100 most used drugs, but the Top 3 P-gp substrates from our list are atorvastatin, omeprazole and losartan. P-gp is encoded by the human multidrug-resistance (*MDR1*) gene,[71] which is regulated by two receptors, PXR and CAR.[72]

Rifampicin (not on the list) is a well-known inducer of P-gp, and its impact on P-gp is widely studied with different substrates, for example, fexofenadine (number 84).[73] A clinical study showed that rifampicin decreased area under the curve (AUC) of fexofenadine by 51%.[73] Verapamil (not on the list) is a well-known P-gp inhibitor, and coadministration with fexofenadine leads to a 2.5-fold increase in AUC of fexofenadine in male volunteers.[74]

Genetic polymorphisms in *MDR1* can potentially alter the functional expression and activity, but despite extensive research within this field, there is still no consensus regarding the significance of P-gp genetic polymorphism.[75–77]

3.3.2 | Breast cancer resistance protein (BCRP)

Our review shows that BCRP is known to transport 11 drugs, and besides a substrate overlap of five drugs with P-gp, BCRP shares substrates of 3–4 drugs with OAT and MRP1–4 (Figure 4). Further, BCRP has substrate overlap with CYP2D6, CYP2C9 and CYP2C19 (1–5 drugs; Figure 5B). From our list, BCRP is not categorized as the major transporter in drug transport of the 100 most used drugs, but The top 3 BCRP substrates from our list are pantoprazole, furosemide and rosuvastatin.

BCRP is located in, for example, the brain, gastrointestinal tract, reproductive organs and muscle tissues.[11,12] A prominent BCRP substrate from our list includes allopurinol (number 51). BCRP belongs to the ABC transporter superfamily, and the BCRP transporter is encoded by the *ABCG2* gene.[78,79] BCRP is regulated by AhR, CAR, PXR, GR, oestrogen receptor β (ER-β), PPAR-γ and nuclear factor erythroid 2-related factor 2 (Nrf2).[80]

Febuxostat (not on the list) is a newer xanthine oxidase inhibitor that inhibits BCRP-mediated transport of rosuvastatin (number 24) both in vitro and in vivo.[81] The *ABCG2* gene is polymorphic, and the *ABCG2* c.421C>A variant is well studied. The minor A allele results in decreases of 30%–40% BCRP protein expression compared to the reference allele.[82] A study showed that *ABCG2* c.421C>A variant resulted in poor response to the BCRP substrate allopurinol.[83] Pharmacokinetic data show that patients carrying the ABCG2 c.421C>A variant have increased rosuvastatin exposure (144% increased AUC), which leads to higher risk of myopathy. Furthermore, genome-wide association studies showed that carriers of the variant have improved cholesterol-lowering response of rosuvastatin.[82] Based on these results, the CPIC guideline recommends that patients with poor function *ABCG2* reduce the starting dose of the BCRP substrate rosuvastatin to ≤20 mg or consider alternative statins if more than 20 mg is needed.[82]

3.3.3 | Organic anion transporting polypeptide 1B1 (OATP1B1) and OATP1B3

OATP1B1 and OATP1B3 are both known to transport nine drugs. The largest substrate overlap for the two isoforms are with each other (eight drugs; Figure 4) and

