Published in final edited form as:

Clin Pharmacol Ther. 2016 January ; 99(1): 92–100. doi:10.1002/cpt.277.

Pharmacoepidemiologic Methods for Studying the Health Effects of Drug-Drug Interactions (DDIs)

S Hennessy¹, CE Leonard¹, JJ Gagne², JH Flory^{1,3}, X Han¹, CM Brensinger¹, and WB Bilker¹

¹Center for Pharmacoepidemiology Research and Training, Center for Clinical Epidemiology and Biostatistics, and Department of Biostatistics and Epidemiology, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA

²Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, 1620 Tremont Street, Suite 3030, Boston, Massachusetts, USA

³Division of Comparative Effectiveness and Outcomes Research, Department of Healthcare Research and Policy, Weill Cornell Medical College, New York, New York, USA and Endocrinology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York, USA

Keywords

drug interactions; pharmacoepidemiology; research design

Introduction

A drug-drug interaction (DDI) occurs when one or more drugs affect the pharmacokinetics (the body's effect on the drug) and/or pharmacodynamics (the drug's effect on the body) of one or more other drugs. Pharmacoepidemiologic studies are the principal way of studying the health effects of potential DDIs. This paper discusses aspects of pharmacoepidemiologic research design that are particularly salient to the design and interpretation of pharmacoepidemiologic studies of DDIs.

Correspondence: Sean Hennessy, PharmD, PhD, University of Pennsylvania Perelman School of Medicine, 423 Guardian Drive / 803 Blockley Hall, Philadelphia, Pennsylvania 19104 USA, fax: 215-573-5315, phone: 215-898-9112, hennessy@upenn.edu.

Author Contributions

SH wrote the first draft, which all authors provided input on.

Conflict of Interest / Disclosure

SH receives salary support through his employer for a study funded by AstraZeneca and Bristol-Myers Squibb, oversees a pharmacoepidemiology training program that receives support from Pfizer Inc and Sanofi, and in the past year has served as a consultant to Abbvie Inc, Merck Sharpe & Dohme Corp, Collegium Pharmaceutical Inc and a law firm representing Hoffman-LaRoche. JJG is a consultant to Aetion, Inc., a software company. WBB serves as a consultant to Johnson & Johnson. None of the other authors reports relevant relationships.

Why Conduct Pharmacoepidemiologic Studies of the Health Effects of DDIs?

Although the frequency with which DDIs cause adverse health outcomes is not well known, in older adults, DDIs are estimated to cause 13% of adverse drug events (ADEs) (1) and 5% of hospital admissions.(2) Because per capita drug consumption continues to rise, especially in older adults, the clinical and public health consequences of DDIs will rise correspondingly. In 2014, the US Department of Health and Human Services issued a national action plan for ADE prevention that focuses on three common, severe, and potentially preventable ADEs: bleeding from anticoagulants; hypoglycemia from antidiabetic drugs; and overdose, sedation, and respiratory depression from opioids.(3) This national action plan lists the identification and prevention of DDIs as crucial steps in reducing the frequency of ADEs of high clinical and public health importance.

Numerous pharmacokinetic and pharmacodynamic mechanisms are responsible for DDIs. (4,5) In two-drug DDIs, the affected drug in a DDI is called the *object* (or *victim*) and the affecting drug is called the *precipitant* (or *perpetrator*). Many pharmacokinetic DDIs result in an exaggerated pharmacologic response of the object. The precipitant may or may not have an inherent effect on the rate of the outcome in the absence of the object. For example, in a study of potential DDIs with warfarin as the object, nonsteroidal anti-inflammatory drugs but not antibiotics as precipitants would be expected to increase bleeding risk in persons not taking warfarin.

Because the pharmacokinetic and pharmacodynamic pathways of most drugs are not fully elucidated, it can take many years to identify, confirm, and fully understand a DDI. For example, tamoxifen and paroxetine were approved in 1977 and 1992 respectively, although it was not until 2003 that scientists identified a potential DDI between them that may reduce tamoxifen's effectiveness in reducing the frequency of breast cancer.(6) Despite over a decade of subsequent research, the clinical importance of this DDI remains controversial.(7)

An unknown but probably small proportion of potential DDIs that can be predicted based on mechanism actually result in observable health outcomes. False warnings about DDIs that are sent to clinicians in the context of computerized clinical decision support reduce the use of otherwise valuable medications and contribute to "alert fatigue".(8) Therefore, important aspects of the DDI research agenda include evaluating the health consequences of hypothesized DDIs and stratifying individual patients with regard to risk. Risk stratification is challenging, however, because pharmacoepidemiologic studies of even average health effects of DDIs require very large population databases, since only a small proportion of any population will concomitantly receive the object together with the precipitant, and because the study outcomes are often rare. Characterizing treatment effect heterogeneity naturally requires even larger databases than identifying population-average effects.

