Clinical and Translational Science

ARTICLE OPEN ACCESS

Development and Validation of an Approach to Assessing Clinical Relevance of Potential Drug–Drug Interactions Inducing Rare but Serious Adverse Events

Menghuan Song[1,2] | Hui Zhou[3] | Zhirong Yang[4,5] | Yunfeng Lai[6] | Carolina Oi Lam Ung[1,2,7] | Hao Hu[1,2,7]

[1]State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences, University of Macau, Avenida da Universidade, Taipa, Macao Special Administrative Region, China | [2]Centre for Pharmaceutical Regulatory Sciences, University of Macau, Avenida da Universidade, Taipa, Macao Special Administrative Region, China | [3]Department of Pharmacy, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, China | [4]Department of Computational Biology and Medical Big Data, Shenzhen University of Advanced Technology, Shenzhen, China | [5]Shenzhen Institute of Advanced Technology, Chinese Academy of Sciences, Shenzhen, China | [6]School of Public Health and Management, Guangzhou University of Chinese Medicine, Guangzhou, Guangdong, China | [7]Department of Public Health and Medicinal Administration, Faculty of Health Sciences, University of Macau, Avenida da Universidade, Taipa, Macao Special Administrative Region, China

Correspondence: Carolina Oi Lam Ung (carolinaung@um.edu.mo) | Hao Hu (haohu@um.edu.mo)

Received: 29 November 2024 | **Revised:** 7 April 2025 | **Accepted:** 30 April 2025

Funding: This study is supported by the Centre for Pharmaceutical Regulatory Sciences Fund (CPRS-0005), University of Macau.

Keywords: a systematic approach | clinical relevance | DDI | depression | pharmacoepidemiology | pharmacovigilance

ABSTRACT

Evaluating clinical relevance of potential drug–drug interactions is significant for managing safety risks. However, current approaches to the evaluation lack data on rare but serious adverse events. This study aims to develop an approach to assessing clinical relevance of potential drug–drug interactions that induce rare and serious adverse events, and test its performance. In the development, three key dimensions for evaluating clinical relevance were synthesized based on a literature review. A systematic five-step approach was proposed through designated dimensions and discussions within the research team. Subsequently, the approach was applied to patients with depression to validate its ability of demonstrating the dimensions, and exacting data on rare but serious adverse events. The test results showed varying signal intensities among different drug combinations in relation to adverse events including serotonin syndrome, long QT syndrome, and Torsade de Pointes. Advanced age was identified as a confounding factor for the QT prolongation signal. These findings operationalize Dimension one: Probabilities and risk factors for the occurrence of rare and serious adverse events. Besides, in the test, fatality occurred in 22.01% of the cases having drug-triggered QT prolongation. Advancing age was associated with the fatality (odds ratio = 1.03, 95% confidence interval = 1.01–1.07). The findings manifested Dimension two: Magnitude of adverse events and associated factors. Dimension three was achieved by findings of median time-to-onset of fatal serotonin syndrome and QT prolongation, which was one and 8 days, respectively. In summary, the proposed approach demonstrates effects in assessing the clinical relevance of potential drug–drug interactions.

Carolina Oi Lam Ung and Hao Hu contributed equally to this article.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2025 The Author(s). *Clinical and Translational Science* published by Wiley Periodicals LLC on behalf of American Society for Clinical Pharmacology and Therapeutics.

Summary

- What is the current knowledge on the topic?
  - Current evidence demonstrates significant limitations in characterizing rare but serious adverse events associated with pDDIs, particularly in establishing their clinical relevance.
- What question did this study address?
  - The absence of a standardized approach to evaluating the clinical relevance of pDDIs that may cause rare but severe adverse events. Current inconsistencies in measurement approaches across studies investigating pDDI–clinical–relevant outcomes.
- What does this study add to our knowledge?
  - Establishment of a novel approach to evaluating clinical relevance, demonstrating: Probability analysis of adverse event occurrence and associated risk factors; Severity quantification of adverse events with associated risk factors; and Temporal pattern assessment of TTO metrics. Standardized methodologies of the approach including five steps: Step one. Determining target population; Step two. Detecting pDDIs in high frequency and potentially inducing severe reactions; Step three. Ensuring the pivots; Step four. Signal mining of the adverse events and investigating confounders; and Step five. Examining fatality of the adverse events and associated risk factors, and researching in TTO of the adverse events. Demonstration of effects through a test in patients with depression, confirming both feasibility and clinical utility of the proposed framework.
- How might this change clinical pharmacology or translational science?
  - The proposed approach is promising in demonstrating clinical relevance of pDDIs in inducing rare and serious adverse events. The proposed approach significantly enhances clinical practice by facilitating evidence-based treatment adjustments and enabling targeted monitoring strategies following pharmacological interventions.

1 | Introduction

Drug–drug interactions (DDIs) occur when two or more drugs are coadministered to a patient and interact with each other [1]. DDIs are contributors to treatment failures, hospital admissions, and health service costs which should be avoided [2]. Potential drug–drug interactions (pDDIs) are assessed based on the pharmacodynamic and pharmacokinetic properties of drugs in combined use [3]. Their manifestations are different across populations, while severe outcomes such as death occurring in high-risk cases [4]. In the real world, DDIs are inevitable, especially in patients with complex health conditions which usually require comedications. Therefore, evaluating the clinical relevance of pDDIs is significant for identifying and mitigating safety risks related to drug interactions. A key component of this evaluation involves stratifying patient populations based on susceptibility to adverse outcomes, enabling targeted monitoring for those at highest risk.

Current research in the clinical relevance of pDDIs primarily relies on pharmacoepidemiology studies utilizing electronic health record data [5–7]. These studies evaluate clinical relevance through changes in vital signs, laboratory results, patient-reported symptoms, treatment discontinuation, and clinician assessments [5–7]. However, pharmacoepidemiology studies are often limited by sample size, resulting in insufficient characterization of rare but serious adverse events [5–7]. Consequently, specifications of rare but serious adverse events are in dearth [5–7]. Additionally, they frequently lack critical data on time-to-onset (TTO) and risk factors for adverse events [5–7], which are essential for developing personalized monitoring strategies. Pharmacovigilance signal mining offers a complementary approach by detecting signals of rare and serious adverse events from spontaneous individual case safety reports [8], and has been validated as a reliable method of identifying and characterizing severe drug interaction outcomes [9]. The significance of pharmacovigilance research can also be strengthened by targeting towards drug combinations with high prevalence in clinical practice, which combinations can be recognized from pharmacoepidemiology studies.

Therefore, we aimed to develop an integrative approach involving pharmacoepidemiology and pharmacovigilance research to assess the clinical relevance of pDDIs in triggering rare but serious adverse events. Furthermore, in order to examine the effects of the approach, we applied it to people with depression. Patients with depression were chosen as the group of interest due to their large population size and elevated risks of DDIs. There are approximately 280 million people having depression worldwide [10]. Treatment resistance and comorbidities are common in this group [11–13], which potentially lead to a high frequency of concomitant use of medications, which creates a great chance for DDIs.

2 | Materials and Methods

The research team established study aims to develop an integrative pharmacoepidemiology-pharmacovigilance approach for assessing the clinical relevance of pDDIs inducing rare but serious adverse events, and to evaluate its performance in depression patients (Figure 1). Firstly, a state-of-the-art literature review was conducted to synthesize key dimensions of assessing clinical relevance in current literature. The research team subsequently explored strategies for employing pharmacoepidemiology and pharmacovigilance studies to address the key dimensions, and investigated pivots of integration. Then, the proposed approach was applied to patients with depression to examine its performance. Finally, validation of performance was achieved from two aspects: whether the approach could excavate data on the clinical relevance of rare but serious adverse events induced by pDDIs; and whether it could successfully operationalize the predefined assessment dimensions.

