Use of Real-World Claims Data to Assess the Prevalence of Concomitant Medications to Inform Drug–Drug Interaction Risk in Target Patient Populations

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A common issue in clinical drug development involves drug–drug interactions (DDI) that may lead to altered drug exposure and subsequent altered safety and efficacy of an investigational drug or concomitant medications (conmeds) in the target patient population. The drug development pipeline therefore involves DDI risk assessment of the investigational drug based on in vitro studies, in silico modeling, and clinical trials. Real-world data (RWD), particularly claims databases with reliable information on pharmacy dispensing, provide an opportunity to understand conmeds usage in the target indication in a real-world setting as one approach to assess potential DDI risk. We describe two cases of characterizing DDI-related conmeds usage with a large closed US-based claims database, IQVIA PharMetrics® Plus, and identified potential DDI risk for multiple sclerosis and hormone receptor-positive breast cancer. For example, prevalent and chronic use of statins (atorvastatin and simvastatin), which are CYP3A4 substrates, were identified among both disease cases. Further examples, limitations, and future directions are also discussed. These insights can therefore help augment decision-making during clinical drug research and development.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Drug–drug interactions (DDIs) can significantly impact drug exposure, safety, and efficacy. Using real-world data (RWD) is of increasing interest for providing insights into concomitant medication usage and potential DDI risks in target patient populations to augment drug development efforts.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ This study aimed to assess the prevalence of concomitant medication use and the associated DDI risks in patients with multiple sclerosis (MS) and hormone receptor-positive breast cancer (HR+ BC) using the IQVIA PharMetrics® Plus claims database.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ The study identified commonly used medications that pose clinically relevant DDI risks, such as antifungals and statins, in MS and HR+ BC populations. It provides insights and interpretations into the real-world usage patterns of these medications.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ This study highlights the importance of considering real-world concomitant medication usage in DDI risk assessments during drug development. The findings can inform safer and more effective clinical trial designs, inclusion/exclusion criteria, and treatment regimens, ultimately enhancing patient care and drug safety.

Drug–drug interactions (DDIs), causing drug exposure, safety, and efficacy changes, pose a significant risk to patients and can have far-reaching implications on both individuals and society. The potential for adverse events and variations in drug efficacy resulting from concomitant use of multiple medications, and causing a DDI, have prompted regulatory bodies, such as the United States (US) Food and Drug Administration (FDA), to prioritize the evaluation of DDIs during the development of new molecular

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entities.[1] Various preclinical and clinical studies, as well as computational analyses, can be used to assess DDI liability, including in vitro screening studies (e.g., reaction phenotyping, inhibition, and induction studies), modeling and simulation approaches (e.g., mechanistic static models and physiologically-based pharmacokinetic (PBPK) models), and dedicated clinical DDI studies.[2,3] Nevertheless, *in vitro* screening and modeling may not predict all clinically relevant *in vivo* effects of DDIs, and while clinical trials are useful, there are challenges due to the need for financial resources and recruitment of appropriate patient populations. A thorough DDI risk assessment can thus guide drug research and development in multiple ways, including identifying the ideal candidate molecule, guiding the optimization of molecule structure and properties, and informing inclusion/exclusion criteria on the use of concomitant medications for the target patient populations in clinical trials. Therefore, a better understanding of the use of DDI-related concomitant medications in target patient populations could support more realistic and clinically relevant DDI risk assessments.

In the recent decade, real-world data (RWD) has played an increasing role in providing valuable insights to inform decision-making in healthcare and pharmaceutical research and drug development.[4–6] Common RWD sources include electronic health records (EHR), claims databases, registries, and patient-generated data. One benefit of RWD includes the potential inclusion of patients across age, race, ethnicity, and healthcare access based on insurance. Among these sources, claims data, extracted from insurance claims submitted by healthcare providers and pharmacies, stands out as a reliable source of information for studying prescription medication usage and its impact on patient outcomes. It encompasses a wide range of information, such as outpatient visits, inpatient visits, procedures performed, drugs dispensed, and other care services rendered. One of the key strengths of claims data, relative to other RWD sources such as EHR data, is its representation of medication information with high reliability and completeness; this is largely because claims data captures and includes information on prescribed drugs that have been dispensed and paid for (implying higher likelihood that the drugs are actually consumed rather than just prescribed).[6] More specifically, claims data includes details, such as the dosage, route of administration, days supply, and quantity dispensed. Duration of treatment, frequency of administration, and average daily dose, which are valuable information for evaluating the impact of potential DDI risk, can be estimated from populated fields. Thus, claims data provides a unique resource and opportunity to investigate the use of concomitant medications in the real-world setting.

In this study, we demonstrate how we utilized a US Claims database (IQVIA PharMetrics® Plus) to extract information on the use of prescribed concomitant medications in two example diseases with a risk of adverse events from polypharmacy both in non-oncology (multiple sclerosis, > 50% with polypharmacy[7]) and oncology (hormone receptor-positive (HR+) breast cancer, > 50% with potential DDI risk[8]). We focus on drugs that pose a clinically relevant DDI risk for cytochrome P450 enzyme subtype 3A4 (CYP3A4) and transporters (P-glycoprotein (P-gp), and breast cancer resistance protein (BCRP)). More specifically, we investigated the use of clinically relevant (as defined by the FDA) inhibitors/inducers/substrates of CYP3A4, inhibitors of P-gp, and inhibitors of BCRP in the two patient populations.[2,9] In addition to prevalence, we investigated and summarized administration details (i.e., daily dose, route of administration, treatment duration (acute or chronic)), patient demographics (i.e., age, sex, race/ethnicity), and use of disease-related treatments and proton pump inhibitors (PPIs). By leveraging the extensive data available on concomitant medication usage in real-world patient populations, we can gain comprehensive and realistic insights on potential DDI risks for investigational drugs in development and ultimately help inform and support drug development decision making.

