ISPOR Europe 2025, Glasgow

Real-World Evidence in Action: Assessing Drug-Drug Interactions to Drive Value-Based Decisions

RWD153

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Background and Objective

- Drug-drug interactions (DDIs) can lead to adverse drug events, reduced efficacy and increased healthcare costs.
- However, because most evidence for DDIs is derived from early-phase studies and case reports, their complexity and prevalence in diverse, real-world populations are often not well characterized.
- Real-world evidence (RWE) can better quantify the true impact of DDIs, offering actionable insights for clinicians and decision-makers.
- This study explores how RWE can support value-based decision making to enhance patient safety and resource optimization.

Methods

- We conducted a targeted review of case studies where real-world data (RWD) have been leveraged to assess DDIs for value-based healthcare.
- Methodological approaches for selected real-world use cases were critically analyzed, focusing on how RWE is integrated into decision-making frameworks. Each case was evaluated for its impact on clinical and economic outcomes, including clinical practice, payer and reimbursement strategies, as well as policy implications.

Case study: Quantifying the potential impact of DDIs in diverse patient groups to inform healthcare pricing and value-based delivery (Dagenais *et al.,* 2024)

DDI challenge
- Drugs can be subject to pharmacokinetic DDIs, especially among subpopulations with high comorbidity and polypharmacy.
- Traditional DDI risk assessment is often limited to clinical studies and mechanistic models, which may not fully represent the complexity of real-world prescribing or patient heterogeneity.
- Quantifying the real-world impact of DDIs is key to anticipate safety risks, optimize clinical use, and justify value-based approaches.

Solution
- Retrospective observational analysis based on a large US healthcare database.
- Mapping of the medications from pharmacy claims to the Certara Drug Interaction Database (DIDB).
- Development of a quantitative framework leveraging RWD on drug usage and patient characteristics.
- Simulation of DDI risk across diverse subpopulations to identify those exposed to high-risk drug combinations and predict potential clinical outcomes.

Impact on value-based decisions
- Enables manufacturers and payers to align drug pricing and reimbursement with actual safety profiles and clinical risks observed in routine care.
- Supports value-based pricing and risk-sharing models tied to measured safety outcomes in real populations by providing robust and actionable DDI risk quantification.

Type of victim substrate	Type 2 diabetes (%)	Points	Obesity (%)	Points	Migraine (%)	Points	Control group	Points
CYP3A moderate sensitive substrates	54.4%	10	47.2%	8	56.1%	10	33.8%	6
CYP3A sensitive substrates	49.9%	10	30.0%	10	30.3%	10	19.6%	6
CYP3A substrates with NTI	2.0%	4	1.4%	2	1.2%	2	0.9%	0
CYP3A substrates with QT prolongation	10.5%	10	9.8%	10	14.9%	10	7.1%	10
Subtotal - CYP3A pathway	71.3%	34	57.1%	30	64.1%	32	41.4%	22
CYP2D6 moderate sensitive substrates	26.9%	4	21.0%	4	31.1%	6	13.9%	2
CYP2D6 sensitive substrates	26.3%	10	19.9%	6	22.6%	8	12.7%	4
CYP2D6 Substrates with NTI	0.1%	0	0.0%	0	0.1%	0	0.0%	0
CYP2D6 Substrates with QT prolongation	8.0%	10	8.6%	10	15.5%	10	5.9%	10
Subtotal - CYP2D6 pathway	44.3%	24	34.6%	20	44.0%	24	23.1%	16
CYP2C9 moderate sensitive substrates	26.1%	4	13.9%	2	7.5%	0	7.7%	0
CYP2C9 sensitive substrates	27.1%	10	21.7%	8	24.3%	8	14.5%	4
CYP2C9 substrates with NTI	3.3%	6	1.7%	2	0.9%	0	1.0%	0
CYP2C9 substrates with QT prolongation	0.0%	0	0.0%	0	0.0%	0	0.0%	0
Subtotal - CYP2C9 pathway	44.3%	20	31.0%	12	28.9%	8	19.9%	4

Abbreviations: DDI, drug-drug interaction; NTI, narrow therapeutic index.

