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Core Concepts in Pharmacoepidemiology: Evaluation of Drug-Drug Interactions in Pharmacoepidemiologic Research

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Abstract

Drug-drug interactions (DDIs) represent a significant concern for clinical care and public health, but the health consequences of many DDIs remain largely underexplored. This knowledge gap underscores the critical need for pharmacoepidemiologic research to evaluate real-world health outcomes of DDIs. In this review, we summarize the definitions commonly used in pharmacoepidemiologic DDI studies, discuss common sources of bias, and illustrate through examples how these biases can be mitigated.

Keywords

Drug-drug interaction; design considerations; biases; methodology; study design; review

1. Introduction

A drug-drug interaction (DDI) occurs when one drug's effect is altered by another drug.¹ Previous studies have estimated that DDIs account for 10.3% of adverse drug events (ADEs) in the U.S. general population (2000-2002)² and 4.8% of hospital admissions among older

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adults worldwide (1990-2006).³ The number of potential DDIs and associated ADEs is expected to increase as more patients with multimorbidity require polypharmacy.⁴ While clinically significant DDIs are an important cause of preventable ADEs, not all DDIs cause harm or require therapy modification.⁵

Although all investigational new drugs undergo testing for DDI potential during development,^{6,7} little is known about the clinical consequences of most DDIs. Large randomized controlled trials rarely evaluate DDIs,⁸ and many putative DDIs are inferred from pharmacologic predictions or case reports,^{9,10} resulting in over 100,000 hypothesized interactions¹¹—many of which may not be clinically significant. This uncertainty makes DDI compendia unreliable¹²⁻¹⁶ and leads to excessive DDI alerts in computerized provider order entry systems,¹⁷ the vast majority of which are routinely overridden.¹⁸⁻²⁰ While, in some cases, DDIs can result in preventable ADEs, in other cases, concerns about potential, yet non-clinically significant DDIs, can lead to underutilization of safe and effective therapies.^{5,9,10} These knowledge gaps highlight the need for pharmacoepidemiologic studies to evaluate the real-world health outcomes of DDIs.²¹⁻²³

This paper reviews core concepts in pharmacoepidemiologic research on DDIs, including definitions, common sources of bias, design strategies to address these biases, and recent advancements in the field. By focusing on core concepts applicable across study designs (cohort, case-control, or self-controlled) and incorporating recent examples, this paper serves as an introductory resource for trainees and researchers new to the field, providing a foundation before they delve into more in-depth, design-specific methodology papers.

2. Definitions

Table 1 presents a summary of definitions commonly used in pharmacoepidemiologic DDI research. Based on their biologic mechanisms, DDIs can be categorized into pharmacokinetic (PK) and pharmacodynamic (PD) interactions.²⁴

PK DDIs occur when one drug (the precipitant)⁹ affects the absorption, distribution, metabolism, or elimination (ADME) of another drug (the object).²⁴⁻²⁶ The clinical outcome of a PK DDI can be a change in either object's effectiveness or toxicity; the precipitant may or may not have its own direct effect on the outcome. For example, gemfibrozil inhibits liver enzymes that metabolize warfarin, increasing warfarin's blood concentration and bleeding risk.²⁷ In this example, gemfibrozil is the precipitant and warfarin is the object. The most common mechanism for recognized clinically significant PK interactions involves inhibition or induction of cytochrome P450 (CYP) enzymes.²⁴ As most CYP substrates are metabolized into inactive metabolites,²⁸ inhibiting CYP enzymes may elevate object drug levels and increase the likelihood of their adverse effects, whereas inducing CYP enzymes may lower object drug concentrations and reduce their effectiveness. However, the opposite may occur when pro-drugs (pharmacologically inactive substances that can be metabolized into active compounds [e.g., clopidogrel]) are metabolized into active metabolites. Other common mechanisms include modulation of UDP-glucuronosyltransferase enzymes²⁹ and drug transporters, such as P-glycoprotein and organic anion-transporting polypeptides.^{24,30-32}

PD DDIs occur when the mechanisms of action of two drugs act synergistically (or antagonistically), resulting in a combined effect on outcome risk that is larger (or smaller) than the effect of either drug alone. PD DDIs do not involve alterations of exposure.²⁵ Examples include the interaction between angiotensin-converting enzyme inhibitors and thiazide diuretics, leading to excessive urine production and low blood pressure,³³ or between naloxone and opioids, where naloxone antagonizes the opioids' effect. In PD DDIs, both drugs typically affect the outcome independently, making the concepts of precipitant and object less applicable.^{9,10} However, when designing a study, one can consider precipitant as the drug that triggers the interaction and object as the drug whose effect is primarily altered. Unlike PK interactions, which are challenging to predict without knowing a drug's potential to affect another drug's ADME, potential PD interactions can usually be inferred from the drugs' mechanisms of action.