Research on DDIs occurs in many different systems and over many different scales across the translational spectrum, including *in vitro* studies of drug-enzyme interactions; physiologically-based pharmacokinetic modeling to predict pharmacokinetic DDIs; experimental studies of animals and humans on the effects DDIs on serum drug

concentrations; hypothesis-free scanning (i.e., data mining) of data such as published literature, anecdotal case reports of ADEs, and healthcare data to identify previously unhypothesized DDIs; observational studies of the effects of DDIs on biomarkers such as hemoglobin A1c; pharmacoepidemiologic studies of the health effects of hypothesized DDIs; and studies of the optimal design and performance of systems to reduce the frequency or clinical impact of deleterious DDIs.(9) These diverse research goals and approaches are complementary in identifying, confirming, elucidating and hopefully preventing harmful DDIs. This review focuses on the methods for pharmacoepidemiologic studies using systematically collected, longitudinal healthcare data (i.e., excluding databases of anecdotal ADE reports) to study the effects of hypothesized DDIs on health outcomes and clinically-measured biomarkers. Readers are referred elsewhere (10,11) for overviews of design considerations for pharmacoepidemiologic studies in general.

Selecting an Overall Research Design

Because of ethical and logistical considerations, studies designed to examine adverse health effects of potential DDIs in humans are almost always non-experimental pharmacoepidemiologic studies. This is because equipoise seldom exists to intentionally expose human research subjects to a potentially harmful and avoidable DDI. Further, even if ethical, it would be impractical to enroll in a trial the number of subjects needed to identify effects on rare health outcomes. Table 1 lists pharmacoepidemiologic designs used to study the health effects of DDIs. The most basic and intuitive epidemiologic design is the cohort study, which compares the frequency of an outcome in different groups (i.e., cohorts) that are defined based on exposure. One possible but, as we shall see, generally unhelpful approach to assessing whether a health-affecting DDI exists is to measure the incidence rate (IR) of the adverse health outcome in four cohorts: 1) those taking the object with the precipitant (IR_{11}), 2) those taking the object without the precipitant (IR_{10}), 3) those taking the precipitant without the object (IR_{01}), and 4) those taking neither the object nor the precipitant (IR_{00}) (Table 1, Design 1). For DDI effects defined as a departure from multiplicity, an effect would be inferred if the following null hypothesis (H_0) were rejected:

$$H_0:(IR_{11}/IR_{00})=[(IR_{10}/IR_{00}) \times (IR_{01}/IR_{00})].$$

This is to say that an effect of a DDI defined as departure from multiplicity would be inferred if the rate ratio for both-exposed vs. neither-exposed were statistically different (i.e., either higher or lower) than the object-exposed vs. neither-exposed rate ratio multiplied by the precipitant-exposed versus neither-exposed rate ratio. For DDI effects defined as a departure from additivity, an effect would be inferred if the following null hypothesis were rejected:

$$H_0:(IR_{11}-IR_{00})=[(IR_{10}-IR_{00})+(IR_{01}-IR_{00})].$$

This is to say that an effect of a DDI defined as a departure from additivity would be inferred if the rate difference between the both-exposed versus the neither-exposed were statistically different than the object-exposed versus neither-exposed rate difference plus the

precipitant-exposed vs. neither-exposed rate difference. In practice, Design 1 is rarely if ever used to identify either multiplicative or additive effects of potential DDIs. This is because Design 1 implausibly assumes that neither the object nor the precipitant have clinical indications (i.e., reasons for taking the drug) that affect the outcome rate, or that these indications can be fully measured and controlled for. However, persons taking a given drug (whether object or precipitant) generally have an indication for that drug, while persons not taking the drug generally do not. Pharmacoepidemiologists often use the term “indication” as shorthand for denoting all of the observed and unobserved factors that lead to a given patient receiving a particular medication rather than a comparator medication, or no treatment. If any aspect of this indication (or contraindication, i.e., reason to avoid a given drug) directly affects the risk of the outcome or is otherwise associated with the outcome, then *confounding by indication* exists. Such confounding can cause the observed association to differ from the true causal effect. Confounding by indication is among the most important challenges facing pharmacoepidemiologists. Given the widespread potential for confounding by indication, it is often unrealistic to assume that the baseline rate of those taking a drug is the same as that in those not taking the drug.