2.1 | Identification of Key Dimensions

The state-of-the-art literature review employed a systematic search strategy using the key terms “clinical relevance” AND “potential drug–drug interactions” along with their Medical

Subject Headings terms and synonyms to identify relevant articles across PubMed and Web of Science (Table S1). The search was temporally restricted to studies published between 1 January 2015 and 31 March 2025 to capture the most recent evidence. Inclusion criteria were rigorously applied, requiring studies to: (1) be peer-reviewed English-language publications; (2) target at human subjects; (3) adopt systematic reviews, randomized controlled trials, or observational study designs; (4) quantitatively report pDDIs and associated adverse events in result sections; and (5) explicitly define both pDDIs and clinical relevance within their methodology.

Our systematic search yielded an initial pool of 3062 articles, from which 23 duplicates were removed. Following screening depending on predesigned inclusion criteria, 2954 articles were excluded during title/abstract review and an additional 70 articles during full-text assessment, resulting in 15 studies that met all inclusion criteria (Figure S1) [5–7, 14–25]. Two independent reviewers (M.S. and H.Z.) conducted the literature evaluation, with any discrepancies resolved through consensus discussions. Study quality was assessed using Joanna Briggs Institute (JBI) critical appraisal tools specific to each study design: the JBI Checklist for Analytical Cross-Sectional Studies (max score: 8), Case Control Studies (max score: 10), Cohort Studies (max score: 11), and Prevalence Studies (max score: 9). For cross-design comparability, raw quality scores were converted to percentage scales, revealing substantial variability (range: 45.5%–100%) (Table S2). Involved studies generally encompassed three key dimensions for assessing clinical relevance: Dimension one. Probabilities and risk factors for occurrence of adverse events induced by pDDIs; Dimension two. Magnitude of the adverse events and associated risk factors; and Dimension three. TTO of the adverse events (Table S3).

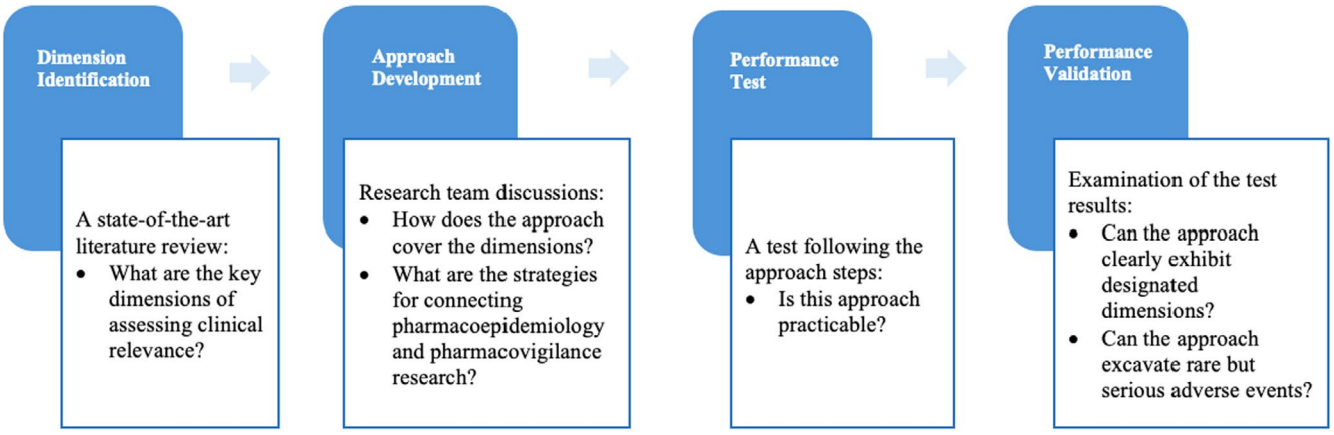


FIGURE 1 | Procedure of the study.

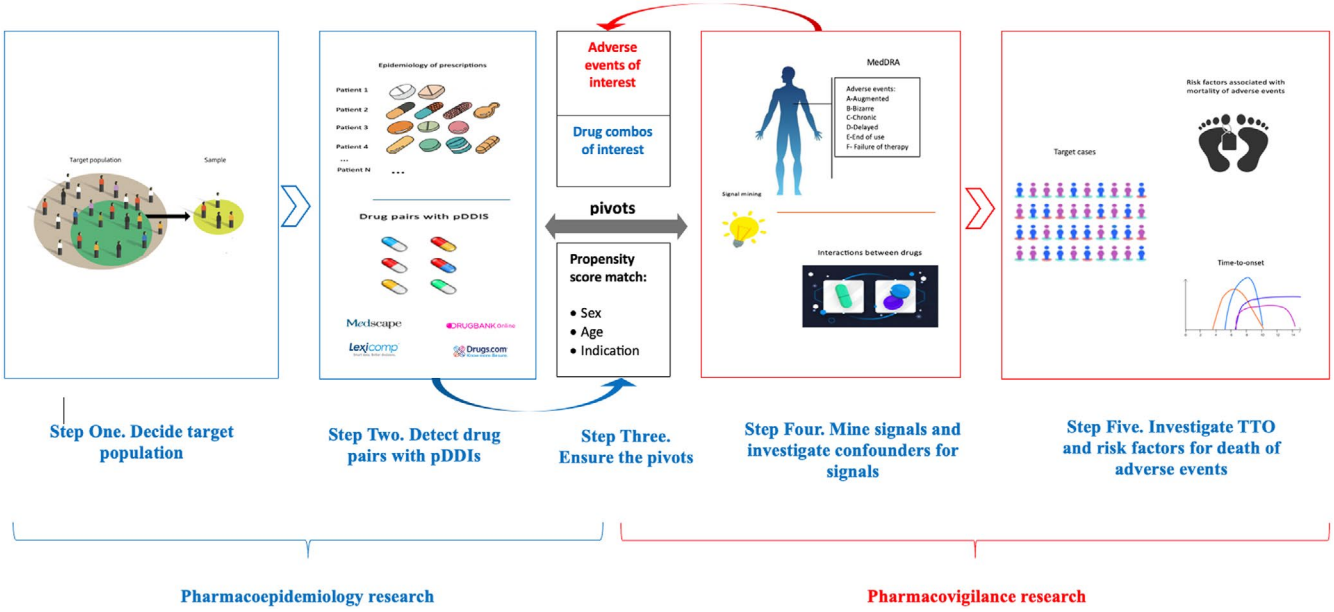


FIGURE 2 | Design of the systematic approach.

TABLE 1 | PDDIs with serious or significant adverse reactions.