The phenomenon of DDI aligns with the epidemiologic concept of interaction, wherein the term interaction refers to one exposure's effect on an outcome being dependent on another exposure's presence.³⁴ Quantitatively, interaction can be assessed on an additive or multiplicative scale as a departure of the effect when both exposures are present from either the sum or product of the effects of the two exposures considered separately, respectively (Figure 1).³⁴ However, pharmacoepidemiologic DDI studies rarely, if ever, evaluate such statistical interactions, as the complexity of confounding (outlined below) precludes valid inferences from simple evaluations of a sum or product term in a statistical model.^{9,10,35}

3. Sources of Bias

This section discusses common sources of bias in pharmacoepidemiologic DDI studies. While many biases affecting single-drug studies also affect DDI studies, the complexity of assessing concomitant exposures presents unique challenges. Here, we highlight biases that are either unique to or more pronounced in DDI studies.

3.1. Exposure misclassification

Exposure misclassification occurs when a patient's drug exposure status is inaccurately categorized.³⁶ In studies using secondary data in real-world settings (e.g., healthcare claims, electronic medical record data), this can result from missing information on medications not captured in the data (e.g., free samples, over-the-counter purchases) and from lack of objective data on actual medication consumption.³⁷ Even when information on days' supply is provided, patients may stop the medication early or never take it.

In DDI studies, where exposure is the concomitant use of multiple drugs, this misclassification is more complex. First, misclassification can occur when measuring the use of each drug. Second, if healthcare providers and patients are aware of a potential interaction, patients may stop one drug or reduce the dose of the interacting drugs. Third, certain interactions can also be avoided by appropriately spacing the medications during the day. In all cases, despite dispensing records showing overlapping supplies of both drugs, patients may not take them concurrently.

3.2. Confounding

Confounding poses a significant challenge in pharmacoepidemiologic studies and is more complex in DDI studies for several reasons. First, each drug involved in a potential DDI can have its own set of confounders.⁹ Second, unless both drugs are one-time exposures like vaccines, it may be uncommon for individuals to initiate both drugs on the same day. For example, in a cohort study of opioid (object) and skeletal muscle relaxant (SMR; precipitant) interactions, patients may: 1) initiate both medications on the same day (synchronically-triggered), 2) initiate SMRs followed by opioids (object/opioid-triggered), or 3) initiate opioids followed by SMRs (precipitant/SMR-triggered) (Figure 2). While biologically it may not matter which drug comes first (with some exceptions^{9,10}), patient characteristics and confounding patterns can vary across these scenarios. On the first day of combination therapy, the synchronically-triggered and opioid-triggered groups are new opioid users, whereas the SMR-triggered group includes prevalent, and more likely, chronic opioid users. These groups may have different outcome risks when they encounter a potential DDI, and different reasons for initiating the second drug (or both drugs simultaneously), which may have different associations with the outcome. For this reason, DDI studies are often designed to evaluate these scenarios separately when sample size allows.³⁸⁻⁴¹ Moreover, assessing these scenarios separately examines different clinical questions. In the example above, the questions are 1) the effect of initiating SMRs among new opioid users; 2) the effect of initiating opioids in patients already using SMRs; and 3) the effect of initiating SMRs in patients already using opioids.

3.3. Immortal time bias

Immortal time bias arises when eligibility criteria are applied after follow-up begins or when exposure is misclassified by using post-eligibility information,⁴² resulting in an artificially lowered outcome rate in one of the exposure groups.⁴³ Pharmacoepidemiologic DDI research is particularly prone to this bias because exposure often involves the concomitant use of multiple drugs that may not be initiated at the same time. For example, in studies comparing two-drug combination therapy to single-drug therapy, follow-up may begin with the initiation of the object drug, but patients are classified as “exposed” only after the precipitant is added. To be eligible as exposed, patients must remain outcome-free during the “immortal time” between starting the object and adding the precipitant, which biases the results in favor of the combination therapy group.