If use of the precipitant in the absence of the object has no effect on the outcome, and if the precipitant is not used for an acute indication that affects or is otherwise associated with the outcome, then one can use Design 2. Design 2 is a cohort or nested case-control design that measures, within person-time exposed to the object, the incidence rate ratio of the outcome in those taking the precipitant versus in those not taking the precipitant. For example, Juurlink et al. used a healthcare database from older adults in Ontario to conduct a case-control study, nested within person-time exposed to glyburide. Their aim was to examine the association between use versus non-use of cotrimoxazole and severe hypoglycemia.(12) They found that the adjusted odds ratio (OR) for the association between cotrimoxazole use and severe hypoglycemia was 6.6 (95% confidence interval [CI]: 4.5 – 9.7). The exposure OR is the measure of association produced in case-control studies. If a case-control study uses a sampling frame known as *risk set sampling* for selection of controls, then the resulting OR is an unbiased estimator of the incidence rate ratio (IRR) that would have been produced by an analogous cohort study.(13) Risk set sampling randomly selects controls from the underlying cohort of those who were still at risk of the outcome when the corresponding case experienced the outcome. The advantage of the nested case-control design for studies that use existing data is that it is less computationally intensive than the corresponding cohort study. Given the high computational intensity of cohort studies that account for time-varying exposures and potential confounders like concomitant medications, this computational efficiency can be more important in studies of DDIs than in studies of individual drugs that do not account for time-varying exposures and confounders. However, when conducting nested case-control studies, care is needed in defining the time at which potential confounding variables are assessed. In a cohort study, it is intuitive and correct to assess confounding variables at baseline, before exposure has begun. However, many nested case-control studies assess potential confounders as of the index date. In case-control studies, the index date is the date of the outcome in cases and some corresponding date in controls. Potential confounders that are assessed after exposure can be affected by exposure. Adjusting for factors that are affected by exposure can introduce bias unless the analysis

uses appropriate methods for handling time-varying confounding.(14) Therefore, ascertaining covariates at the index date can introduce bias into nested case-control studies.

The IRR for presence vs. absence of the precipitant among persons taking the object can be interpreted as the effect of a DDI (as in Table 1, Design 2) if there is no unmeasured confounding by the indication for the precipitant. Unfortunately, this assumption is often implausible. To assess its validity, investigators sometimes measure the corresponding association with a *negative control precipitant*. A negative control precipitant is a drug that is used in similar clinical circumstances as the potential precipitant under study, yet by virtue of the control precipitant's pharmacology is not believed to interact with the object. In the setting of Design 2, the association with the negative control precipitant is used qualitatively to place into context and aid in the interpretation of the association measure for the precipitant of interest. For example, in the previously-described study that measured the OR for the association between cotrimoxazole as the precipitant and severe hypoglycemia among persons receiving glyburide (the object), the investigators also examined the association with amoxicillin as a negative control precipitant. In that study, the association between amoxicillin and severe hypoglycemia (adjusted odds ratio 1.5; 95% 0.8 – 2.9) helped provide reassurance that the association with cotrimoxazole (adjusted odds ratio 6.6) was unlikely to be due primarily to confounding by the need for an antibiotic. (12) To help distinguish a DDI between an inherent effect of the precipitant, one can measure the association between the precipitant and the outcome within the person-time exposed to a *negative control object*. A negative control precipitant is a drug that is used for similar indications as the object under study, but is not believed to interact pharmacologically with the precipitant. For example, in a study of DDIs between sulfonylureas as objects and antihyperlipidemics as precipitants, Leonard et al. (15) used metformin as a negative control object, which is not believed to interact with the precipitants.

Design 3 is just like Design 2 except that the association measure is the IRR (or OR) of the precipitant of interest explicitly versus the control precipitant, among persons taking the object. For example, Leonard et al. conducted a cohort study of persons taking clopidogrel, examining the rate of ischemic stroke among persons taking individual proton pump inhibitors, each versus pantoprazole as the negative control precipitant.(16) Pantoprazole was selected as the control precipitant because it is not a potent inhibitor the enzyme responsible for activating clopidogrel (CYP2C19) and therefore considered to have a low potential for interacting with with clopidogrel. The advantage of Design 3 over Design 2 is that it uses the association between the outcome and the control precipitant quantitatively rather than qualitatively.

Although using a negative control precipitant can be a valuable strategy, there are at least three reasons why it is not a panacea for the problem of confounding by the indication for the precipitant. First, there are potential DDIs for which there is not a plausible negative control precipitant. For example, if one wanted to examine whether aspirin as the precipitant increased the risk of serious bleeding in patients receiving warfarin as the object, it would be difficult to identify a negative control precipitant that had the same set of indications as aspirin and was not believed to increase the risk of bleeding in patients taking warfarin. Second, even if there is a plausible negative control precipitant, there may still be residual

unmeasured confounding between the precipitant and the negative control precipitant. For example, when amoxicillin is used as a control precipitant in studies examining cotrimoxazole as a potential precipitant, there may be residual confounding because amoxicillin and cotrimoxazole are not used in identical groups of patients. Third, there can be no guarantee that the control precipitant does not have an unknown interaction with the object or unknown direct effect on the outcome. This is particularly true for older drugs, for which pharmacokinetic pathways and pharmacodynamic effects are often less well studied than for newer drugs.