METHODS

The IQVIA PharMetrics Plus claims database was used for all analyses presented, with the identification of cohorts based on diagnosis from 2017 to 2022, and then medication prevalence was evaluated within the year 2022. This database contains fully adjudicated medical and pharmacy claims from de-identified patients in all 50 US states and the District of Columbia.[10] Data contributors to the database are primarily commercial health plans with some Medicare Advantage, Medicare Supplemental, and Medicaid plans. The database contains information on patient demographics (e.g., birth year, sex, 3-digit zip code, state of residence), health plan enrollment, and inpatient, outpatient, and pharmacy claims.

To focus on characterizing the usage of concomitant medications that may pose a clinically relevant DDI risk, we utilized the FDA guidance on drug–drug interactions to curate a list of substrates, inhibitors, and inducers,[9] with the full list available in **Supplement S1**. This list includes 49 CYP3A4 substrates, 40 CYP3A4 inhibitors, 25 CYP3A4 inducers, 17 P-gp inhibitors, 11 BCRP inhibitors, and 6 PPIs. The list was utilized to query the claims database to extract prevalence and administration details for conmeds as CYP3A4 substrates/inhibitors/inducers, as well as P-gp and BCRP inhibitors, patient demographics, and use of disease-related treatments and PPIs in the two example indications: multiple sclerosis and HR+ breast cancer. Details about DDI severity are defined on the FDA guidance and copied in **Supplement S1**. For example, substrates that have increase in drug plasma area under the curve (AUC) of ≥ 5-fold with strong inhibitors of a pathway are categorized as "sensitive substrate," and increase of AUC ≥ 2 to < 5-fold categorized as "moderate sensitive substrate."

Multiple sclerosis cohort selection

Identifying a population of interest is critical when performing RWD analyses. We extracted patients diagnosed with multiple sclerosis (MS) by first identifying the relevant ICD10 code (International Classification of Diseases) G35, used between 2017 and 2022 (ICD9 code 340 is no longer utilized after 2015). Although we tried to stratify by disease subtypes, distinguishing between remitting–relapsing MS and primary progressive MS was not achievable with the available ICD10 codes. However, we were able to use a previously published, validated algorithm from Culpepper *et al*.,[11] which utilized both ICD diagnoses and the use of disease-modifying treatments (DMTs) for improved accuracy and specificity, to extract the specific MS cohort. We utilized algorithm E from Culpepper *et al*. to identify a large sample of patients; more specifically, the criteria implemented were as follows: ≥ 3 either inpatient or outpatient diagnoses of MS or usage of a relevant DMT (**Supplement S2A**), within a single year, where the year spans within 2017–2022. Next, to account for data missingness, we only included patients who had insurance coverage for the entire year of 2022 (to capture a year's worth of medication usage); this allowed us to characterize the use as well as lack of use of relevant DDI-related

medications within a calendar year. In addition, pre-specific covariates include sex (female, male) and age categories (≤ 18, 18–55, 56–65, > 65).

HR+ breast cancer cohort selection

To extract a hormone receptor-positive (HR+) breast cancer (BC) cohort, we first identified patients with at least two outpatient diagnoses of breast cancer or both an inpatient and outpatient diagnosis with at least a 14-day gap between 2017 and 2022. Breast cancer codes include ICD9 code 174 and 175, ICD10 code C50, and all subsequent children codes that belong within these ICD code categories. Next, we filtered to only include female patients and identified concurrent procedure or diagnosis codes related to HR+ status between 2017 and 2022 (ICD10 Z17.0; ICD9 V86.0; CPT 3315F; and HCPCS G9071, G9073, G8380, G8381). As for the MS indication, we only included patients with insurance coverage for the whole year of 2022 to minimize bias from data missingness and to characterize the use and lack of use of relevant medications within a calendar year. Prespecified covariates included age (≤ 18, 18–50, 51–65, > 65), exposure to breast cancer treatment in 2017–2022 (**Supplement S2B**), and/or concurrent metastatic diagnosis in 2017–2022 (**Supplement S2D**).

Extracting drugs of interest

We identified clinically relevant drugs of interest based on the FDA guidance for drug–drug interactions, including a list of substrates, inhibitors, and inducers for CYP3A4, and inhibitors for P-gp and BCRP.[9] We also identified PPIs based on the RxNorm Proton Pump Inhibitor class (mor.nlm.nih.gov/RxClass/search?query=Proton%20pump%20inhibitors%7CMOA). All drugs, including PPIs, were string-matched to the claims reference database, and the final matched drug codes per drug string can be found in **Supplement S1**. For all mapped drugs, codes for both prescriptions and procedures (within the year 2022) were extracted for the identified cohorts of patients (as described above) and aggregated based on the original drug name queried. Drug prevalence was then quantified based on percentage among the whole cohort and within pre-defined subpopulations (e.g., age groups).