3.4. Direct effect of precipitant drug versus an interaction

In some DDI research, a unique challenge is discerning the effect of DDI from the direct effect of the precipitant. This is particularly relevant in evaluating PD DDIs, where each drug may independently affect the outcome, producing an additive effect (the sum of individual effects), rather than a true DDI (synergistic effect above and beyond the additive effect) as defined in Figure 1. For instance, when examining the interaction between opioids and gabapentinoids and its effect on fall-related injury, either drug can independently cause central nervous system (CNS) depression and increase fall risks.³⁹ Comparing combination therapy to each drug alone may show differences in fall risks due to the precipitant’s direct effect rather than a true DDI. Therefore, accounting for the direct effect of the individual

drug is essential when the aim is to evaluate the pure effects of the DDI. In many PK DDIs, the precipitant usually does not directly affect the outcome, making this distinction less relevant; however, if the precipitant may have an effect, it must be accounted for, if the goal is to assess only the interaction effect.

3.5. Other sources of bias in DDI studies

Like pharmacoepidemiologic studies of single-drug exposures, DDI studies can incur bias due to depletion of outcome susceptible individuals, outcome misclassification, informative censoring, differential outcome surveillance, and other sources, as described in the pharmacoepidemiology literature.⁴⁴⁻⁴⁶

4. How to design a DDI study

This section covers strategies to avoid or mitigate previously described biases when designing a pharmacoepidemiologic DDI study. While most of these strategies apply to any study design (cohort, case-control, or self-controlled), most examples are from cohort studies, as cohort design remains the most commonly used design for investigating DDIs. For a concise overview, refer to Table 2, which outlines various design considerations, including those not elaborated below, along with examples from the literature.

4.1. Formulating the research question

The first step is to formulate the research question by determining the study population, the drug combination of interest, the comparison group, and the outcome. For example, one may investigate whether, in patients receiving oxycodone, the concurrent use of clarithromycin versus non-use is associated with the risk of opioid overdose. As previously discussed, if the precipitant has a direct effect on the outcome, it is crucial to decide whether the research aims to assess the overall effect of combination therapy, regardless of whether the effect is due to the direct (additive) effect of the added drug or a DDI, or to specifically evaluate the interaction effect itself (e.g., synergistic effect above and beyond the additive effect). This decision may change the study design: for the former objective, a nested active comparator design can be used (see Section 4.2).^{9,10} For the latter objective, a more complex design may be necessary (see Section 4.6).

4.2. Restricting to person-time exposed to one of the drugs

Selecting an appropriate study design is crucial to addressing the multiple sources of confounding in a DDI study. Specifically, by requiring that all study individuals take one of the drugs, we can largely, though not always completely, control for confounding associated with the use of that drug. For example, to study the effect of potential DDI between opioids (object) and SMRs (precipitant) on the risk of opioid overdose, one can require that both treatment groups are taking opioids at the start of follow-up.^{41,47} Restricting person-time under evaluation to that exposed to one of the drugs is a common technique not only in cohort or (nested) case-control studies^{38,41,47-49} but also in self-controlled designs.⁵⁰⁻⁵³ This approach makes treatment groups more similar, reduces confounding, and simplifies the complex dual-drug exposure study into a single-drug exposure study nested in the person-time exposed to one of the drugs. It generally makes sense to ensure treatment

groups are similar regarding object drug exposure, as it is the object's effect on the outcome that is often modified by a potential DDI. With PD DDIs, where the distinction between an object and a precipitant is less applicable, the clinical/research question should drive the study design decision on restriction. For example, in a study evaluating the effect of adding a gabapentinoid to an opioid on the risk of falls, one may require that all individuals in the study are on opioid therapy.³⁹

4.3. Choosing a comparator for the precipitant

Once the study question is defined and the decision to restrict the study population to those exposed to one of the drugs is made, the next step is to choose a comparator for the precipitant, considering the associated confounding. For example, when studying the potential PK DDI between oxycodone (a CYP3A4 substrate, object) and clarithromycin (a CYP3A4 inhibitor, precipitant) and the risk of opioid overdose, one could compare patients exposed to both oxycodone and clarithromycin to those exposed to oxycodone only. However, as in studies of single-drug exposure, using a non-user comparator presents challenges such as residual confounding, differential surveillance, and potential for immortal person-time.^{54,55} Using an active-comparator, new-user design can help avoid or mitigate these challenges. An ideal active comparator for the precipitant drug should meet at least three criteria: 1) clinical interchangeability with the precipitant to minimize confounding by indication; 2) no interaction with the object, allowing elucidation of the interaction's effect; and 3) no direct effect on the outcome that is different from the precipitant's. In the example above, a suitable active comparator for clarithromycin may be a macrolide antibiotic that neither inhibits CYP3A4 nor interacts with oxycodone. Since all macrolide antibiotics inhibit CYP3A4 to some extent, azithromycin, with the weakest inhibitory effect, may be suitable.^{56,57}