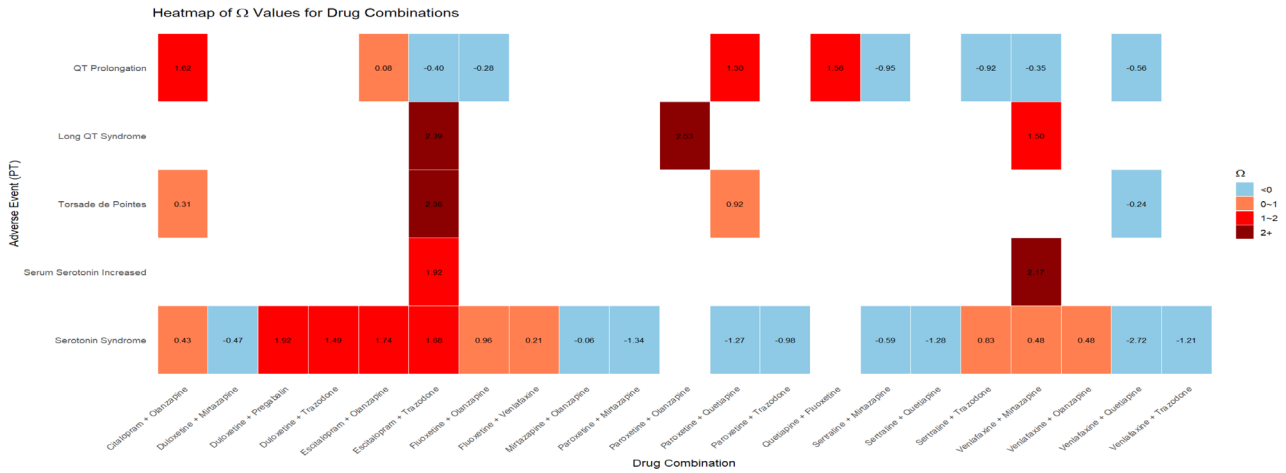
Drugs	Potential adverse reactions	Severity	Frequency
Paroxetine + trazodone	Increase serotonin levels	Serious	322 cases
Paroxetine + buspirone	Increase serotonin levels	Serious	308 cases
Paroxetine + olanzapine	Increase QTc interval	Serious	298 cases
Sertraline + trazodone	Increase serotonin levels, increase QTc interval	Serious	178 cases
Escitalopram + trazodone	Increase serotonin levels	Serious	172 cases
Trazodone + buspirone	Increase serotonin levels	Serious	141 cases
Duloxetine + trazodone	Increase serotonin levels	Serious	133 cases
Escitalopram + buspirone	Increase serotonin levels	Serious	129 cases
Venlafaxine + mirtazapine	Decrease QTc interval	Serious	112 cases
Sertraline + buspirone	Increase serotonin levels	Serious	106 cases
Sertraline + quetiapine	Increase QTc interval	Serious	101 cases
Venlafaxine + trazodone	Increase serotonin levels	Serious	95 cases
Citalopram + olanzapine	Increase QTc interval	Serious	95 cases
Fluoxetine + venlafaxine	Increase serotonin levels	Serious	89 cases
Duloxetine + buspirone	Increase serotonin levels	Serious	38 cases
Sertraline + olanzapine	Increase QTc interval	Significant	179 cases
Venlafaxine + quetiapine	Increase the risk for neuroleptic malignant syndrome and serotonin syndrome	Significant	167 cases
Duloxetine + mirtazapine	Increase serotonin levels	Significant	162 cases
Venlafaxine + olanzapine	Increase the risk for neuroleptic malignant syndrome and serotonin syndrome, decrease QTc interval	Significant	154 cases
Fluoxetine + olanzapine	Increase QTc interval	Significant	141 cases
Escitalopram + olanzapine	Increase QTc interval	Significant	135 cases
Sertraline + mirtazapine	Increase serotonin levels, increase QTc interval	Significant	108 cases
Paroxetine + quetiapine	Increase the risk for neuroleptic malignant syndrome and serotonin syndrome	Significant	99 cases
Duloxetine + pregabalin	Increase risks of respiratory depression or sedation	Significant	76 cases
Quetiapine + fluoxetine	Increase QTc interval	Significant	73 cases
Mirtazapine + buspirone	Increase serotonin levels	Significant	71 cases
Paroxetine + mirtazapine	Increase QTc interval, increase serotonin levels	Significant	71 cases
Sertraline + donepezil	Increase QTc interval	Significant	58 cases
Mirtazapine + olanzapine	Increase QTc interval, increase sedation	Significant	51 cases
Quetiapine + trazodone	Increase sedation	Significant	51 cases

Note: PDDIs with less than 50 cases were not reported.
Abbreviation: PDDI, potential drug–drug interaction.

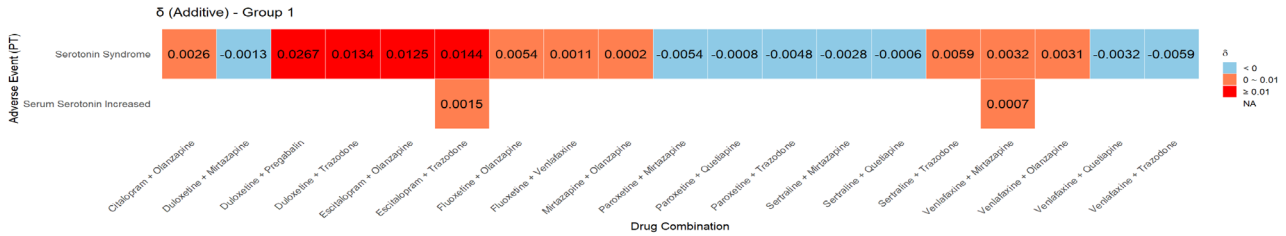
2.2 | Development of the Approach

The research team engaged in discussions on the topics of "strategies for using the integrative approach to address the three dimensions" and "pivots of integrating pharmacoepidemiology and pharmacovigilance research", until a consensus was reached.

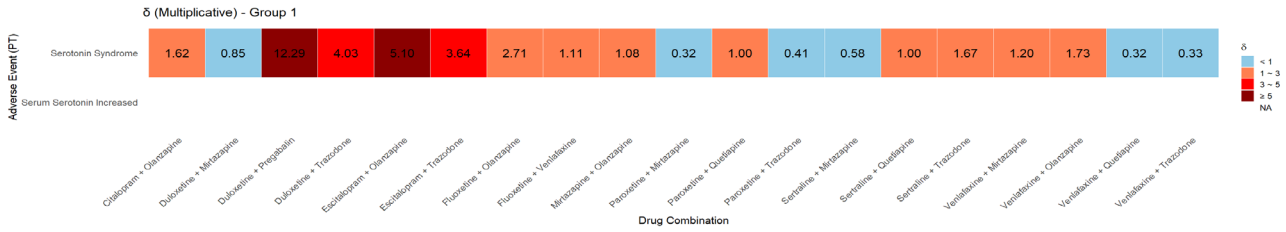
To address the dimensions, we employed pharmacovigilance signal intensity as a quantitative proxy for the probability of adverse event occurrence (Dimension one). Risk factors for adverse events were identified by examining patient characteristics that served as confounding factors for pharmacovigilance signals. For Dimension two, the magnitude of adverse events was assessed based on the severity of their outcomes (e.g.,



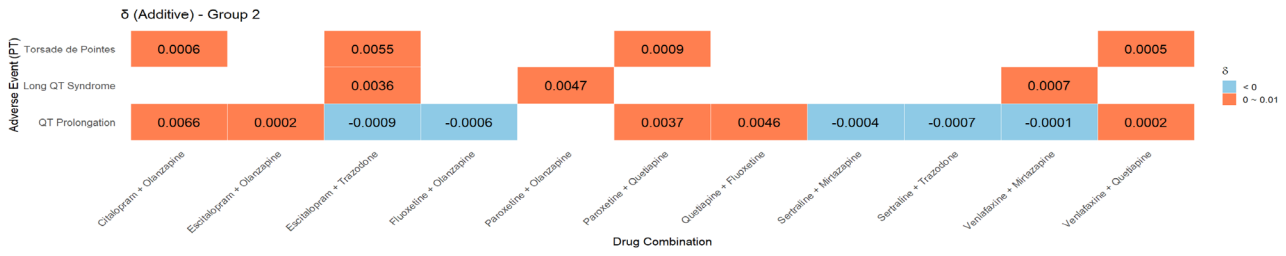
A



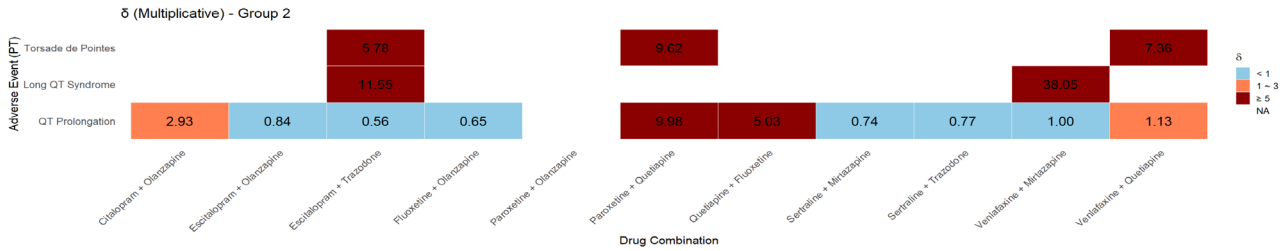
B



C



D



E

FIGURE 3 | Legend on next page.