FIGURE 5 (A) Substrate overlap between P-gp and CYP3A4/5, CYP2C9, CYP2C19 and CYP2D6. (B) Substrate overlap between BCRP and CYP3A4/5, CYP2C9, CYP2C19 and CYP2D6. (C) Substrate overlap between OATP1B1/3 and CYP3A4/5, CYP2C9 and CYP2C19. The size and darkness of the lines between drug transporter and enzymes illustrate the substrate overlap. Thin/light-grey line corresponds to 1–5 drugs as substrate overlap. Medium/grey line corresponds to 6–10 drugs as substrate overlap. Thick/black line corresponds to >10 drugs as substrate overlap. BCRP, breast cancer resistance protein; CYP, cytochrome P450 enzyme; OATP, organic anion transporting polypeptide; P-gp, P-glycoprotein.
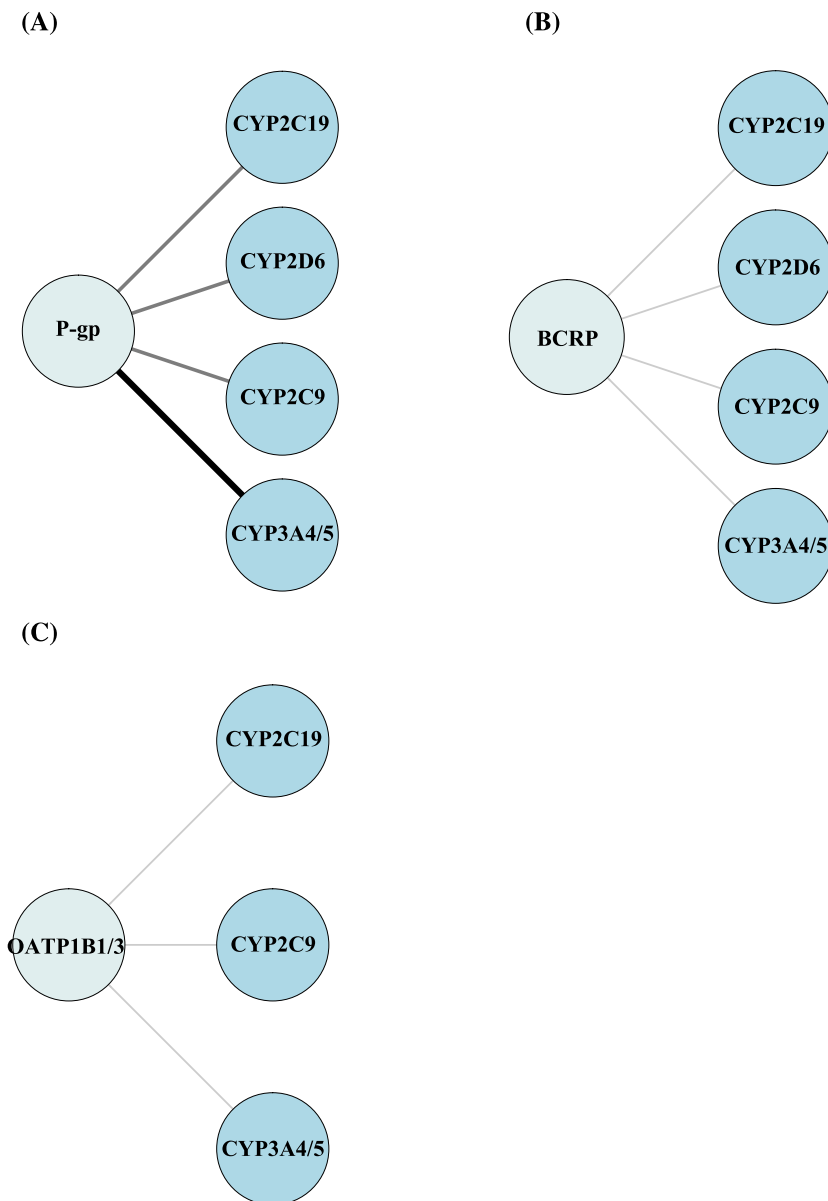
with MRP1–4 (five drugs; Figure 4). OATP1B1 and OATP1B3 has also substrate overlap of three drugs with OAT (Figure 4) and substrate overlap with CYP3A4/5, CYP2C9 and CYP2C19 (1–5 drugs; Figure 5c). OATP1B1 and OATP1B3 are primarily expressed in the liver,[11,12] and they have 80% amino acid homology.[84] From our list, OATP1B1 and OATP1B3 are not categorized as the major transporter in drug transport of the 100 most used drugs, but the Top 3 OATP1B1 and OATP1B3 substrates from our list are atorvastatin, simvastatin and furosemide. OATP1B1 and OATP1B3 are members of the solute carrier (SLC) family that regulates cellular uptake and is encoded by *SLCO1B1* (OATP1B1) and *SLCO1B3* (OATP1B3).[85,86] Both transporters function as active uptake transporters.[86] The transcriptional regulation of OATP1B1 and OATP1B3 differ. The major transcriptional

regulators for OATP1B1 are FXR and LXRα, but only FXR is known to be involved in regulation of OATP1B3.[87]

Rifampicin (not on the list) is an inhibitor of OATP1B1 and OATP1B3.[88] A study with healthy volunteers gave the trial subjects a single dose of rifampicin and showed a sevenfold increase in AUC of atorvastatin (number 2), a substrate to OATP1B1 and OATP1B3.[88]

The c.521T>C genotype in *SLCO1B1* is the most widely studied polymorphism. This variant leads to reduced transport activity in vitro.[89] Several studies have shown that carriers of the c.521T>C genotype are at increased risk of simvastatin-related myotoxicity (number 5).[90] CPIC guideline states that patients with decreased or poor function of OATP1B1 are at increased risk of myopathy upon treatment with atorvastatin and

simvastatin, and dose should be adjusted accordingly.[82] There is currently no well-validated polymorphism in *OATP1B3* that require altered pharmacotherapy.

4 | DISCUSSION

In this review, we identified the 100 most prescribed drugs in five European countries and Australia. We found that 89 of the 100 drugs are metabolized either by Phase I metabolism or Phase II metabolism or are known to be substrates for drug transporters, whereas 11 drugs are not subject to drug metabolism or drug transport. In total, 67 of the 100 drugs undergo Phase I metabolism where CYP3A4/5 is the predominant enzyme followed by CYP2D6, CYP2C9, CYP2C19, CYP1A2 and CYP2C8. UGTs are the most dominant Phase II enzymes responsible for metabolism of 17 of the 100 drugs. Lastly, P-gp is the dominant transporter and is known to be responsible for the transport of 30 of the 100 drugs. CYP3A4/5 and P-gp share a large substrate overlap of 15 drugs, and if expression or activity is altered for CYP3A4/5 or P-gp, it will potentially affect 73 drugs, and this is of substantial clinical relevance.