Details for drug usage

Specific details for drug use were extracted from the claims data and summarized: (1) Daily dose (described in mg and calculated as *(strength*quantity)/days supply*; for example, a dispensing for 60 atorvastatin tablets at 20 mg each for 30 days would have a daily dose of [20*60]/30 mg/day): (2) Number of 30-day equivalent fills (a 30 day fill was defined as the days supply divided by 30 if the days supply was > 34 or set to 1 if the days_supply was less than or equal to 34; for example, fill with 60 days supply is two 30-day equivalents[12]); (3) Number of fills (for example, a drug that is utilized daily for 6 months may be dispensed for 30 days at a time with 6 refills); (4) Frequency (for oral routes, number of doses per day, defined as quantity/days supply; for example, a fill for 30 tablets with 30 days supply would be 1 tablet per day); (5) Route of administration (i.e., oral, rectal, subcutaneous, inhaled, injectable, intramuscular, or intravenous); (6) Acute vs. chronic use (acute use was defined as duration of treatment ≤ 90 days, and chronic use was defined as duration of treatment is > 90 days; duration of treatment included all non-overlapping days of prescription coverage that occurred during the study period (only includes fills that occurred in the study period and truncate days supply at the end of the study period)) A grace period of 10 days was used to bridge any gaps between prescriptions; (7) Intermittent use (defined as two or more gaps of 30+ days between when one fill runs out

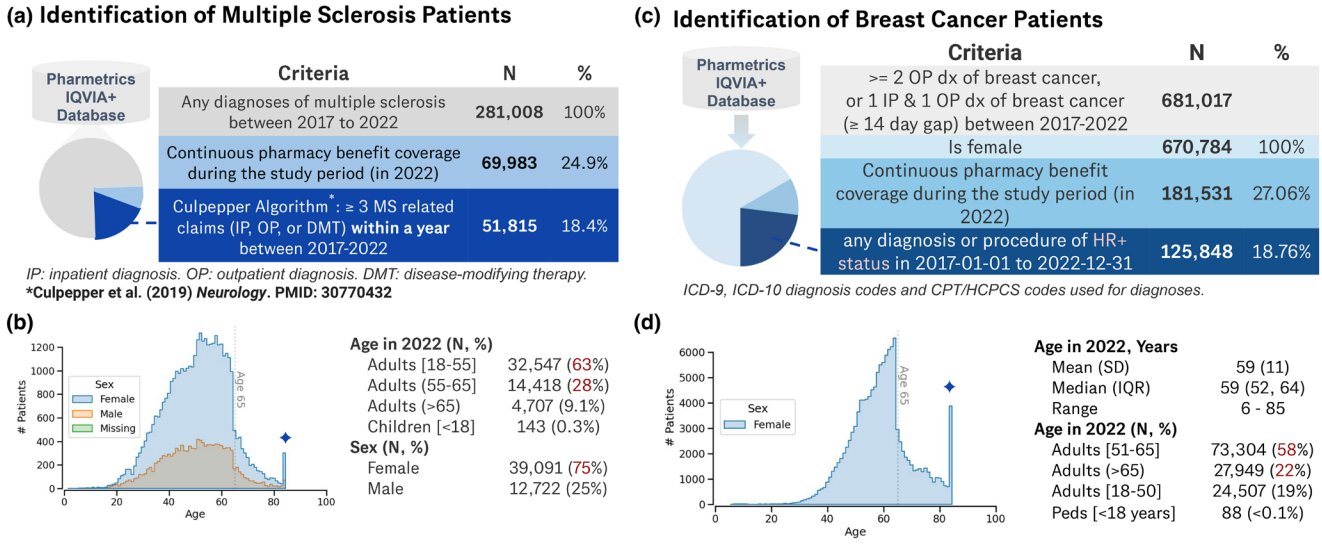


Figure 1 Selection of multiple sclerosis and hormone receptor-positive breast cancer cohorts. (**a**) Multiple sclerosis attrition table based upon algorithm from Culpepper *et al*. (**b**) Age and sex distribution for final MS cohort. Age distribution is also further stratified by sex recorded in the database. Note that patients over 85 in 2022 are represented as being 85 for de-identification purposes. (**c**) Hormone receptor-positive breast cancer (includes both estrogen receptor-positive and/or progesterone receptor-positive cancer) cohort attrition table. (**d**) Age distribution for final HR+ breast cancer cohort. Note that patients over 85 in 2022 are represented as being 85 for de-identification purposes. Patients of age 85+ in 2022 have their date of birth shifted so they are represented as being 80 years old.

Figure 2 Use of MS-specific DMTs, PPIs, CYP3A4 inhibitors, inducers, and substrates, and P-gp/BCRP inhibitors in MS patients. (**a**) Use of disease-modifying treatments among the MS population within the year 2022. (**b**) Use of any proton pump inhibitor among the MS population within the year 2022. (**c**) CYP3A4 inhibitors and inducers use among the MS population, as well as within age and sex strata. Further details on dosing, route, duration, and indication diagnoses (from DrugBank) are shown. (**d**) CYP3A4 substrates use among the MS population. (**e**) P-gp inhibitors use among the MS population. (**f**) BCRP inhibitors use among the MS population.

(a) Disease Modifying Treatment[+] (2022) — 28,255 (55%)