FIGURE 3 | Pharmacovigilance signals: (A) Signals of adverse events associated with drug pairs of interest; (B) Signals of interactions in Group one-drug pairs (Additive Model); (C) Signals of interactions in Group one-drug pairs (Multiplicative model); (D) Signals of interactions in Group two-drug pairs (Additive Model); (E) Signals of interactions in Group two-drug pairs (Multiplicative model).

death and hospitalization), with patient characteristics linked to higher severity. Dimension three was assessed through temporal association analyses, evaluating the chronological relationship between therapy initiation and onset of adverse events in pharmacovigilance data. Given the study's prospective focus on rare and clinically significant adverse events, the pharmacovigilance component served as the primary methodological foundation for investigating all three dimensions in the approach.

Additionally, the pharmacoepidemiology component was employed to investigate real-world prescribing data. PDDIs in high frequency and severity can be decided through frequency threshold (e.g., Top 20 interaction-drug-pairs by coprescription rate) and severity threshold (e.g., severities examined by Medscape Interaction Checker based on drug pharmacokinetics and pharmacodynamics). This quantitative prioritization ensured clinical relevance through exposure prevalence. The rationale for assessing prevalence in pharmacoepidemiology research stems from the inherent limitations of pharmacovigilance studies relying on individual case safety reports—these spontaneous reporting systems predominantly capture adverse events postoccurrence, thereby introducing reporting bias and failing to reflect real-world medication exposure frequencies.

The integration pivots between pharmacoepidemiology and pharmacovigilance components were supported by literature rationale, emphasizing modifiable factors both affecting patient exposure to pDDIs and confounding the associations between drug combinations and clinically relevant adverse events. Previous studies have identified demographic characteristics (sex, age) and clinical severity of primary drug indications as consistent risk modifiers for pDDI exposure and drug combination-related adverse events [26–30]. Consequently, these evidence-based parameters were selected as the pivots in the approach design.

The study approach was developed under team consensus and implemented through five sequential steps (Figure 2). Step one: Study cohorts were defined according to research aims, with inclusion/exclusion criteria established a priori. Step two: PDDIs were systematically identified using validated instruments (e.g., Medscape Interaction Checker, and Lexicomp Drug Interaction Checker) [12, 31], with severity classifications based on pharmacokinetic/pharmacodynamic mechanisms. Frequencies of pDDIs were quantified through descriptive analyses of prescription patterns. Step three: Patient-level linkage between pharmacoepidemiology and pharmacovigilance datasets was achieved via propensity score matching on three key variables: age, sex, and severity of primary drug indications. Severe pDDIs in high frequency were mapped to corresponding adverse events using standardized terminologies (e.g., Medical Dictionary for Regulatory Activities [MedDRA]) [13] Step four: Pharmacovigilance signal mining was done targeting adverse events of interest, with drug pairs exhibiting severe pDDIs designated as targeted therapies. Multivariate analyses were employed to investigate potential confounding factors for signals. Step five: Regression analyses were used to examine risk factors associated with the fatality of adverse events, with research in TTO of the adverse events. Steps One to Three were based on the pharmacoepidemiology component. Steps Three to Five were based on the pharmacovigilance component.

2.3 | A Test of Approach Performance

Patients with depression were selected as the target population because of their high risks of DDIs (Step one). A pharmacoepidemiology study was done in a cohort of patients with depression, whose sample frame was described in detail in Data S1. In Step two, psychotropic prescriptions of participants were retrospectively collected. Medscape Drug Interaction Checker was used to detect pDDIs from any drug pair and categorize levels of adverse reactions as contraindicated, serious—use alternative, significant—monitor closely, and minor [31].

In Step three, FAERS data from Quarter one of 2004 to Quarter one of 2024 were used in the pharmacovigilance research (Figure S2). To identify cases for pharmacovigilance signal mining, we performed patient-level linkage between pharmacoepidemiology and pharmacovigilance databases using propensity score matching (caliper width = 0.2). The matching algorithm incorporated three key factors: age, sex, and depression severity (including both depressive episodes and depressive disorders). Each case in the pharmacoepidemiology cohort was matched to one or more corresponding cases in the pharmacovigilance database. Adverse events of interest were determined by matching preferred terms (PTs in MedDRA) in FAERS data to serous and significant reactions identified in Step two. Therapy of interest consisted of drug pairs with serious or significant pDDIs, which were also recognized in Step two.

In Step four, signals of potential associations between adverse events and drug combinations were detected based on a variety of methods including Ω shrinkage measure, additive models, and multiplicative models (formulars in Data S1). The Ω shrinkage measure compares the observed reporting ratio of an adverse event associated with a combination of two drugs to its expected value [32]. Significant signals were decided by the threshold of $\Omega_{025} > 0$ [33]. Synergistic interactions were identified through parallel modeling approaches: additive models and multiplicative models [34]. Thresholds of $\delta > 0$ in the additive model, and $\delta > 1$ in the multiplicative model were used for identifying the occurrence of synergistic interactions [33]. Furthermore, the cut-off of 0.1 was used in the additive model; and cut-offs of 3 and 5 were used in the multiplicative model to differentiate the signal intensity. Antagonistic effects were decided when $\delta < 0$ in the additive model, and $\delta < 1$ in the multiplicative model. Heatmaps were used to visualize the

TABLE 2 | Potential associations between patient characteristics and occurrence of adverse events.

Drug combos	Yes case No. (%)	No case No. (%)	AOR (95% CI)
Occurrence of serotonin syndrome			
Duloxetine + pregabalin			
Sex (Ref: male)	2083 (1.98)	102,943 (98.02)	0.67 (0.57–0.79)*
Age/years, mean (SD)	54.64 (16.23)	53.12 (15.32)	1.00 (0.94–1.00)
Diagnosis (Ref: depression episode)	2083 (1.98)	102,943 (98.02)	1.16 (0.83–1.62)
Escitalopram + olanzapine			
Sex (Ref: male)	2083 (1.98)	102,943 (98.02)	0.73 (0.30–0.96)*
Age/years, mean (SD)	54.64 (16.23)	53.12 (15.32)	1.00 (0.90–1.10)
Diagnosis (Ref: depression episode)	2083 (1.98)	102,943 (98.02)	1.16 (0.82–1.62)
Escitalopram + trazodone			
Sex (Ref: male)	2083 (1.98)	102,943 (98.02)	0.68 (0.52–0.86)*
Age/years, mean (SD)	54.64 (16.23)	53.12 (15.32)	1.00 (0.99–1.01)
Diagnosis (Ref: depression episode)	2083 (1.98)	102,943 (98.02)	1.16 (0.83–1.62)
Duloxetine + trazodone			
Sex (Ref: male)	2083 (1.98)	102,943 (98.02)	0.67 (0.56–0.80)*
Age/years, mean (SD)	54.64 (16.23)	53.12 (15.32)	1.00 (0.99–1.01)
Diagnosis (Ref: depression episode)	2083 (1.98)	102,943 (98.02)	1.15 (0.83–1.61)
Occurrence of serotonin increase			
Venlafaxine + mirtazapine			
Sex (Ref: male)	25 (0.02)	105,001 (99.98)	1.87 (0.39–9.02)
Age/years, mean (SD)	58.37 (15.64)	53.13 (15.35)	1.00 (0.95–1.04)
Diagnosis (Ref: depression episode)	25 (0.02)	105,001 (99.98)	12.40 (3.44–44.90)*
Occurrence of Torsade de Pointes			
Escitalopram + trazodone			
Sex (Ref: male)	249 (0.24)	104,777 (99.76)	1.02 (0.61–1.73)
Age/years, mean (SD)	59.52 (15.96)	53.13 (15.42)	1.04 (1.03–1.06)*
Diagnosis (Ref: depression episode)	249 (0.24)	104,777 (99.76)	1.08 (0.34–3.44)
Occurrence of long QT syndrome			
Escitalopram + trazodone			
Sex (Ref: male)	91 (0.09)	104,935 (99.91)	0.61 (0.23–1.62)
Age/years, mean (SD)	57.29 (11.03)	53.13 (15.42)	1.00 (0.97–1.03)
Diagnosis (Ref: depression episode)	91 (0.09)	104,935 (99.91)	0.41 (0.02–1.89)
Occurrence of QT prolongation			
Citalopram + olanzapine			
Sex (Ref: male)	686 (0.65)	104,340 (99.35)	0.68 (0.52–0.86)*
Age/years, mean (SD)	93.29 (113.02)	80.54 (30.30)	1.03 (0.01–1.04)
Diagnosis (Ref: depression episode)	686 (0.65)	104,340 (99.35)	2.99 (2.01–4.43)*
Quetiapine + fluoxetine			