Self-controlled designs include only persons who experienced the outcome, using each person as her/his own control. Such designs therefore inherently control for both measured and unmeasured potential confounding factors to the extent that such factors do not change within individual over the study period. Self-controlled designs are useful for identifying short-term effects of acute or intermittent exposures, which are often of interest in studies of DDIs. The self-controlled case series (SCCS) design is a self-controlled design that is analogous to the cohort design.⁽¹⁷⁾ The case-crossover design is a self-controlled design that is analogous to the nested case-control study design.⁽¹⁷⁾ Design 4 is a SCCS or case-crossover study nested within person-time exposed to the object, examining the incidence rate ratio (or OR) associated with use versus nonuse of the precipitant. For a SCCS or case-crossover study to be feasible, there must be within-person variability in exposure to the precipitant while the person is taking the object. That is, a person whose entire time taking the object is either always co-exposed or never co-exposed to the precipitant will not contribute any information to the analysis of a self-controlled study of the DDI. Thus, on one hand, self-controlled designs are better suited to examine DDIs involving precipitants that are taken acutely or episodically rather than chronically. On the other hand, acutely-taken drugs often have acute indications that may affect the rate of the outcome, rendering the design susceptible to within-person confounding by indication. For example, Schelleman et al. used the case-crossover design to examine the within-person association between use of antibiotics as precipitants and hospitalization for gastrointestinal bleeding among persons taking warfarin as the object.⁽¹⁸⁾ They found that all antibiotics examined were associated with an elevated rate of bleeding, including those not believed to interact pharmacokinetically with warfarin. However, there were large differences among antibiotics. The fact that all antibiotics were associated with an increased rate of bleeding suggests either that 1) all antibiotics share a mechanism for causing bleeding in persons taking warfarin (and possibly even those not taking warfarin), or that 2) the indication for antibiotics—acute infection—itself is associated with bleeding in those taking warfarin (and possibly even those not taking warfarin). Clinically, whether the increased bleeding risk observed during antibiotic use is due to a DDI, is a shared effect of all antibiotics, or is an inherent effect of infection may not matter as long as clinicians monitor anticoagulated patients carefully during episodes of acute infection. Thus, from a methodologic perspective, even though self-controlled designs are generally useful to study acute exposures, within-person confounding by the indication for drugs with acute indications may complicate their use for DDIs when the precipitants have acute indications. Therefore, in the setting of acutely-administered precipitants, a cohort study using a negative control precipitant (Design 3) may be useful in addition to or perhaps instead of a self-controlled study (Design

4), provided that a good negative control precipitant is available. Although self-controlled studies are generally thought of as a poor choice for studying chronically-administered drugs, exposure to medications that are intended to be chronically administered is often actually intermittent because of incomplete adherence or other reasons. Therefore, self-controlled designs can sometimes be useful for studying precipitants that are intended to be used chronically.

Design 5 is a self-controlled case series (or case-crossover study) nested within person-time exposed to the object, explicitly comparing person-time exposed to precipitant vs. a control precipitant. This design would include only persons who took both the precipitant and the negative control precipitant while taking the object, and who experienced the outcome while taking the object plus either the precipitant or the control precipitant. Suppose for example that an investigator wished to perform a self-controlled study to compare bleeding risk in warfarin users associated with concomitant use of cotrimoxazole vs. amoxicillin. A self-controlled study of this question would include only persons who experienced bleeding while treated concomitantly with warfarin plus either cotrimoxazole or amoxicillin as a precipitant, and who also took the alternative precipitant at some point during warfarin therapy. Because few if any such persons are likely to exist even in a large population database, this design seems unlikely to be of practical use.

As is evident from the discussion above, selection of a pharmacoepidemiologic design to study a specific potential DDI includes consideration of numerous factors including the existence of a plausible negative control precipitant and control object, the relative importance of among-person confounding versus within-person confounding, and whether the precipitant is in real life taken acutely or intermittently versus chronically. Investigators studying a given potential DDI should consider using multiple, complementary research designs.