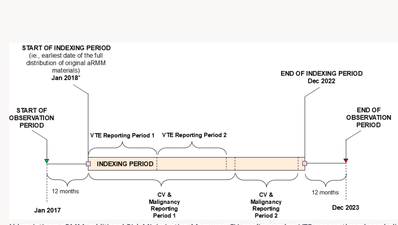
Fig. 1. Prevalence and predicted DDI impact scores for use of different types of victim substrates in study populations. Adapted from Dagenais *et al.,* 2024.

Case study: Monitor prescribing practices and identify co-medications that could increase risks in a post-authorisation safety study (EUPAS1000000247)

DDI challenge
- Tofacitinib (Xeljanz®) has clinically significant DDIs.
- These interactions pose challenges for patient safety and treatment management in real-world settings due to risks like infections and toxicity.
- Monitoring of prescribing practices and identification of co-medications that could increase risks is needed to support dose adjustments and clinical recommendations tailored to patient profiles in routine care.

Solution
- Retrospective observational study based on the French administrative healthcare database SNDS.
- Evaluation of real-world prescribing patterns of tofacitinib.
- Identification of potential DDI exposures.

Impact on value-based decisions
- Provides insights on the adherence to clinical recommendations regarding tofacitinib prescribing and co-medication management in real-world settings.
- Supports manufacturers and regulators in optimizing risk management and refining product information to encourage safer use.



Abbreviations: aRMM, additional Risk Minimization Measures; CV, cardiovascular; VTE, venous thromboembolism

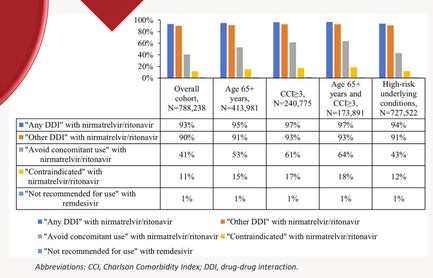
Fig. 3. Study design

Case study: Characterize the prevalence of potential DDIs in targeted patient subgroups to guide prescriber decision-making (Mozaffari *et al.,* 2024)

DDI challenge
- Hospitalized COVID-19 patients, especially older adults and those with multiple comorbidities, often receive multiple medications for underlying conditions.
- This polypharmacy increases the risk of DDIs with direct-acting antivirals (DAAs) used to treat COVID-19.
- RWE on the potential for DDIs between SARS-CoV-2 DAAs and other medications during hospitalization was needed, particularly for vulnerable subpopulations.

Solution
- Retrospective observational study based on a US hospital-based administrative database.
- Included 788,238 hospitalized COVID-19 patients from 920 hospitals.
- Medications were classified according to interaction potential with DAAs, specifically nirmatrelvir/ritonavir and remdesivir.
- Multivariable models identified patient and hospital factors associated with higher DDI risk.

Impact on value-based decisions
- Provides clinicians and healthcare providers with insights on the prevalence and types of DDIs in vulnerable populations.
- Supports safer prescribing practices and tailored selection of COVID-19 antiviral therapies.



	Overall cohort, N=788,238	Age 65+ years, N=413,981	CCI≥3, N=240,775	Age 65+ years and CCI≥3, N=173,891	High-risk underlying conditions, N=727,522
"Any DDI" with nirmatrelvir/ritonavir	93%	95%	97%	97%	94%
"Other DDI" with nirmatrelvir/ritonavir	90%	91%	93%	93%	91%
"Avoid concomitant use" with nirmatrelvir/ritonavir	41%	53%	61%	64%	43%
"Contraindicated" with nirmatrelvir/ritonavir	11%	15%	17%	18%	12%
"Not recommended for use" with remdesivir	1%	1%	1%	1%	1%

Abbreviations: CCI, Charlson Comorbidity Index; DDI, drug-drug interaction.

Fig. 2. Potential DDIs with nirmatrelvir/ritonavir and remdesivir among patients hospitalized for COVID-19 between May 2020 and December 2022 by subgroups of age, CCI, and high-risk underlying conditions. From Mozaffari *et al.,* 2024.

Conclusions

- Given the global rise in polypharmacy which heightens the risk of DDIs, this review underscores the urgent need for RWE to guide safer, more informed medication use.
- Using RWE to assess DDIs can bridge the gap between clinical trials and everyday practice, enhancing prescribing safety, reducing avoidable costs, and enabling more precise, patient-centered care.
- Future efforts should aim to harmonize RWE methods and strengthen collaboration across stakeholders to better leverage RWD for safer, and more efficient treatment strategies aligned with value-based healthcare goals.

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