(Continues)

TABLE 2 | (Continued)

Drug combos	Yes case No. (%)	No case No. (%)	AOR (95% CI)
Sex (Ref: male)	686 (0.65)	104,340 (99.35)	0.68 (0.51–0.90)*
Age/years, mean (SD)	93.29 (113.02)	80.54 (30.30)	1.03 (1.02–1.04)*
Diagnosis (Ref: depression episode)	686 (0.65)	104,340 (99.35)	3.01 (2.03–4.47)*
Paroxetine + quetiapine			
Sex (Ref: male)	686 (0.65)	104,340 (99.35)	0.67 (0.49–0.85)*
Age/years, mean (SD)	93.29 (113.02)	80.54 (30.30)	1.03 (1.01–1.05)*
Diagnosis (Ref: depression episode)	686 (0.65)	104,340 (99.35)	3.00 (3.02–4.45)*

Note: Drug combos with signals 1+ were reported.
Abbreviations: 95% CI, 95% confidence interval; AOR, adjusted odds ratio.
*$p < 0.05$.

signals. Logistic regression models were employed to investigate potential associations between the occurrence of adverse events and the use of therapy of interest, sex and age of patients, or severity of the drug indication. Estimates of effect were shown as odds ratios (ORs) with 95% confidence intervals (CIs).

In Step five, cases were further screened if they had concurrent presence of adverse events and therapy of interest. Magnitude of adverse events was categorized into fatal (death and life-threatening) and nonfatal outcomes (hospitalization, disability, congenital anomaly, required intervention to prevent permanent impairment/damage, or others). Logistic regression models were applied to investigate potential fatality of adverse events associated with sex and age of patients, and severity of the drug indication, with estimates of effect shown as ORs (95% CIs). Besides, TTO was defined as the time differences in days by subtracting the event date from the date of initiating therapy of psychotropic comedications. Cumulative distribution curves were used to present the TTO by the fatality of target adverse events. Two-tailed $p < 0.05$ was considered statistically significant. All analyses were done by R (Version 4.3.2 for Windows).

2.4 | Results of the Test

In Step one, a cohort of 5837 cases with depression was included in the pharmacoepidemiology study (Table S4). In Step two, their prescriptions were reviewed, resulting in the identification of 30 drug pairs with serious or significant pDDIs (Table 1). Among the 30 drug pairs, 18 pairs (Group one) had interactions potentially leading to increased serotonin levels, while 12 pairs (Group two) had interactions potentially prolonging QT intervals. Use frequency of all the 30 drug pairs ranged from 51 to 322 cases.

In Step three, 197,174 cases from FAERS database (in pharmacovigilance research) were matched to the 5837 cases in the pharmacoepidemiology study. Pharmacovigilance signal mining was conducted among the 197,174 cases. Postmatching standardized mean differences (SMD) for age, sex, and depression severity was 0.05, 0.03, and 0.08 respectively. In the pharmacovigilance component, the 30 drug-pairs identified in Step two were designated as the target therapies. Specifically, elevated serotonin levels were mapped to the PTs of "serotonin syndrome" and "serum serotonin increased"; while QT prolongation was associated with PTs including "long QT syndrome", "Torsade de Pointes", and "QT prolongation". These PTs constituted the adverse events of interest for pharmacovigilance analysis (Figure S2).

In Step four, intense signals of serotonin syndrome were identified in association with specific drug combinations (Figure 3A). The combination of duloxetine + pregabalin showed an Ω_{025} value of 1.92, followed by escitalopram + olanzapine (1.74), escitalopram + trazodone (1.68), and duloxetine + trazodone (1.49) (Table S5). Additionally, the combination of venlafaxine + mirtazapine was strongly associated with serotonin increase (2.17). Escitalopram + trazodone exhibited significant signals for long QT syndrome (2.39) and Torsade de Pointes (2.36). Combinations strongly associated with QT prolongation included citalopram + olanzapine (1.62), quetiapine + fluoxetine (1.56), and paroxetine + quetiapine (1.30).

In drug combinations with the signal of serotonin syndrome, the intensity of interactions was $\delta = 0.03$, 0.01, 0.01, and 0.01 for duloxetine + pregabaline, escitalopram + olanzapine, escitalopram + trazodone, and duloxetine + trazodone, respectively in the additive model (Figure 3B and Table S6). In the multiplicative model, the intensity of interactions was 12.29, 5.10, 3.64, and 4.03 separately (Figure 3C). Strong interaction was found in escitalopram + trazodone (additive model: 0.006 and 0.004, respectively; multiplicative model: 5.78 and 11.55, respectively) in inducing the signals of Torsade de Pontes and long QT syndrome (Figure 3D,E). Intense interactions were also in paroxetine + quetiapine (additive model: 0.004, multiplicative model: 9.98), and quetiapine + fluoxetine (0.005, 5.03) for QT prolongation.

Female patients were less likely to develop serotonin syndrome when having duloxetine + pregabalin (OR = 0.67, 95% CI = 0.57–0.79), escitalopram + olanzapine (0.73, 0.30–0.96), escitalopram + trazodone (0.68, 0.52–0.86), and duloxetine + trazodone (0.67, 0.56–0.80) (Table 2). While age was positively associated with the occurrence of Torsade de Pointes in cases using escitalopram + trazodone (1.04, 1.03–1.06); and QT prolongation in cases using citalopram + olanzapine (1.03, 1.01–1.04), quetiapine + fluoxetine (1.03, 1.02–1.04), and paroxetine + quetiapine (1.03, 1.01–1.05).

TABLE 3 | Potential associations between patient characteristics and fatality of adverse events.

	Fatal case No. (%)	Nonfatal case No. (%)	OR (95% CI)
Serotonin syndrome			
Sex (Ref: male)	308 (14.79)	1775 (85.21)	1.01 (0.79–1.30)
Age/years, mean (SD)	77.23 (20.20)	54.53 (16.22)	1.00 (0.99–1.01)
Diagnosis (Ref: depression episode)	308 (14.79)	1775 (85.21)	0.52 (0.32–0.83)*
Serotonin increase			
Sex (Ref: male)	6 (24.00)	19 (76.00)	0.59 (0.04–7.91)
Age/years, mean (SD)	58.52 (16.21)	58.39 (15.81)	1.00 (0.94–1.06)
Diagnosis (Ref: depression episode)	6 (24.00)	19 (76.00)	0.75 (0.07–8.38)
Torsade de Pointes			
Sex (Ref: male)	83 (33.33)	166 (66.67)	1.04 (0.53–2.02)
Age/years, mean (SD)	60.01 (16.27)	59.04 (15.84)	1.01 (0.99–1.02)
Diagnosis (Ref: depression episode)	83 (33.33)	166 (66.67)	1.22 (0.51–2.93)
Long QT syndrome			
Sex (Ref: male)	31 (34.07)	60 (65.93)	1.61 (0.31–8.50)
Age/years, mean (SD)	59.73 (10.56)	56.01 (11.24)	1.03 (0.99–1.07)
Diagnosis (Ref: depression episode)	31 (34.07)	60 (65.93)	0.84 (0.23–2.98)
QT prolongation			
Sex (Ref: male)	151 (22.01)	535 (77.99)	1.43 (0.95–2.15)
Age/years, mean (SD)	62.02 (16.68)	57.34 (15.79)	1.03 (1.01–1.07)*
Diagnosis (Ref: depression episode)	151 (22.01)	535 (77.99)	0.75 (0.40–1.40)

Abbreviations: 95% CI, 95% confidence interval; OR, odds ratio; SD, standard deviation.
*$p < 0.05$.