A previous study investigated how the 200 most widely used drugs in the United States are metabolized through CYP enzymes and found the same five CYP enzymes to be the major contributors to drug metabolism.[7] A newer and updated version by the same authors looked at 248 clinically relevant drugs and found that the contribution of CYP3A4/5 to drug metabolism was 30% and therefore lower compared to their previous study (37%) and ours (43%).[7,91] Another literature review described that UGTs are involved in the metabolism of almost 8% of the 200 most prescribed drugs in the United States in 2002,[92] which is a smaller contribution compared to ours at 17%. They also found that UGT2B7 is the most dominant UGT isoform followed by UGT1A4 and UGT1A1.[92] Our update highlights that the latter two have a minor role today, while UGT2B7 retains its role as the most important UGT. The methods used to collect data on drug metabolism from the three previous articles differ from ours and may impact the results. Two articles[7,92] retrieved information on elimination route for the 200 most prescribed drugs through Rxlist. com. The third article[91] did not describe how the 248 drugs were chosen but found literature on drug metabolism. Contribution of drug transport to the most widely prescribed drugs has not previously been investigated. Drug transporters are known to be involved in the transport of more than half of the most prescribed drugs and are therefore important to consider in pharmacotherapy.

In our literature search, we assessed drug metabolism for each drug. For prodrugs activated through metabolism, drug metabolism covers both the activation route and the elimination route of the ingested drug. Different enzymes are responsible for either one of these routes, and this is important to consider as changes in one of these enzymes will affect the efficacy differently.

Our updated list is a snapshot of the enzymes and transporters known to be involved in drug metabolism and drug transport at the time of data extraction. It should be noted that pharmacotherapy is constantly evolving especially regarding Phase II enzymes and drug transporters, and thus, new knowledge is continuously obtained. Additionally, new drugs are approved, while others become obsolete. It is therefore important to update this list in the future.

The strengths of this review are that we obtained data on prescription medicine from five countries in Europe and from Australia, which makes the list applicable for multiple countries. Furthermore, we used original literature based on human in vitro studies. We chose human in vitro studies as these studies are the most accurate to explain underlying mechanisms for drug metabolism and drug transport. Additionally, a third author double-checked our results from the literature search to reduce the risk of errors. The first limitation to our study is that we included prescription data from Scotland that were obtained 6 years ago and thus slightly outdated. Secondly, two authors each screened articles for 50 drugs until metabolism and drug transport were confirmed by a valid article. This could result in slight under-representation of minor enzyme contributions though we believe this will be of minor relevance. Thirdly, we excluded animal studies in our literature search. If the assessment is performed in animal models or with murine drug transporters without utilization of human cell models, it is not included in our literature search. This might underestimate the contribution of especially drug transporters as knockout rodent models are widely used to establish involvement of drug transporters. One such example is the involvement of OAT3 in ciprofloxacin transport, which was studied in a mouse model[93] but not caught by our literature search. As this limitation is only relevant for drugs that are exclusively studied in animal models, we suspect that there is a relatively low risk of missing major metabolism and transport pathways. Fourthly, we were not able to confirm the proportional contribution (major or minor contribution) of enzymes and drug transporters to metabolism or drug transport as conclusive data are not available for most drugs. Fifthly, we only assessed metabolism and transport of the parent drug. Thus, we did not cover downstream metabolism and transport of metabolites. Sixthly, in some countries,

drugs are available both as over-the-counter drugs and as prescriptions, whereas a prescription is required in others. This could result in slight under-representation of specific drugs as we only included prescription data. Finally, we only had prescription data from pharmacies, while data on medicine used in hospitals were not available. Thus, drugs primarily prescribed in hospitals were not included. These may include chemotherapeutic drugs, biologics, etc.

5 | CONCLUSION

In conclusion, we found that 89 of the 100 most prescribed drugs are metabolized and/or known to be transported. Only 11 drugs are not subject to either drug metabolism or drug transport. As involvement and overlap of enzyme and transporters are high, this study highlights the risk of drug–drug interactions in patients taking multiple medications. Thus, understanding variability of drug metabolism and drug transport remains a priority.

CONFLICT OF INTEREST
Ann-Cathrine Dalgård Dunvald has given paid lectures for Astellas Pharma. Tore B. Stage has given paid lectures for Pfizer and Eisai and done consulting for Pfizer. Anton Pottegård has participated in research projects funded by Alcon, Almirall, Astellas, AstraZeneca, Boehringer-Ingelheim, Novo Nordisk, Servier and LEO Pharma, all regulator-mandated Phase IV studies. All of this is unrelated to the work done in this review. Ditte Bork Iversen and Nanna Elman Andersen declare that they have no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.