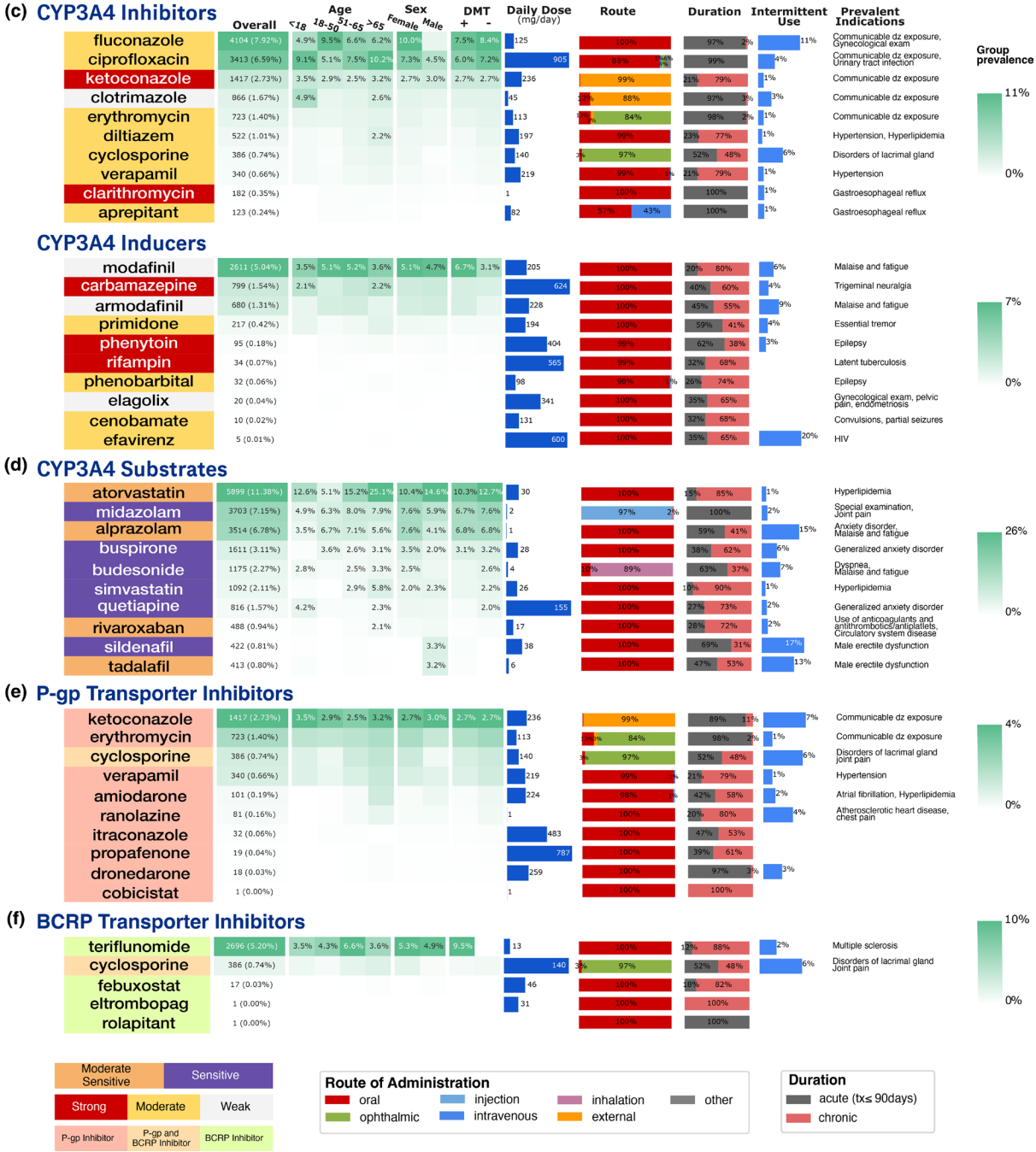
Ocrelizumab	7,920 (15%)
Glatiramer Acetate	3,970 (7.7%)
Dimethyl Fumarate	3,244 (6.3%)
Teriflunomide	2,696 (5.2%)
Natalizumab	2,484 (4.8%)
Fingolimod	2,354 (4.5%)
Interferon Beta-1a	2,155 (4.2%)
Ofatumumab	1,848 (3.6%)
Diroximel Fumarate	1,343 (2.6%)
Cladribine	478 (0.9%)
Ozanimod	445 (0.9%)
Siponimod Fumarate	356 (0.7%)
Interferon Beta-1b	320 (0.6%)
Peginterferon Beta-1a	296 (0.6%)

(b) Any PPI Treatments[+] (2022) — 8,175 (16%)

Omeprazole	3,980 (7.7%)
Pantoprazole Sodium	3,810 (7.4%)
Esomeprazole Magnesium	366 (0.7%)
Lansoprazole	239 (0.5%)
Pantoprazole Sodium, Per Vial	198 (0.4%)
Dexlansoprazole	189 (0.4%)

List from RxNav.gov

[+] *Both prescription claims and clinic/hospital procedures are utilized for defining treatments.*



and the next fill begins during a study period); (8) Comorbid diagnosis during the study period (for the most frequently used drugs, top diagnoses, aggregated to three characters from the ICD codes, were identified for patients prescribed drugs with DDI risk; diagnoses that overlap with labeled indication from DrugBank were highlighted).

RESULTS

Top medication usage among multiple sclerosis cohort

From the 281,008 patients with an MS diagnosis between 2017 and 2022, we identified 51,815 patients who had continuous insurance coverage in 2022 and satisfied Algorithm E described in Culpepper *et al.*[11] (attrition table in **Figure 1a**). Among this cohort, 75% of patients were female and 91% of patients were between the ages of 18–65 years old, with a median age of 51 years old (**Figure 1b**). Within the year 2022, 55% of patients in the cohort were exposed to a DMT (DMT), and ~16% had at least one claim for a prescribed PPI (**Figure 2a,b**).Top CYP3A4 inhibitors used in the overall MS population include fluconazole (7.9% prevalence, moderate inhibitor), ciprofloxacin (6.5%, moderate inhibitor), and ketoconazole (2.7%, strong inhibitor) (**Supplement S3**). Among age and sex strata, fluconazole was most utilized among the 18–55 years old age group and females, while ciprofloxacin was most utilized among patients < 18 or > 65 years old. With regard to drug utilization, fluconazole and ciprofloxacin were primarily administered orally and used acutely. For fluconazole, the mean average daily dose was 125 mg/day, and the top prevalent indication includes fungal infections. For ciprofloxacin, the average daily dose was 905 mg/day and the top indicated diagnosis includes urinary tract infection (**Figure 2c**). Ketoconazole was found to be administered primarily externally, utilized acutely, and prescribed with an average daily dose of 236 mg/day and a prevalent indication of skin infections.