When no active comparator is available, one can compare exposure to both drugs with exposure to only one of the drugs (no use of the precipitant).^{48,50,51} However, the likelihood and amount of residual confounding and time-related bias are often much greater without an active comparator.⁵⁸ Self-controlled designs can be considered as a means of controlling between-person confounding in such scenarios,^{35,50-53} but they remain susceptible to bias due to time-varying confounding associated with the initiation or discontinuation of the precipitant.^{46,59}

4.4. Choosing the start of follow-up

In single-drug studies, a new user design reduces bias by standardizing the start of follow-up and ensuring that covariate and eligibility assessments precede treatment assignment and follow-up.⁶⁰ This approach is also crucial in DDI studies, where follow-up for DDI-exposed individuals (or person-time) begins with the incident use of combination therapy. To avoid immortal time bias in a cohort study, follow-up for patients using combination therapy should only begin when they initially meet the definition for exposure to combination therapy, such as the first day with active supplies of both prescriptions, regardless of which drug was initiated first. Section 3.2 discusses different initiation orders of a two-drug combination and the importance of examining each initiation order separately. Figure 2 illustrates the index date and follow-up for each order.

In studies comparing combination therapy versus single-drug therapy, the latter group often lacks a clear anchor time point for the start of follow-up. Several approaches have been adopted to assign an index date for the single-drug therapy group, such as applying time-varying exposure⁶¹⁻⁶³ and using the prevalent new user design.^{64,65} For instance, when examining a potential PD interaction between sulfonylureas and β -blockers and its impact on hypoglycemia risk, Dimakos *et al.* began following patients at their first prescriptions for sulfonylureas,⁶³ and classified each day during follow-up based on exposure status as: solely to sulfonylureas, concurrent usage of sulfonylureas and β -blockers, or no sulfonylureas exposure. The comparison of interest was the outcome rate during person-time co-exposed to sulfonylureas and β -blockers versus that during single-drug exposure to sulfonylureas only. This time-varying exposure approach helps assign the index date for the single-exposure group and avoid immortal time bias; however, time-varying confounding should be taken into account.⁶¹ Prevalent new user design and target trial emulation have emerged recently as robust alternatives to time-varying exposure in situations when an active comparator is not available.^{66,67} Both approaches hold substantial promise for DDI studies comparing a combination therapy with a single-drug therapy.

4.5. Sensitivity analysis for defining exposure and at-risk time

In most claims-based DDI studies, concomitant exposure is defined based on overlapping days' supply of the drugs of interest. For example, in a cohort study, concomitant exposure may start at the initiation of the precipitant while the patient is still taking the object and continue for as long as both drugs are taken, based on recorded or estimated days' supply for each. A grace period might be added to the object, the precipitant, or both, to account for non-adherence, late refilling, or long half-life of a medication.⁶⁸ However, as described in Section 3.1, some patients may stop a drug early or while they are on a course of the precipitant, but this may not be apparent in the data. Therefore, sensitivity analyses varying the definition of exposure can be useful to assess the robustness of findings to assumptions about utilization patterns.⁶⁸

4.6. Using a negative control for the object

A negative control for the object can serve several purposes, such as distinguishing the effect of a DDI from the direct effects of the precipitant and assessing the extent of residual bias after other bias-mitigating strategies have been implemented.^{9,10} An ideal negative control for the object would be a medication used for the same indications as the object under investigation but known not to interact with the precipitant.^{9,10} For example, in a cohort study assessing the risk of hypoglycemia among users of sulfonylureas (object) and fenofibrate (precipitant), Leonard *et al.* used metformin as a negative control object to distinguish the effect of DDI from the potential hypoglycemic effect of fenofibrate in the absence of sulfonylureas, as metformin is an antidiabetic not believed to interact with fenofibrate.⁶⁹ Negative control objects are often used in self-controlled designs to control confounding and design-related bias.^{52,70,71} The extent to which a negative control object accounts for bias depends on how similar the mechanism and magnitude of bias are between the potentially interacting drug pair of interest and the negative control drug pair. Negative controls can be used not only to assess remaining bias qualitatively but also to estimate the effect of DDI quantitatively. For example, when assessing the potential PD