Outcome Validity

The expected outcome of most hypothesized DDIs is an extension of a major pharmacologic effect of object, such as severe hypoglycemia from sulfonylurea antidiabetic agents or bleeding resulting from anticoagulants. Other DDIs may result in reduced effectiveness of the object, such as an increased risk of breast cancer in patients taking tamoxifen concomitantly with drugs that inhibit tamoxifen's conversion to a more active moiety. As noted above, because pharmacoepidemiologic studies of DDIs need to include very large cohorts of persons receiving the object, they are usually performed using pre-existing healthcare data. Thus, investigators' ability to validly (and hopefully completely, or at least in a way that does not lead to biased results) ascertain outcomes that represent toxicity or lack of effectiveness using healthcare data is essential.

Many studies have used review of medical records to examine the validity and performance characteristics of algorithms to identify outcomes using electronic billing data.⁽¹⁹⁾ Such studies usually examine outcomes that reliably result in treatment in the emergency department (ED) and/or hospital admission rather than office-based treatment. Thus, investigators studying the effects of potential DDIs on acute health outcomes usually study

events that lead to ED treatment or hospitalization. Given the transition in the US from the International Classification of Diseases, 9th revision, clinical modification (ICD-9-CM) to ICD-10-CM in October 2015, researchers using administrative data from the US will need to examine the validity of algorithms that use ICD-10-CM codes for identifying outcomes.

As healthcare databases increasingly include laboratory values and vital signs, such measures can also be used as outcomes in DDI studies. A typical study design using such outcomes would examine change in a laboratory value from baseline when a precipitant is initiated in a person receiving an object. For example, changes in serum glucose were used to identify a possible DDI between the antidepressant paroxetine and the statin pravastatin. (20) Changes in average serum glucose were also used in a study of a possible DDI between proton-pump inhibitors and metformin. (21) Compared to studies that rely on binary outcomes such as the occurrence of severe hypoglycemia, studies examining a continuous measure such as serum glucose require much smaller sample sizes and may raise fewer concerns about outcome validity. A related limitation is that such measures are generally intermediate endpoints or biomarkers, rather than the actual clinical events that matter most to patients. In addition, handling of missing data deserves careful consideration, particularly if drug exposure affects the likelihood that providers measure or record the study endpoint.

Using a Positive Control Pair to Assess Assay Sensitivity

The use of a negative control precipitants and control object is discussed above, either as an explicit control group or implicitly to help assess the potential for confounding by the indication for the precipitant, or to help assess an inherent effect of the precipitant in the absence of the object. To assess the sensitivity of the pharmacoepidemiologic study to capture a known DDI similar to the one being studied (i.e., demonstrate the sensitivity of the pharmacoepidemiologic assay), investigators should consider studying a *positive control precipitant*, which is a precipitant known to produce an association with an outcome in patients receiving the object of interest. For example, if one were to study a DDI between warfarin as the object and an antibiotic as the precipitant with bleeding as the outcome, it may be useful to reproduce the well-established DDI between warfarin and cotrimoxazole as a positive control to demonstrate the ability of the study procedures and database to reproduce this known positive association.

Considering Initiation Order of Object and Precipitant

Concomitant administration of an object and a precipitant can be divided into three categories based on order of initiation of the two drugs. When both drugs are initiated simultaneously, the concomitancy is *combination-triggered*. When the object is started in a person already taking the precipitant, concomitancy is *object-triggered*. When the precipitant is started in a person already taking the object, concomitancy is *precipitant-triggered*. An adverse event due to a DDI involving a dose-titrated object may more likely if concomitancy is precipitant-triggered rather than either object-triggered or combination triggered. This is because in precipitant-triggered concomitancy, the dose of the object is titrated to produce its desired effect in a patient who is not receiving the precipitant, which is later followed by initiation of the precipitant. For example, if warfarin is started and

atorvastatin is later added, the prescriber may be unaware of the need to re-titrate the dose of warfarin, (22) and over-anticoagulation and bleeding may result. In contrast, if warfarin and atorvastatin are started simultaneously or if warfarin is started in a patient already receiving atorvastatin, the warfarin dose will be titrated to the desired level of laboratory-measured anticoagulation in the presence of atorvastatin, avoiding clinical consequence of the DDI in that patient, provided that the patient continues to take atorvastatin. Naturally, if the atorvastatin is later discontinued, the patient may be at risk of the effects of under-anticoagulation, i.e., thromboembolic events.

If an investigator wished to include only instances of precipitant-triggered concomitancy to increase the likelihood of identifying a clinically important DDI, a larger study population would naturally be needed to detect the same level of increased risk, since only a subset of all instances of concomitancy are precipitant-triggered. If sufficient sample size is available, it may be desirable to calculate separate measures of association for precipitant triggered, object triggered, and combination triggered concomitancy when studying dose-titrated objects.