Top CYP3A4 inducers in the overall MS cohort included modafinil (5% prevalence, weak inducer), followed by carbamazepine (1.5%, strong inducer). Within strata, most users prescribed modafinil were in the18–65-year-old age range. Regarding usage, modafinil was taken primarily orally with an average daily dose of 228 mg/day. More than 50% were chronic users, with the main relevant diagnoses of fatigue and sleepiness. For carbamazepine, despite a low overall prevalence, more than 50% of patients were chronic users, with relevant diagnoses of trigeminal neuralgia (**Figure 2c**).

Top CYP3A4 substrates in the overall MS cohort (**Figure 2d**) include moderately sensitive substrates atorvastatin (11.4% prevalence) and alprazolam (6.8%), as well as sensitive substrates buspirone (3%), budesonide (2.3%), simvastatin (2.1%), midazolam (1.9%), and quetiapine (1.6%). Within strata, atorvastatin and simvastatin had the highest use among the elderly (> 65 years), with atorvastatin also having over 12% usage among the pediatric (< 18 years) and 56–65 age groups. Regarding utilization, atorvastatin and simvastatin have a median dose of 20 mg daily via oral administration, have 85% and 90% chronic users respectively, and both have a prevalent indication diagnosis of hyperlipidemia. Alprazolam, buspirone, and quetiapine were used mostly chronically for anxiety and depression. Budesonide was used via inhalation for asthma, mostly acutely. Midazolam is administered via injection, acutely, and mainly for procedures.

With regards to transporters in the overall MS cohort, the top P-gp inhibitors include ketoconazole (2.7% prevalence) and erythromycin (1.4%) (**Figure 2e**). Ketoconazole was primarily administered externally, while erythromycin was administered ophthalmologically. The most prevalent BCRP inhibitor is teriflunomide (5.2%) followed by cyclosporine (0.7%). Teriflunomide also had high chronic usage (88%) (**Figure 2f**).

Top drug usage among HR+ breast cancer cohort

Within the database, 681,017 patients were identified who had at least two breast cancer diagnoses between 2017 and 2022 (see Methods). Of these, 670,784 patients were labeled female, and 125,848 patients had continuous insurance coverage in 2022 and had a diagnosis or procedure indicating hormone receptor-positive (HR+) BC (**Figure 1c**). Among this cohort, 80% of patients are over the age of 50 years with a median age of 59 years (**Figure 1d**). Within 2022, 68% of patients were exposed to at least one BC treatment, and ~17% were exposed to at least one PPI (**Figure 3a,b**).

The top prevalent CYP3A4 inhibitors in the overall HR+ BC cohort include fluconazole (7% prevalence), ciprofloxacin (6.9%), fosaprepitant (2.8%, weak inhibitor), and aprepitant (2.2%, moderate inhibitor) (**Supplement S3**). Among subgroups, fosaprepitant and aprepitant have greater prevalence in the younger age groups, those exposed to prior BC treatments, and those with diagnostic codes indicating metastatic disease. Regarding usage, both fluconazole (average dose: 122 mg/day) and ciprofloxacin (average dose: 922 mg/day) are moderate inhibitors that are mainly taken orally and acutely (**Figure 3c**). Top relevant diagnoses included infection, particularly of the vagina and urinary tracts. Fosaprepitant and aprepitant are mostly taken intravenously with relevant indications as a chemotherapy antiemetics (**Figure 3c**).

CYP3A4 inducers all had a very low prevalence in the overall HR+ BC population (< 0.3%). Modafinil was the top CYP3A4 inducer (0.27%, weak inducer), with other prevalent inducers of strong inducers carbamazepine and rifampin and moderate inducer primidone. Modafinil showed enrichment in the subgroup with metastatic disease and had top relevant diagnoses of fatigue and anxiety (**Figure 3c**).

Prevalence of CYP3A4 substrates in the overall HR+ BC cohort was generally high (up to 20%); top substrates included midazolam (19.1%), atorvastatin (14.1%), alprazolam (7%), aprepitant

Figure 3 Use of BC-specific DMTs, PPIs, CYP3A4 inhibitors, inducers, and substrates, and P-gp/BCRP inhibitors in HR+ BC patients. (**a**) Exposure to any breast cancer-related treatment within the year 2022 among the HR+ breast cancer cohort. (**b**) Use of any proton pump inhibitor among the HR+ BC population within the year 2022. (**c**) CYP3A4 inhibitors and inducers use among the HR+ BC population, as well as within age and sex strata. Further details on dosing, route, duration, and indication diagnoses (from DrugBank) are shown. (**d**) CYP3A4 substrates use among the HR+ BC population. (**e**) P-gp inhibitors use among the HR+ BC population. (**f**) BCRP inhibitors use among the HR+ BC population.