interaction between nonsteroidal anti-inflammatory drugs (NSAIDs) and renin-angiotensin system (RAS) inhibitors on the risk of acute kidney injury (AKI), since either drug has a direct effect on the outcome, Miano *et al.* used oxycodone as a negative control for NSAIDs and amlodipine as a negative control for RAS inhibitors.⁷² The effect of interaction was examined as a difference-in-difference, comparing the difference in AKI rate between NSAID versus oxycodone among RAS inhibitor users, to the difference in AKI rate between NSAID versus oxycodone among amlodipine users.⁷²

5. Recent Advancements

Recent years have seen substantial research into high-throughput pharmacoepidemiologic DDI screening or data-mining that identify potential DDI safety signals in electronic healthcare data.^{41,71,73-75} These studies, often using self-controlled designs, include users of object drugs who have experienced an outcome of interest and screen numerous concomitant drugs to identify those potentially associated with the outcome. Key strengths of these studies include their ability to screen hundreds-to-thousands of drug combinations simultaneously and control for time-invariant confounders, making them ideal for hypothesis generation. These studies can also integrate with other disciplines; for example, Miano *et al.* combined pharmacoepidemiologic screening with pharmacokinetic approaches to identify clinically significant DDIs involving methadone and buprenorphine.⁶⁸

However, limitations such as time-varying confounding and the possibility of chance findings mean that DDI signals identified in these studies require further vetting and/or validation before they can inform clinical practice. For example, a recent cohort study tested a previously identified signal of overdose risk associated with concomitant use of methadone and simvastatin. Using a more robust design with an active comparator, the study found no similar risk, highlighting the need for formal pharmacoepidemiologic evaluations to confirm or refute DDI signals identified in high-throughput screening.²³

6. Summary

In summary, the real-world health outcomes of many DDIs remain largely unknown, which can lead to preventable ADEs from clinically significant yet unrecognized DDIs, or the underuse of effective therapies due to concerns over DDIs that may not be clinically significant. Pharmacoepidemiologic studies evaluating the real-world health outcomes of potential DDIs are therefore needed to address this knowledge gap. Although designing pharmacoepidemiologic DDI studies presents unique challenges, employing thoughtful design strategies can help mitigate confounding and bias.

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Key Points

- The real-world health outcomes of many drug-drug interactions (DDIs) are largely unknown, potentially leading to preventable adverse drug events from clinically significant yet unrecognized DDIs, or the underuse of effective therapies due to concerns about DDIs that may not be clinically significant.
- Pharmacoepidemiologic studies evaluating the real-world health outcomes of DDIs are critically needed to address this knowledge gap.
- These studies face unique challenges, including bias from multiple sources of confounding, exposure misclassification, mixing the precipitant drug's effect with the interaction effect, and immortal time bias.
- To minimize bias, various design strategies can be applied, such as restriction, active comparators, examining different drug initiation orders, sensitivity analyses for exposure definitions, and using negative controls.

Exposure Groups Defined by Two-Drug Combinations (Drugs A and B)

Exposure Groups	A=0	A=1
B=0	O_{00}	O_{10}
B=1	O_{01}	O_{11}

Interaction on **Additive Scale**:

$$IC_D = (O_{11} - O_{10}) - (O_{01} - O_{00})$$

$IC_D \neq 0$ indicates interaction between drugs A & B

Interaction on **Multiplicative Scale**:

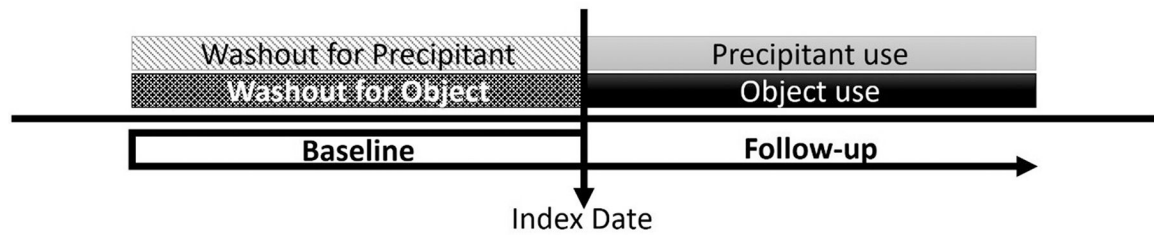
$$IC_M = (O_{11}/O_{10}) \div (O_{01}/O_{00})$$