When studying precipitant-triggered and object-triggered concomitancy, it is critical to avoid including immortal-person time. Immortal person-time is a period of observation that is guaranteed to be event-free through design of the study. (23) In an analysis of a putative DDI between clopidogrel (object) and proton pump inhibitors (precipitant), Stockl et al. compared clopidogrel initiators to clopidogrel initiators who also filled a prescription for a proton pump inhibitor. (24) Follow-up began at clopidogrel initiation and patients were classified into clopidogrel-only or clopidogrel-plus-proton pump inhibitor groups based on whether they had at least one prescription for a proton pump inhibitor in the 90 days before or the 90 days after the clopidogrel initiation date. Thus, patients who qualified inclusion by receiving a proton pump inhibitor in the 90 days following the clopidogrel initiation contributed immortal person-time to the analysis—the time from clopidogrel initiation to the proton pump inhibitor prescription—since patients that entered the analysis in this way, by definition, could not have had a fatal outcome in this period. Beginning follow-up after or at the time of (but not before) concomitancy can help to avoid immortal person-time bias.

Studying the Time Course of the DDI

Even in the absence of a potentially interacting drug, the rate of an ADE often varies with amount of time since initiating the drug. This is part of the rationale for the increasingly standard practice in pharmacoepidemiology to restrict studies to new users of the drugs being examined, an approach known as the *inception cohort design*. (25) For many drug-outcome pairs, the incidence rate would be expected to peak shortly after starting the drug and decline thereafter. Such a declining pattern may be attributed to at least four different mechanisms. The first mechanism is depletion of susceptible patients, in which patients with an inherent susceptibility to the drug's adverse effect experience the adverse effect soon after initiation, and subsequently discontinue the drug because of the adverse event or a prodrome thereof. (26,27) Under this mechanism, the patients who remain on the drug for the long-term are more robust to the drug's adverse effects, since the susceptible patients have been depleted from the cohort. The second mechanism leading to a declining event rate

over time is biological adaptation to the drug's pharmacologic effects. The third mechanism involves biological adaptation to the precipitant in which the precipitant inhibits one or more enzymes that metabolize the object, resulting in an initial increase in the concentration of the object, after which the body compensates by up-regulating the affected enzyme or other enzymes to metabolize the object. The initial increase in plasma concentration of the object may cause a rise in the rate of the ADE initially, followed by a reduction in the rate as the metabolism of the object returns to baseline. The fourth mechanism that may contribute to declining rate is dose reduction prompted either by early signs of toxicity (e.g., a reduction in the dose of a statin due to mild myopathy that reduces the risk of rhabdomyolysis) or in response to measurement of the serum drug concentration or other biomarker used in clinical practice to adjust doses (e.g., a reduction in warfarin dose due to supra-therapeutic values of the international normalized ratio, a laboratory marker of warfarin's pharmacologic effect). While each of these mechanisms would be expected to produce a declining rate, an increasing rate can be observed for drug-outcome pairs that are characterized by cumulative toxicity, such as corticosteroid-induced avascular necrosis and anthracycline-induced cardiomyopathy.

Given that the rate of an ADE often varies with the amount of time since initiating the drug, it is predictable that the rate of an outcome caused by a DDI may vary as a function of the amount of time since initiation of concomitancy, particularly for DDIs acting through a metabolic inhibition. (28) Figure 1a illustrates a scenario in which initiation of a precipitant to a person already receiving an object (i.e., precipitant-triggered concomitancy) leads to an event rate that is transiently increased but then declines to baseline. The rate might actually decline to below the baseline rate because the persons susceptible to the adverse effect become depleted from the cohort or because the body compensates to increase pharmacologic clearance of the object. If the scenario illustrated in Figure 1a is operating, and one evaluates a potential DDI by calculating the average rate during all time treated with the object-precipitant combination and dividing this rate by the rate observed during the time treated with the object alone, then one could falsely conclude that the potential DDI had no effect on the adverse event, even if the precipitant has a large but transient effect. This is because, as illustrated in Figure 1s, the transiently increased rate seen shortly after the initiation of the precipitant in patients is outweighed by the prolonged time during which the rate of the adverse event has reverted back to (or even below) the baseline rate associated with use of the object alone. In other scenarios, the increased risk associated with a precipitant-triggered DDI may remain elevated throughout the course of concomitancy, as illustrated in Figure 1b.

Careful consideration must also be given to the timing of concomitancy when the rate of the ADE varies with the amount of time since initiating the object. For example, a study of a DDI between corticosteroids and some precipitant on induced avascular necrosis should account for time on corticosteroids since the rate of avascular necrosis increases with time on corticosteroids. If, for example, an investigator conducted an analysis in which a large portion of the time exposed to corticosteroids only was shortly after corticosteroid initiation and the majority of time concomitantly exposed to the corticosteroids and the precipitant was longer after corticosteroid initiation, then there would be a lower baseline risk of avascular necrosis in the former than in the latter.