In Step five, fatal outcomes were in 14.79% of the 2083 cases with serotonin syndrome. There was no significant association between sex, age, or depression severity with the fatality of serotonin syndrome (Table 3). Fatal outcomes of serotonin syndrome occurred within 1 day since therapy initiation (Figure 4). The median TTO of nonfatal outcomes was 23 days. Fatal outcomes were in 151 cases (22.01%) among 686 cases with QT prolongation. Increase of age was associated with the fatality of QT prolongation (OR = 1.03, 95% CI = 1.01–1.07) (Table 3). Fatality of QT prolongation ensued within 39 days since therapy initiation, with the median TTO of 8 days (Figure 4). Median TTO of nonfatal outcomes was 19 days.

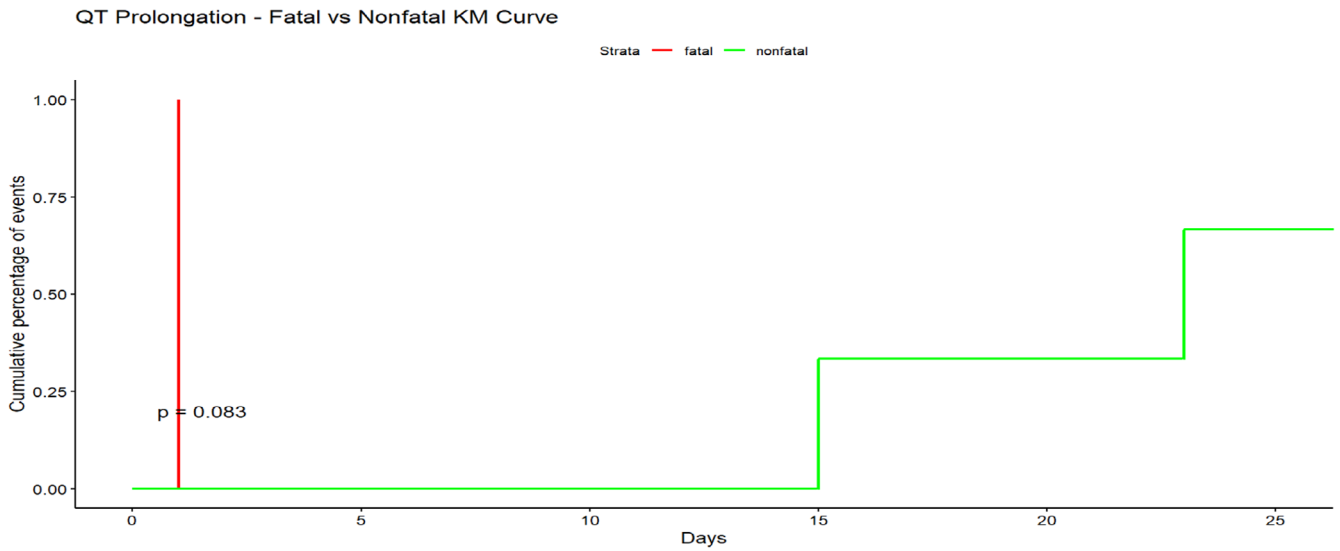
3 | Discussion

3.1 | Main Findings

In this study, we developed a systematic approach to evaluate the clinical relevance of pDDIs in triggering rare but serious adverse events. The approach was designed to demonstrate three critical dimensions of clinical relevance, which are: Dimension one. Probability and risk factors for the occurrence of rare and serious adverse events inducted by pDDIs; Dimension two. Magnitude of adverse events and associated risk factors; and Dimension three. TTO of adverse events. Then, the approach was applied to patients with depression as a test. Its effects were validated through assessing its ability to exact data on rare but serious adverse events, and empirically establish clinical relevance according to the established dimensions.

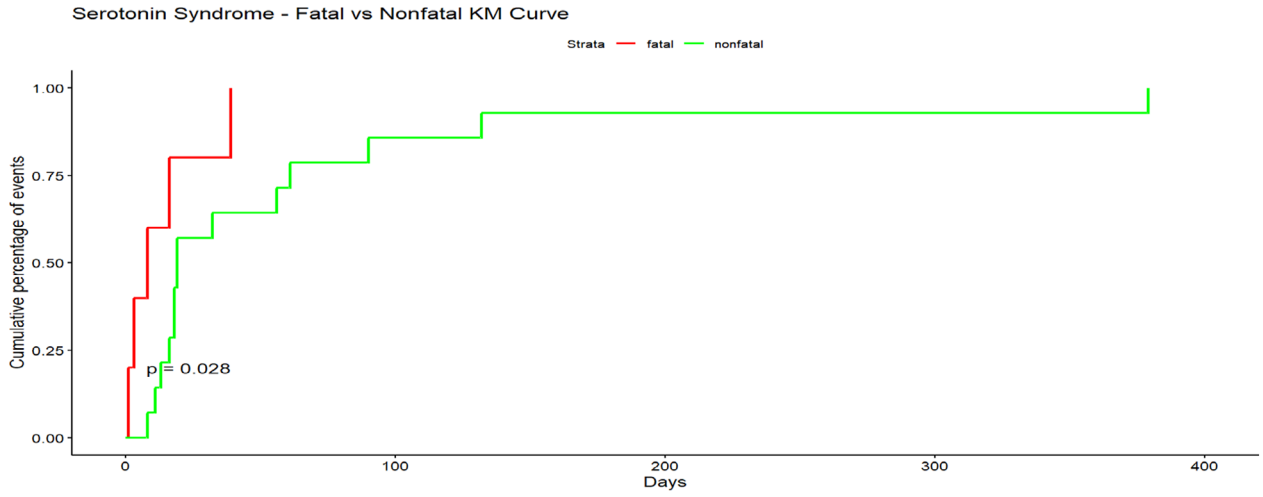
3.2 | Validation of the Performance-Exaction of Data on Rare and Serious Adverse Events

In the test, increased serotonin level, serotonin syndrome, QT prolongation, long QT syndrome, and Torsade de Pointes were the adverse events of interest for investigations on clinical relevance. Serotonin syndrome and Torsade de Pointes are rare, but can be life threatening in clinical practice. Drug-induced incidence of serotonin syndrome was 0.23% [35]. Torsade de Pointes was in 0.3% of patients exposed to drugs potentially causing long QT [36]. Previous studies reporting these adverse events primarily targeted drug mechanisms [37, 38], lacking comprehensive data on the three critical dimensions of clinical relevance. Our



Group	Min_TTO	Median_TTO	Max_TTO
Fatal	1	1	1
Nonfatal	15	23	27

A



Group	Min_TTO	Median_TTO	Max_TTO
Fatal	1	8	39
Nonfatal	8	19	379

B

FIGURE 4 | Time-to-onset of adverse events: (A) Serotonin syndrome; (B) QT prolongation.

findings have suggested the signal intensity of these adverse events, with their associated risk factors. We also quantify the fatality rate of the adverse events with risk factors associated with fatal outcomes. These substantive differences between our study and previous research underscore the key advantage of our systematic approach: its capacity to quantitatively assess the clinical relevance of drug–drug interactions that may induce rare but serious adverse events. Our methodology provides clinicians with actionable data for risk stratification and clinical decision-making.