$IC_M \neq 1$ indicates interaction between drugs A & B

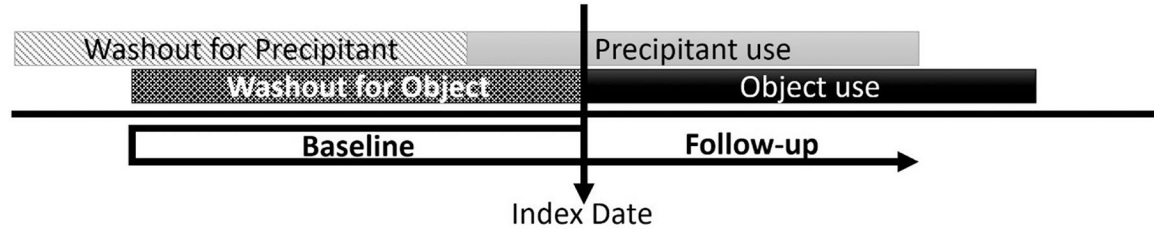
Figure 1. Epidemiologic assessment of interaction between two drugs.

Consider two drugs of interest, labeled A and B. We use a binary indicator to denote exposure to each drug, where '0' indicates no exposure and '1' indicates exposure. Based on the possible combinations of exposure, patients are classified into four groups: 1) unexposed to both A and B (A=0, B=0), 2) exposed to A only (A=1, B=0), 3) exposed to B only (A=0, B=1), and 4) exposed to both A and B (A=1, B=1). The outcomes for these groups are represented as O_{00} , O_{10} , O_{01} , O_{11} , respectively. The interaction is assessed either on an additive scale, with the interaction contrast (IC) IC_D defined as $(O_{11} - O_{10}) - (O_{01} - O_{00})$, or on a multiplicative scale, where IC_M is calculated as $(O_{11}/O_{10}) \div (O_{01}/O_{00})$. A finding of $IC_D \neq 0$ or $IC_M \neq 1$ indicates an interaction between drugs A and B.

Synchronically-Triggered: individuals initiate object and precipitant on the same day



Object-Triggered: individuals with ongoing precipitant use initiate object



Precipitant-Triggered: individuals with ongoing object use initiate precipitant

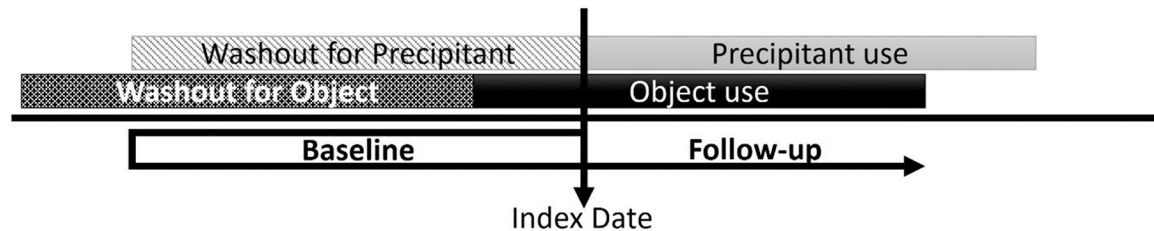


Figure 2. Initiation orders for a two-drug combination and the appropriate timing for follow-up start.

For a two-drug combination, there are three possible orders in which the combination therapy is initiated: 1) Synchronically-triggered, where individuals initiate both object and precipitant on the same calendar day; follow-up starts on the day both drugs are initiated. 2) Object-triggered, where individuals initiate precipitant first and object later; follow-up starts on the day the object is initiated. 3) Precipitant triggered, where individuals initiate the object first and precipitant later; the follow-up starts on the day the precipitant is initiated.