Given that, as illustrated in Figure 1a, the *overall* rate ratio may not be observably elevated for a DDI with a substantial but transient effect, it can be important to look for an association within time-specific strata (i.e., examine the duration-response relationship of the DDI) regardless of whether or not an overall association is observed over the entire period of concomitancy. However, looking for associations both overall and within strata defined by time since initiation of concomitancy can raise potential concerns about multiple testing. Given that DDI studies using even very large population databases can have marginal or insufficient statistical power, adjusting for multiple comparisons across time strata may have a crippling effect on investigators' ability to identify important risks associated with DDIs. For example, Schelleman et al. used a population database of approximately 108 million person-years of follow-up to evaluate potential DDIs involving sulfonylureas as objects and lipid lowering drugs as precipitants. (29) They studied only precipitant-triggered instances of concomitancy. For each object-precipitant pair they examined the overall association as well as associations for 0–29 days, 30–59 days, 60–119 days, and 120 days. They found statistically elevated association measures for several time-specific strata, but would not have done so had they accounted for multiple testing due to the 56 possible duration-specific association measures, many of which had insufficient data even to estimate a multiplicity-unadjusted measure of association. We believe that for exploratory analyses of time-specific measures of association, refraining from accounting for multiplicity is justified because of the manifestly low statistical power and precision associated with multiplicity-adjusted estimates, provided that such association measures are interpreted as exploratory in light of their corresponding higher-than-nominal type-1 error rate.

Pharmacoepidemiologic Screening to Identify Potential DDIs

In addition to performing hypothesis-driven DDI studies, pharmacoepidemiologic methods can be used to perform hypothesis-free screening of healthcare data to identify potential DDIs. For example, Han et al. used the SCCS design to screen healthcare data for precipitants that are associated with severe hypoglycemia in persons taking insulin secretagogues (Design 4)(30). The SCCS design is well-suited to screening because it includes only persons who experienced the outcome while taking the object. This makes this design highly computationally efficient and thus more amenable to high-throughput analysis than the cohort or nested case-control designs. Because of the large number of candidate precipitants that they examined, the investigators used a semi-Bayesian shrinkage approach to limit the variability of the resulting measures of association and to limit the type-1 error rate.

Conclusion

Pharmacoepidemiologic studies are essential to confirming (or refuting) and elucidating (e.g., describing the timing and identifying who is at greatest risk) the health effects of potential DDIs. The information that they provide is complementary to that provided by other approaches to studying DDIs. In addition to considering the overall design principles of pharmacoepidemiology, researchers planning to study DDIs should incorporate additional considerations that are specific to DDI studies because of their focus on inferring the effects

of combinations rather than on individual drugs. We hope that the considerations described in this paper are useful to those conducting and interpreting pharmacoepidemiologic studies of the health effects of DDIs.

Acknowledgments

The authors thank Mary A. Leonard for preparing Figure 1 and Maria Kalai for assistance with manuscript preparation and submission. Writing of this paper was supported by grants R01AG025152 and R01DK102694 from the US National Institutes of Health and by grants R01HS023122 and K08HS023898 from the US Agency for Health Care Research and Quality.