(a) Any Breast Cancer Related Treatment[+] (2022) — 85,204 (68%)

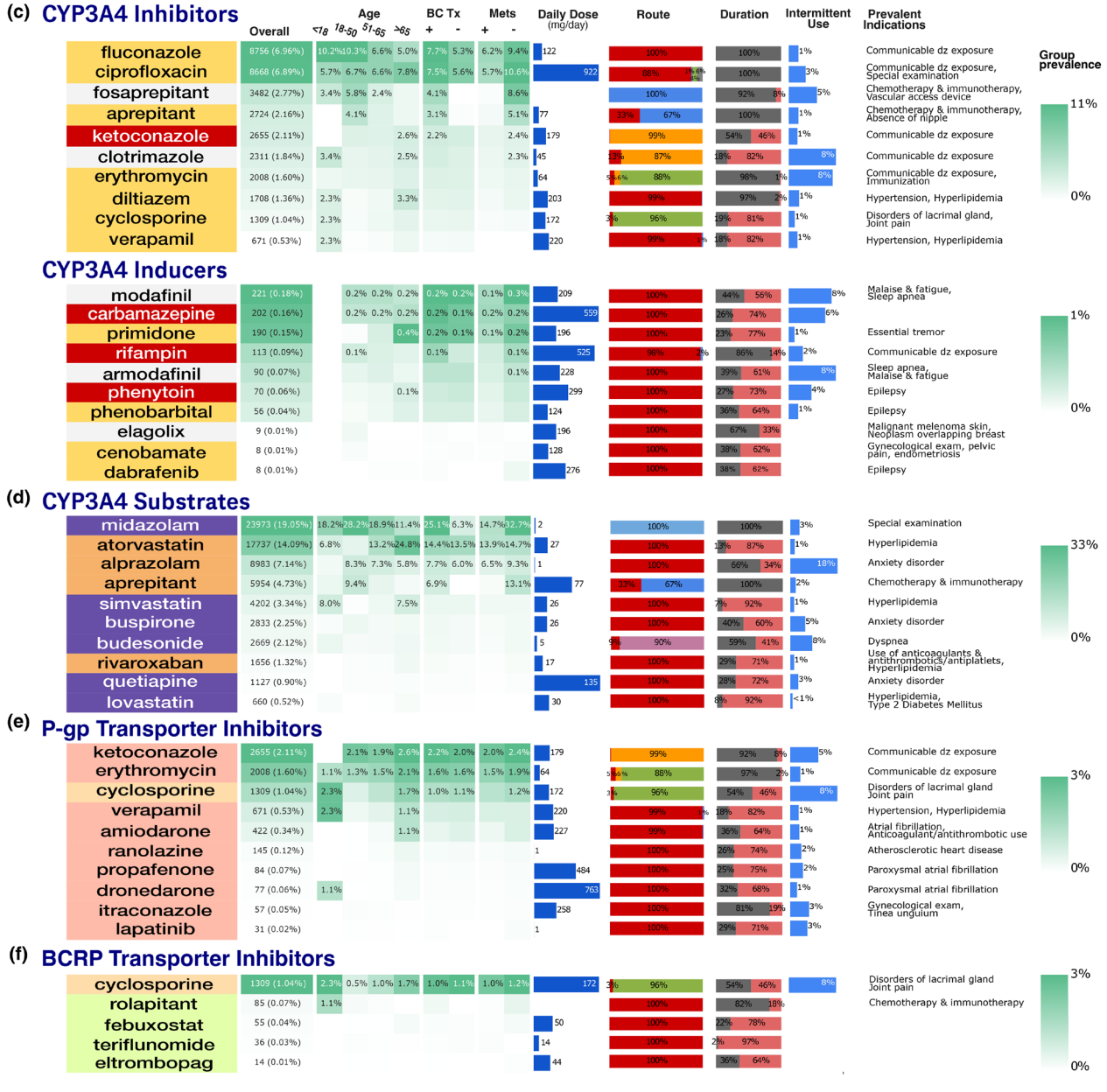
Anastrozole	30,075 (24%)	Abemaciclib	1,981 (1.6%)
Mastectomy	27,203 (22%)	Capecitabine	1,234 (1.0%)
Tamoxifen	21,203 (17%)	Methotrexate	1,070 (0.9%)
Letrozole	17,846 (14%)	Ado-Trastuzumab Emtansine	960 (0.8%)
Lumpectomy	10,966 (8.7%)	Fluorouracil	950 (0.8%)
Exemestane	6,613 (5.3%)	Pembrolizumab	879 (0.7%)
Trastuzumab	4,736 (3.8%)	Raloxifene	535 (0.4%)
Cyclophosphamide	4,075 (3.2%)	Ribociclib	514 (0.4%)
Paclitaxel	3,946 (3.1%)	Bevacizumab	437 (0.3%)
Docetaxel	3,144 (2.5%)	Gemcitabine	322 (0.3%)
Pertuzumab	2,686 (2.1%)	Olaparib	278 (0.2%)
Doxorubicin	2,617 (2.1%)	Everolimus	246 (0.2%)
Carboplatin	2,380 (1.9%)	Alpelisib	226 (0.2%)
Palbociclib	2,077 (1.7%)	Sacituzumab Govitecan-Hziy	226 (0.2%)
Fulvestrant	2,018 (1.6%)	Neratinib	215 (0.2%)

(b) Any Proton Pump Inhibitors[+] (2022) — 21,421 (17%)

Omeprazole	10,910 (8.7%)
Pantoprazole Sodium	9,531 (7.6%)
Esomeprazole Magnesium	949 (0.8%)
Lansoprazole	520 (0.4%)
Pantoprazole Sodium Vial	470 (0.4%)
Dexlansoprazole	361 (0.3%)
Rabeprazole Sodium	172 (0.1%)
Omeprazole Bicarbonate	16 (<0.1%)
Omeprazole Magnesium	12 (<0.1%)
Amoxicillin W/ Lansoprazole	5 (<0.1%)

[+] *Both prescription claims and clinic/hospital procedures are utilized for defining treatments.*

Red Text: Procedure



(4.7%), simvastatin (3.3%), buspirone (2.3%), budesonide (2.1%), rivaroxaban (1.35%), quetiapine (0.9%), and lovastatin (0.52%). Among subpopulations, midazolam had greater use among the younger and metastatic populations, and the statins (atorvastatin and simvastatin) had greater use among the elderly. Midazolam was primarily administered via injection and used acutely for procedures. Atorvastatin and simvastatin had comorbid indication diagnoses of hyperlipidemia. Alprazolam, buspirone, and quetiapine were utilized chronically, with top diseases related to neurologic and psychiatric diagnoses (**Figure 3d**).