Table 1.
Definitions commonly used in pharmacoepidemiologic DDI research

Terminology	Definition	Example
Pharmacokinetic (PK) interaction	One drug affects the absorption, distribution, metabolism, or elimination (ADME) of another drug.	Omeprazole, a CYP2C19 inhibitor, reduces the effectiveness of clopidogrel, a prodrug, by inhibiting its biotransformation into an active metabolite. ⁷⁶
Pharmacodynamic (PD) interaction	The mechanisms of action of two drugs act synergistically (or antagonistically), resulting in a combined effect on outcome risk that is larger (or smaller) than the effect of either drug alone	Synergistic interactions: Combined use of quinolones and macrolides may result in a greater risk of QT-interval prolongation compared to the use of either drug alone. ⁷⁷ Antagonistic interactions: Combined use of aspirin and ibuprofen leads to reduced antiplatelet effect of aspirin. ⁷⁸
Object drug (the object in the DDI)	The drug whose ADME is affected in a PK interaction. In PD interactions, this definition is less applicable; however, when designing a study, the drug whose effect is primarily altered can be considered the object drug.	In the above example of PK interaction between omeprazole and clopidogrel, clopidogrel is the object drug.
Precipitant drug (the precipitant in the DDI)	The drug that alters the other drug's ADME in a PK interaction. In PD interactions, this definition is less applicable; however, when designing a study, the drug that triggers the interaction can be considered as the precipitant drug.	In the above example of PK interaction between omeprazole and clopidogrel, omeprazole is the precipitant drug.
Substrate	Drugs that bind to the active site of an enzyme or transporter and, while present in the active site, are transformed into metabolites or are transported. ⁷⁹	Clopidogrel is a substrate of CYP2C19.
Inducer	Drugs that increase the metabolic activity of an enzyme or a transporter.	Carbamazepine is an inducer of P-glycoprotein.
Inhibitor	Drugs that decrease the metabolic activity of an enzyme or a transporter.	Omeprazole is an inhibitor of CYP2C19 enzyme.
Direct effect	The independent effect of a drug when administered alone.	In the above example of PD interaction between quinolones and macrolides, each drug class has a direct effect on the risk of QT-prolongation, without the co-presence of the other drug.

Abbreviations: ADME=absorption, distribution, metabolism, or elimination; CYP=Cytochrome P450; DDI=drug-drug interaction; PD=pharmacodynamic; PK=pharmacokinetic.

Table 2.
Key considerations for designing pharmacoepidemiologic studies to evaluate DDI

Key Considerations	Recommendations	Examples
Formulate the research question	For PK interaction, the research question is typically straightforward. For PD interaction, it is crucial to define upfront whether the goal is to assess the clinical outcomes of combining the drugs of interest, regardless of whether the effect is due to the direct (additive) effect of the added drug or a DDI, or to specifically evaluate the effect of the DDI itself (e.g., synergistic effect above and beyond the additive effect).	In a cohort study investigating the combined effect of opioids and gabapentinoids on the risk of fall-related injury, a potential PD interaction, Chen <i>et al.</i> prespecified the aim of the study as determining whether combining opioids with gabapentinoids vs. opioids alone is associated with a risk of fall-related injury, regardless of whether the effect is due to the direct effect of gabapentinoids or to a true DDI (i.e., synergistic effect above and beyond the additive effect).³⁹ In a cohort study examining the nephrotoxic effects of combining nonsteroidal anti-inflammatory drugs (NSAIDs) with renin-angiotensin system inhibitors, a potential PD interaction, Miano <i>et al.</i> focused on the specific effect of the DDI (i.e., synergistic effect above and beyond the additive effect), rather than merely comparing the effects of dual-drug use vs. single-drug use.⁷²
Examine different initiation orders of object and precipitant	The order in which drugs are initiated can lead to differences in patient characteristics and confounding patterns. Therefore, it may be appropriate to examine different initiation orders independently through separate studies. Each initiation order also represents a distinct clinical question for the study to answer.	In a cohort study evaluating the risk of injury associated with concomitant use of opioids and SMRs, Chen <i>et al.</i> created three cohorts for each opioid examined based on the drug initiation order: patients who initiated both drugs simultaneously (synchronously-triggered), those who initiated SMRs first and then opioids (opioid-triggered), and those who initiated opioid first and then SMRs (SMR-triggered). The patient characteristics, confounding patterns, and results differed by the drug initiation order. ³⁸
Restrict study to person-time exposed to one drug in the combination	By restricting the study to person-time exposed to one drug in the combination, we can reduce confounding and simplify a complex multiple-drug exposure study to a single-exposure study nested in the person-time exposed to the other drug.	In a self-controlled case series study examining the potential PK interaction between warfarin (object) and sulfonylureas (precipitant), Nam <i>et al.</i> restricted the analysis to person-time during warfarin use, and compared the outcome rates during person-time with vs. without concomitant sulfonylureas. ⁵¹
Choose a comparator for the precipitant	Using an active comparator for the precipitant can mitigate confounding associated with its use. An ideal comparator for the precipitant should meet at least three criteria: 1) clinical interchangeability with the precipitant to minimize confounding by indication; 2) no interaction with the object, allowing elucidation of the interaction's effect; and 3) no direct effect on the outcome that is different from the precipitant's.	In a cohort study examining the potential PK interaction between oxycodone (object) and SSRIs that were potent CYP2D6 inhibitors (precipitants), and its association with the risk for opioid overdose, Yunusa <i>et al.</i> used other SSRIs that were weak CYP2D6 inhibitors as the active comparator. ⁸⁰
Choose the start of follow-up	Starting follow-up when and only when patients first meet the definition of exposure to the combination therapy can help align the beginning of the observation period and avoid immortal time bias.	In a cohort study comparing the risk of ischemic stroke among users of clopidogrel and different proton pump inhibitors, Leonard <i>et al.</i> started following patients when they were first co-exposed to the combination therapy, irrespective of the order in which the individual drugs were initiated. ⁸¹
Sensitivity analysis to define exposed person-time	Sensitivity analyses can be useful to address potential misclassification of exposure. Possible strategies include: 1) allowing or excluding a grace period following the recorded days' supply for the object, precipitant, or both; and 2) redefining concomitant use by requiring varying lengths of overlapping day's supply.	In a cohort study examining the concomitant use of sulfonylureas and β-blockers and the risk of severe hypoglycemia, Dimakos <i>et al.</i> used different grace periods (30-day, 15-day, and 60-day) to define exposure episodes.⁶³ We did not find examples of redefining concomitant use by requiring varying lengths of overlapping days' supply.
Use a negative control for the object	Using a negative control for the object can help differentiate the effect of DDI from the direct effect of the precipitant. An ideal comparator for the object should meet at least two criteria: 1) clinical interchangeability with the object of interest; 2) no interaction with the precipitant.	In a cohort study assessing the risk of hypoglycemia among users of sulfonylureas (object) and fenofibrate (precipitant), Leonard <i>et al.</i> used metformin as a negative control object to distinguish the effect of a DDI from the potential hypoglycemic effect of fenofibrate in the absence of sulfonylureas, as metformin is an antidiabetic not believed to interact with fenofibrate. ⁶⁹