3.3 | Validation of the Performance-Demonstration of Dimension One

In this test, the signals of adverse events associated with different drug combinations exhibited substantial variability, with some demonstrating particularly strong associations. Notably, the strong signal of serotonin syndrome was identified in four drug pairs, duloxetine + pregabalin, escitalopram + olanzapine, escitalopram + trazodone, and duloxetine + trazodone. Therefore, these four pairs were suggested having remarkably higher probabilities of causing serotonin syndrome when compared to the remaining 14 drug combinations in Group one. Similarly, strong signals of long QT syndrome and Torsade de Pointes were associated with escitalopram + trazodone, depositing comparable probabilities among the rest combinations (among Group two) in leading to these two types of adverse events. Additionally, among drug pairs in Group two, citalopram + olanzapine, quetiapine + fluoxetine, and paroxetine + quetiapine showed their higher potentials of inducing QT prolongation.

We also found that female and advanced age were confounding factors for the signal of serotonin syndrome and QT prolongation, respectively. This suggested the elevated vulnerabilities of elderly people in developing QT prolongation, while male patients were at higher risks of developing serotonin syndrome. These findings manifested Dimension one of clinical relevance.

3.4 | Validation of the Performance-Demonstration of Dimension Two and Three

Our test showed fatal outcomes occurred in approximately one-seventh and one-fifth of the cases with serotonin syndrome and QT prolongation, separately. Elderly people were more likely to experience fatality due to QT prolongation, which association may be attributed to several factors. QTc interval increases with age and potentially augments the severity of QT prolongation [39, 40]. Besides, a higher baseline prevalence of cardiovascular comorbidities in elderly patients can lower the threshold for lethal arrhythmias [41]. Moreover, other concomitant physical or mental disorders may require medications (such as, levofloxacin and donepezil) which potentially cause synergic prolongation of QT intervals with antidepressants [42, 43]. These findings verified the performance of the approach in demonstrating Dimension two. In addition, the death rates of adverse events and risk factors for fatal outcomes underscore clinical relevance by highlighting adverse events and patient groups in high priority for treatment adjustment and careful monitoring after the initiation of pharmacological interventions.

Our analysis revealed distinct temporal patterns in fatal versus nonfatal outcomes: serotonin syndrome fatalities manifested with a TTO of one day, while QT prolongation-related deaths occurred at 8 days, which were significantly faster than their nonfatal counterparts (median TTO: 23 and 19 days, respectively). This temporal dichotomy aligns with Dimension three (clinical urgency) of adverse event stratification. Besides, our findings demonstrate that the accelerated progression to fatal outcomes necessitates real-time TTO surveillance systems to guide urgent clinical decisions (e.g., switch of drugs, cessation, or dose adjustment).

3.5 | Strengths and Limitations of This Study

We propose a systematic approach to address the gaps in research regarding clinical relevance, which is examining data on rare and serious adverse events induced by pDDIs. In the approach, we designated three dimensions that are critical for assessing clinical relevance. This approach not only facilitates structured assessment but also supports the development of precision monitoring protocols and tailored treatment adjustments. Additionally, empirical validation confirms the approach's feasibility, suggesting strong potential for broader clinical and research applications. At the same time, we acknowledged the limitations of this study. Pharmacovigilance signal mining was done based on spontaneous individual case safety reports, which potentially introduce reporting bias. Second, the rarity and severity of the investigated pDDI-related adverse events (e.g., serotonin syndrome) mean existing literature offers limited comparative benchmarks for our quantitative findings. Large-scale RCTs and pharmacoepidemiology studies are expected to enrich data on probabilities and severities of rare but serious adverse events, for example, serotonin syndrome. These studies are also valuable for thorough validation of the performance of this approach. Our research specifically focuses on drug interactions where the clinical significance of adverse reactions remains inconclusive, whereas established contraindications with conclusive evidence on serious outcomes were beyond the investigation scope.

4 | Conclusion

This prospective approach offers a robust methodology for evaluating the clinical relevance of pDDIs associated with rare but serious adverse events through three essential dimensions: Probabilities of occurrence and associated risk factors; Severity magnitude and related risk determinants; and TTO characteristics of adverse events. These dimensions collectively provide a comprehensive evidence base for developing targeted treatment strategies and implementing precision monitoring protocols.

Author Contributions

All authors wrote the manuscript and designed and performed the research. M.S. and H.Z. analyzed the data. All the authors approved the final version.

Acknowledgments

We acknowledge Ms. Li Y.X., Ms. Yang J.Y., and Ms. Li Y.R. for their contributions in data measurement. This work was performed in part at the High-Performance Computing Cluster (HPCC) which is supported by the Information and Communication Technology Office (ICTO) of the University of Macau.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the pharmacoepidemiology research in the application step are available at the requirement from the first and second author. As these data contain patient information which is confidential, they are not publicly accessible. The data that support the pharmacovigilance signal mining can be accessed at the FAERS portal: https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-latest-quarterly-data-files.

References

1. W. Y. Zheng, L. C. Richardson, L. Li, R. O. Day, J. I. Westbrook, and M. T. Baysari, "Drug–Drug Interactions and Their Harmful Effects in Hospitalised Patients: A Systematic Review and Meta-Analysis," *European Journal of Clinical Pharmacology* 74 (2018): 15–27.

2. A. Jacob, C. S. Thomas, A. Deore, and P. Deshpande, "Appraisal and Discernment of Prevalent Drug–Drug Interactions in Patients With Psychiatric Disorders," *International Journal of Basic & Clinical Pharmacology* 10 (2021): 1005–1015.

3. T. S. Navaratinaraja, T. Kumanan, S. Siraj, and N. Sreeharan, "Potential Drug–Drug Interactions Among Hospitalised Elderly Patients in Northern Sri Lanka, a Lower Middle-Income Country: A Retrospective Analysis," *Drugs—Real World Outcome* 10 (2023): 83–95.

4. J. Jazbar, I. Locatelli, N. Horvat, and M. Kos, "Clinically Relevant Potential Drug–Drug Interactions Among Outpatients: A Nationwide Database Study," *Research in Social & Administrative Pharmacy* 14 (2018): 572–580.

5. Y. H. Choi, I. H. Lee, M. Yang, et al., "Clinical Significance of Potential Drug–Drug Interactions in a Pediatric Intensive Care Unit: A Single-Center Retrospective Study," *PLoS One* 16 (2021): e0246754.

6. L. Li, J. Baker, R. Quirk, et al., "Drug–Drug Interactions and Actual Harm to Hospitalized Patients: A Multicentre Study Examining the Prevalence Pre- and Post-Electronic Medication System Implementation," *Drug Safety* 47 (2024): 557–569.

7. Y. Liu, M. Yang, Y. Ding, et al., "Clinical Significance of Potential Drug–Drug Interactions in Older Adults With Psychiatric Disorders: A Retrospective Study," *BMC Psychiatry* 22 (2022): 563.

8. P. Beninger, "Signal Management in Pharmacovigilance: A Review of Activities and Case Studies," *Clinical Therapeutics* 42 (2020): 1110–1129.

9. L. Magro, E. Arzenton, R. Leone, et al., "Identifying and Characterizing Serious Adverse Drug Reactions Associated With Drug–Drug Interactions in a Spontaneous Reporting Database," *Frontiers in Pharmacology* 11 (2021): 622862.

10. World Health Organization, *Depressive Disorder (Depression)* (WHO, 2023), https://www.who.int/news-room/fact-sheets/detail/depression.

11. S. Dodd, M. Bauer, A. F. Carvalho, et al., "A Clinical Approach to Treatment Resistance in Depressed Patients: What to Do When the Usual Treatments Don't Work Well Enough?," *World Journal of Biological Psychiatry* 22 (2021): 483–494.