The top P-gp inhibitors in the HR+ BC cohort included ketoconazole (2.1% prevalence in the cohort), erythromycin (1.6%), and cyclosporine (1%) (**Figure 3e**). The remaining P-gp inhibitors (verapamil, amiodarone, ranolazine, propafenone, and dronedarone) have an overall low prevalence, but some enrichment among the elderly subgroup. For the drug route of administration, ketoconazole was primarily administered externally, while erythromycin and cyclosporine were administered ophthalmologically. P-gp inhibitors tend to be utilized chronically and have cardiovascular-related disease indications such as atrial fibrillation, hypertension, and atherosclerosis (**Figure 3e**). For BCRP inhibitors, cyclosporine was the most prevalent in the HR+ BC cohort (1%), followed by rolapitant (0.07%), an antiemetic for chemotherapy (**Figure 3f**).

DISCUSSION

To illustrate the use of RWD to inform DDI risk, we demonstrate how claims databases can be leveraged to characterize DDI-related concomitant medication prevalence and usage details for two example indications: multiple sclerosis and HR+ breast cancer. By mining comprehensive claims data, specifically PharMetrics Plus, we identified example disease-specific cohorts to characterize prevalent medications and usage patterns. This not only sheds light on the current landscape of medication patterns in real-world settings, but it can also inform potential DDI risk that can affect decisions regarding candidate drug selection, patient safety, or determining conmeds inclusion/exclusion criteria for clinical trials.

For the MS population use case, we found that the top CYP3A4 inhibitors which may pose a relevant DDI risk include moderate inhibitors fluconazole and ciprofloxacin, both with greater prevalence among the female subpopulation. However, these medications were mainly used acutely, so a systemic DDI risk may only be temporarily relevant if an MS patient has a fungal infection (a key indication). One question that may arise from this for future studies is why we see oral antifungal medications use prevalent among MS patients.[13] One possibility is that previously prescribed immunosuppressive MS drugs may cause patients to be at higher risk of fungal infection. If so, concomitant use of antifungals may also decrease with the development of more immune-selective MS therapies.[14–16] Understanding the use of antifungals in this patient population is informative for both pharmaceutical developers and healthcare providers to be vigilant about potential DDI risk when treating infections in the MS patient population.[15,17] While ketoconazole is a strong inhibitor and a top drug in MS patients, the route of administration was predominantly external, suggesting to researchers and clinicians that there may be less of a systemic DDI risk. Top inducers among the MS population include modafinil and carbamazepine, primarily prescribed for indicated diagnosis of fatigue and trigeminal neuralgia. While the general prevalence is low for both of these drugs, concomitant use with an investigational drug can be a DDI concern in MS patients with comorbid neurologic conditions who may be using modafinil or carbamazepine.[18,19]

Moreover, the use of top CYP3A4 substrates was most prevalent among the elderly MS population. Statins are utilized for the treatment of hyperlipidemia, including atorvastatin (moderately sensitive substrate) and simvastatin (sensitive substrate). This is relevant to consider when developing drugs for elderly populations who often have a greater burden of chronic comorbidities and complex disease outcomes. Other medications to note include the concomitant prescription of CYP3A4 substrates buspirone and quetiapine, due to the likelihood of comorbid psychiatric conditions such as depression and anxiety among MS.[20] Next, while the use of sensitive substrate midazolam is prevalent as well, its acute use, likely for procedures, suggests the DDI risk may be low or only be relevant in the acute setting.[21] With regard to transporter inhibitors, the top noteworthy concomitant medications include antibiotics and antifungals: ketoconazole and erythromycin as prevalent P-gp inhibitors, and cyclosporine as a BCRP inhibitor. This makes it prudent to consider MS patient susceptibility to infection that may lead to antifungals/antibiotics as conmeds, which can result in altered exposure and, in turn, safety and/or efficacy of any investigational drugs whose delivery depends on the transporters.[14–16]

For the HR+ BC cohort, despite underrepresentation of patients over 65 compared with the general US population, the 22% over age 65 can still provide insights around comorbidities and DDI risk.[22–24] The top CYP3A4 inhibitors in the HR+ BC cohort include antifungals and antibiotics, with greater prevalence among the metastatic population, perhaps suggesting increased infection risk or immunocompromised status, such as from disease progression or cancer treatment[25,26]; however, usage of antifungals and antibiotics is mostly given short-term with an acute risk of DDI. Chronically utilized CYP3A4 inhibitors include medications for comorbid cardiovascular indications such as diltiazem and verapamil, with greater use among the elderly. This is of relevance since cardiovascular multimorbidity and age are associated with differing treatment approaches.[27,28] Additionally, we see that chemotherapy antiemetics may pose an acute DDI risk within the BC treatment pathway. While the overall prevalence of CYP3A4 inducers is low, notable medications include those for concurrent seizures and psychiatric conditions. CYP3A4 substrates have high prevalence, with the top 10 medications being prescribed to 0.5%–20% of the population. These include medications for acute procedures (midazolam), chronic hyperlipidemia (atorvastatin, simvastatin), and anxiety (alprazolam, buspirone). Relevant P-gp inhibitors have great overlap with both CYP3A4 inhibitors and substrates, particularly verapamil, amiodarone, and ranolazine, with greater usage in elderly patients and patients with metastasis. This complex DDI risk may explain prior studies that identified large differences in treatment approaches and outcomes based on

age.[22,28] For BC, antiemetic use (specifically rolapitant and aprepitant) may provide DDI risk for patients who may be exposed to chemotherapy, with greater use among the young and those with advanced disease.[29–31] This suggests that DDI risk should be considered when cancer treatment-related medications (such as antiemetics) are given concomitantly with chemotherapy, in BC as well as other tumor types.