Key Considerations	Recommendations	Examples
Dual-control design for both object and precipitant	In DDIs where either drug alone can independently affect the outcome, a dual-control design involving negative controls for both the object and the precipitant drugs may be necessary to quantitatively isolate the effect of the DDI (e.g., synergistic effect above and beyond the additive effect) from the direct (additive) effect of the second/precipitant drug.	In a cohort study assessing the potential PD interaction between NSAIDs and renin-angiotensin system (RAS) inhibitors on the risk of acute kidney injury (AKI), since either drug has a direct effect on the outcome, Miano <i>et al.</i> used oxycodone as a negative control for NSAIDs and amlodipine as a negative control for RAS inhibitors. The effect of interaction was examined as the difference-in-difference, comparing the difference in AKI rate between NSAID vs. oxycodone among RAS inhibitor users, to the difference in AKI rate between NSAID vs. oxycodone among amlodipine users. ⁷²
Consider using a negative control outcome*	Using a negative control outcome can help detect unmeasured confounding. An ideal negative control outcome is an outcome known to be unrelated to the combination therapy. ⁸²	In a cohort study comparing the risk of opioid overdose among users of SMRs and opioids, Khan <i>et al.</i> used sepsis as a negative control outcome to assess the presence of confounding by unmeasured illicit opioid use. ⁴¹
Examine the time course of the interaction*	As with single-exposure studies, in DDI research, risk of outcome may change depending on the duration of combination therapy. Stratifying the follow-up time enables one to examine the time course of the interaction.	In a cohort study comparing the risk of gastrointestinal bleeding and intracranial hemorrhage among concomitant users of warfarin and antithyroidipidemics, Leonard <i>et al.</i> stratified follow-up into prespecified, mutually exclusive time intervals (1-10, 11-20, 21-30 days) to examine the duration-response relationship between concomitant therapy and the outcome. ²⁷

Abbreviations: AKI=acute kidney injury; CYP=Cytochrome P450; DDI=drug-drug interaction; NSAIDs=nonsteroidal anti-inflammatory drugs; PD=pharmacodynamic; PK=pharmacokinetic; RAS=renin-angiotensin system.

* Not discussed in the main text.