12. Lexicomp, *Drug Interactions* (Lexicomp, 2024), https://pro.uptodatefree.ir/Drugs-interactions/.

13. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human use, *Medical Dictionary for Regulatory Activities* (ICH, 2024), https://www.meddra.org/.

14. T. Bakker, A. Abu-Hanna, D. A. Dongelmans, et al., "Clinically Relevant Potential Drug–Drug Interactions in Intensive Care Patients: A Large Retrospective Observational Multicenter Study," *Journal of Critical Care* 62 (2021): 124–130.

15. S. Noor, M. Ismail, and F. Khadim, "Potential Drug–Drug Interactions Associated With Adverse Clinical Outcomes and Abnormal Laboratory Findings in Patients With Malaria," *Malaria Journal* 19 (2020): 1–13.

16. J. Zhang, D. Ma, M. Chen, et al., "Prevalence and Clinical Significance of Potential Drug–Drug Interactions Among Lung Transplant Patients," *Frontiers in Pharmacology* 15 (2024): 1308260.

17. K. Agergaard, M. Mau-Sørensen, T. B. Stage, et al., "Clopidogrel-Paclitaxel Drug–Drug Interaction: A Pharmacoepidemiologic Study," *Clinical Pharmacology and Therapeutics* 102 (2017): 547–553.

18. T. E. Balk, I. H. van der Sijs, T. van Gelder, et al., "Drug–Drug Interactions in Pediatric Oncology Patients," *Pediatric Blood & Cancer* 64 (2017): e26410.

19. J. N. D. dos Santos, R. Veloso, M. S. Tinoco, and A. M. M. Reis, "Factors Associated With Clinically Relevant Drug–Drug Interactions With Statins in Outpatients With Coronary Artery Disease," *Mundo Saude* 44 (2020): 506–514.

20. C. Iniesta-Navalón, J. J. Gascón-Cánovas, Z. A. D. S. Gama, et al., "Potential and Clinical Relevant Drug–Drug Interactions Among Elderly From Nursing Homes: A Multicentre Study in Murcia, Spain," *Ciência & Saúde Coletiva* 24, no. 5 (2019): 1895–1902.

21. L. A. Marcath, T. D. Coe, E. K. Hoylman, B. G. Redman, and D. L. Hertz, "Prevalence of Drug–Drug Interactions in Oncology Patients Enrolled on National Clinical Trials Network Oncology Clinical Trials," *BMC Cancer* 18 (2018): 1155.

22. S. Noor, M. Ismail, and Z. Ali, "Potential Drug–Drug Interactions Among Pneumonia Patients: Do These Matter in Clinical Perspectives?," *BMC Pharmacology and Toxicology* 20 (2019): 45.

23. S. Noor, M. Ismail, I. Haider, and F. Khadim, "Drug–Drug Interactions in Hepatitis Patients: Do These Interactions Matter in Clinical Perspectives?," *Annals of Hepatology* 17 (2018): 1001–1011.

24. J. K. Ostermann, A. Berghöfer, F. Andersohn, and F. Fischer, "Frequency and Clinical Relevance of Potential Cytochrome P450 Drug Interactions in a Psychiatric Patient Population—An Analysis Based on German Insurance Claims Data," *BMC Health Services Research* 16 (2016): 482.

25. T. P. van Staa, M. Pirmohamed, A. Sharma, I. Buchan, and D. M. Ashcroft, "Clinical Relevance of Drug–Drug Interactions With Antibiotics as Listed in a National Medication Formulary: Results From Two Large Population-Based Case–Control Studies in Patients Aged 65–100 Years Using Linked English Primary Care and Hospital Data," *Clinical Pharmacology and Therapeutics* 113 (2023): 423–434.

26. J. H. Cotto, E. Davis, G. J. Dowling, J. C. Elcano, A. B. Staton, and S. R. B. Weiss, "Gender Effects on Drug Use, Abuse, and Dependence: A Special Analysis of Results From the National Survey on Drug Use and Health," *Gender Medicine* 7 (2010): 402–413.

27. Q. Yu, K. K. Wong, O. K. Lei, et al., "Comparative Effectiveness of Multiple Exercise Interventions in the Treatment of Mental Health Disorders: A Systematic Review and Network Meta-Analysis," *Sports Medicine—Open* 8 (2022): 135.

28. Y. Yu, J. Chen, D. Li, L. Wang, W. Wang, and H. Liu, "Systematic Analysis of Adverse Event Reports for Sex Differences in Adverse Drug Events," *Scientific Reports* 6 (2016): 24955.

29. M. J. Alomar, "Factors Affecting the Development of Adverse Drug Reactions," *Saudi Pharmaceutical Journal* 22 (2014): 83–94.

30. S. Sundaran, A. Udayan, K. Hareendranath, et al., "Study on the Classification, Causality, Preventability and Severity of Adverse Drug Reaction Using Spontaneous Reporting System in Hospitalized Patients," *Pharmacy (Basel)* 6 (2018): 108.

31. Medscape, "Drug Interaction Checker, WebMD," 2024, https://reference.medscape.com/drug-interactionchecker.

32. G. N. Norén, R. Sundberg, A. Bate, and I. R. Edwards, "A Statistical Methodology for Drug–Drug Interaction Surveillance," *Statistics in Medicine* 27 (2008): 3057–3070.

33. Y. Noguchi, T. Tachi, and H. Teramachi, "Comparison of Signal Detection Algorithms Based on Frequency Statistical Model for Drug–Drug Interaction Using Spontaneous Reporting Systems," *Pharmaceutical Research* 37 (2020): 86.

34. B. T. Thakrar, S. B. Grundschober, and L. Doessegger, "Detecting Signals of Drug–Drug Interactions in a Spontaneous Reports Database," *British Journal of Clinical Pharmacology* 64 (2007): 489–495.

35. J. Francescangeli, K. Karamchandani, M. Powell, and A. Bonavia, "The Serotonin Syndrome: From Molecular Mechanisms to Clinical Practice," *International Journal of Molecular Sciences* 20 (2019): 2288.

36. K. Arunachalam, S. Lakshmanan, A. Maan, N. Kumar, and P. Dominic, "Impact of Drug Induced Long QT Syndrome: A Systematic Review," *Journal of Clinical Medicine Research* 10 (2018): 384–390.

37. B. A. English, M. Dortch, L. Ereshefsky, and S. Jhee, "Clinically Significant Psychotropic Drug–Drug Interactions in the Primary Care Setting," *Current Psychiatry Reports* 14 (2012): 376–390.

38. N. B. Sandson, S. C. Armstrong, and K. L. Cozza, "An Overview of Psychotropic Drug–Drug Interactions," *Psychosomatics* 46 (2005): 464–494.

39. S. W. Rabkin, "Impact of Age and Sex on QT Prolongation in Patients Receiving Psychotropics," *Canadian Journal of Psychiatry* 60 (2015): 206–214.

40. M. L. Ricardo-Silgado, S. Singh, L. Cifuentes, et al., "Association Between CYP Metabolizer Phenotypes and Selective Serotonin Reuptake Inhibitors Induced Weight Gain: A Retrospective Cohort Study," *BMC Medicine* 20 (2022): 261.

41. M. Steenman and G. Lande, "Cardiac Aging and Heart Disease in Humans," *Biophysical Reviews* 9 (2017): 131–137.

42. R. Stahlmann and H. Lode, "Safety Considerations of Fluoroquinolones in the Elderly: An Update," *Drugs & Aging* 27 (2010): 193–209.

43. S. Kuwahata, T. Takenaka, T. Motoya, et al., "Effect of QT Prolongation in Patients Taking Cholinesterase Inhibitors (Donepezil) for Alzheimer's Disease," *Circulation Reports* 3 (2021): 115–121.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.