In both MS and HR+ BC, chronic issues provide the biggest risk given the high prevalence of CYP3A4-sensitive substrates and diagnosis of comorbid conditions such as cardiovascular and neuropsychiatric diseases. Of note, since MS impacts the nervous system itself, the chance of a patient with a concomitant neuropsychiatric diagnosis can be high.[32,33] Although both indications showed a DDI risk with midazolam (CYP3A4 substrate) and antifungals or antibiotics (CYP3A4 inhibitor), the risk was relatively minimal as these drugs seem to have use in acute settings or through routes of delivery that allow for minimal absorption into the systemic circulation. Furthermore, while the use of CYP3A4 inducers is low overall, modafinil was the most prevalent inducer, primarily for fatigue and anxiety.[34–38] Similarly, the use of P-gp and BCRP inhibitors is low overall; however, the most prevalent drugs overlap as CYP3A4 inhibitors. Lastly, for both indications, more than 15% of patients are shown to be prescribed a PPI; however, the use of PPIs may be higher since over-the-counter (OTC) use of PPIs is not captured in claims data. Knowing this lower limit of PPI use can be helpful to account for during the conduct of trials when considering possible impact on bioavailability and dosing.

While there are a lot of valuable insights to be gleaned from this analysis, it is important to consider the limitations of claims data. First, claims data may not include OTC and non-insured medications, such as PPIs, contraceptive medications, and drugs obtained from other sources (e.g., family and friends) or stockpiling of previous dispensings. Second, claims data are limited to patients with insurance coverage, and the patient population may have biases depending on whether insurance is derived from government insurance programs or private insurance providers. Geographical limitations may also exist, as claims data is specific to the regions covered by the insurance plans included in the database. Furthermore, claims data does not include socioeconomic information (e.g. area deprivation index, education). Third, the analyses above are focused on clinically relevant DDI risk, which does not include drugs with in vitro DDI risk or newer molecules with evolving clinically relevant DDI risk. For example, MS patients with comorbid autoimmune conditions may take tofacitinib, a recent immunosuppressive medication that can inactivate CYP3A4.[39] Lastly, since we utilized a commercially available claims database from the US, patients over 65 are less represented (since patients over 65 often transition to Medicare). Nevertheless, the patients over the age of 65 can help provide initial insights, and the same methods can be applied to Medicare databases in the future to better evaluate generalizability. Given the large number of patients captured by the claims database and the efficiency of data analysis compared with clinical trial recruitment, future analysis can focus on studies in lower prevalence subpopulations such as pediatric populations or male breast cancer patients. While this work focused on interactions at CYP3A4, P-gp, and BCRP, the pipeline can be extended to provide insights into interactions at other CYP enzymes or drug transporters. Future directions include expanding to investigate additional CYPs and transporters beyond what is presented here. Despite limitations, pharmaceutical claims data provide researchers with quality and extensive information about prescription medication usage, enabling them to study real-world medication patterns, assess treatment outcomes, and inform evidence-based decision making in pharmaceutical research.[6]

As demonstrated by this analysis, there is great potential unlocked through the integration of RWD in the drug development process and myriad opportunities for further extension of this work. For example, for an investigational small molecule developed for MS shown in vitro to be a sensitive CYP3A4 substrate, fluconazole and clarithromycin (moderately strong and strong CYP3A4 inhibitor) can be chosen as index drugs in PBPK modeling and/or a clinical DDI study. These results can then be utilized to inform drug development. For an investigational small molecule developed for MS that is shown in vitro to be a sensitive CYP3A4 substrate, fluconazole (the most prevalent moderately strong CYP3A4 inhibitor, **Figure 2c**) and clarithromycin (strong CYP3A4 inhibitor with oral usage, **Figure 2c**) can be chosen as index drugs in PBPK modeling and/or a clinical DDI study to further evaluate DDI risk.

For another small molecule developed for HR+ BC which is shown in preclinical studies to be a P-gp substrate, understanding the use of verapamil (prevalent oral P-gp inhibitor) and its impact on the investigational drug exposure can be informative for clinical trial design and inclusion/exclusion criteria. Therefore, understanding drug usage patterns in a real-world setting can help augment decision making during drug research and development, including candidate drug selection, *in vitro* study design, and clinical trial design. The pipeline itself can also be further extended to many other diseases, including both oncology and non-oncology indications. As new medications are approved, claims databases can be utilized to perform DDI safety assessments and cost evaluations while also serving as a reference for clinicians when making decisions about drug prescriptions and dosing adjustments.[40,41]

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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AUTHOR CONTRIBUTIONS

A.S.T., B.V., and R.Z. wrote the manuscript; B.V. and R.Z. designed the research; A.S.T., B.V., L.B., D.M.B., P.C., and R.Z. performed the research and analyzed the data; D.B., P.C., A.J., and A.S.T. contributed new reagents/analytical tools.

CONFLICT OF INTEREST

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