References

1. Gurwitz JH, Field TS, Harrold LR, Rothschild J, Debellis K, Seger AC, et al. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. *JAMA*. 2003 Mar 5; 289(9):1107–1116. [PubMed: 12622580]
2. Becker ML, Kallewaard M, Caspers PW, Visser LE, Leufkens HG, Stricker BH. Hospitalisations and emergency department visits due to drug-drug interactions: a literature review. *Pharmacoepidemiol Drug Saf*. 2007 Jun; 16(6):641–651. [PubMed: 17154346]
3. Harris Y, Hu DJ, Lee C, Mistry M, York A, Johnson TK. Advancing Medication Safety: Establishing a National Action Plan for Adverse Drug Event Prevention. *Jt Comm J Qual Patient Saf*. 2015; 41(8):351–360. [PubMed: 26215524]
4. Jia J, Zhu F, Ma X, Cao Z, Li Y, Chen YZ. Mechanisms of drug combinations: interaction and network perspectives. *Nat Rev Drug Discov*. 2009 Feb; 8(2):111–128. [PubMed: 19180105]
5. Delafuente JC. Understanding and preventing drug interactions in elderly patients. *Crit Rev Oncol Hematol*. 2003 Nov; 48(2):133–143. [PubMed: 14607376]
6. Stearns V, Johnson MD, Rae JM, Morocho A, Novielli A, Bhargava P, et al. Active tamoxifen metabolite plasma concentrations after coadministration of tamoxifen and the selective serotonin reuptake inhibitor paroxetine. *J Natl Cancer Inst*. 2003 Dec 3; 95(23):1758–1764. [PubMed: 14652237]
7. Binkhorst L, Mathijssen RH, Jager A, van Gelder T. Individualization of tamoxifen therapy: much more than just CYP2D6 genotyping. *Cancer Treat Rev*. 2015 Mar; 41(3):289–299. [PubMed: 25618289]
8. Kesselheim AS, Cresswell K, Phansalkar S, Bates DW, Sheikh A. Clinical decision support systems could be modified to reduce ‘alert fatigue’ while still minimizing the risk of litigation. *Health Aff (Millwood)*. 2011 Dec; 30(12):2310–2317. [PubMed: 22147858]
9. Hennessy S, Flockhart DA. The need for translational research on drug-drug interactions. *Clin Pharmacol Ther*. 2012 May; 91(5):771–773. [PubMed: 22513312]
10. Strom, B.; Kimmel, S.; Hennessy, S. *Pharmacoepidemiology*. 5. Chichester: Wiley; 2012.
11. Velentgas, P.; Dreyer, N.; Nourjah, P.; Smith, S.; Torchia, M. Developing a Protocol for Observational Comparative Effectiveness Research: A User’s Guide. Rockville (MD): AHRQ; 2013 Jan. <http://www.ncbi.nlm.nih.gov/books/NBK126190/>
12. Juurlink DN, Mamdani M, Kopp A, Laupacis A, Redelmeier DA. Drug-drug interactions among elderly patients hospitalized for drug toxicity. *JAMA*. 2003 Apr 2; 289(13):1652–1658. [PubMed: 12672733]
13. Greenland S, Thomas DC. On the need for the rare disease assumption in case-control studies. *Am J Epidemiol*. 1982 Sep; 116(3):547–553. [PubMed: 7124721]
14. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology*. 2000 Sep; 11(5):550–560. [PubMed: 10955408]
15. Leonard, C.; Bilker, W.; Brensinger, C.; Han, X.; Flory, J.; Flockhart, D., et al. Severe hypoglycemia in users of sulfonylurea antidiabetic agents and antihyperlipidemics. Submitted
16. Leonard CE, Bilker WB, Brensinger CM, Flockhart DA, Freeman CP, Kasner SE, et al. Comparative risk of ischemic stroke among users of clopidogrel together with individual proton pump inhibitors. *Stroke*. 2015 Mar; 46(3):722–731. [PubMed: 25657176]

17. Maclure M, Fireman B, Nelson JC, Hua W, Shoaibi A, Paredes A, et al. When should case-only designs be used for safety monitoring of medical products? *Pharmacoepidemiol Drug Saf.* 2012 Jan; 21(Suppl 1):50–61. [PubMed: 22262593]
18. Schelleman H, Bilker WB, Brensinger CM, Han X, Kimmel SE, Hennessy S. Warfarin with fluoroquinolones, sulfonamides, or azole antifungals: interactions and the risk of hospitalization for gastrointestinal bleeding. *Clin Pharmacol Ther.* 2008 Nov; 84(5):581–588. [PubMed: 18685566]
19. Carnahan RM. Mini-Sentinel's systematic reviews of validated methods for identifying health outcomes using administrative data: summary of findings and suggestions for future research. *Pharmacoepidemiol Drug Saf.* 2012 Jan; 21(Suppl 1):90–99. [PubMed: 22262597]
20. Tatonetti NP, Denny JC, Murphy SN, Fernald GH, Krishnan G, Castro V, et al. Detecting drug interactions from adverse-event reports: interaction between paroxetine and pravastatin increases blood glucose levels. *Clin Pharmacol Ther.* 2011 Jul; 90(1):133–142. [PubMed: 21613990]
21. Flory J, Haynes K, Leonard CE, Hennessy S. Proton pump inhibitors do not impair the effectiveness of metformin in patients with diabetes. *Br J Clin Pharmacol.* 2015 Feb; 79(2):330–336. [PubMed: 25199921]
22. Schelleman H, Bilker WB, Brensinger CM, Wan F, Yang YX, Hennessy S. Fibrate/Statin initiation in warfarin users and gastrointestinal bleeding risk. *Am J Med.* 2010 Feb; 123(2):151–157. [PubMed: 20103024]
23. Suissa S. Immortal time bias in observational studies of drug effects. *Pharmacoepidemiol Drug Saf.* 2007 Mar; 16(3):241–249. [PubMed: 17252614]
24. Stockl KM, Le L, Zakharyan A, Harada AS, Solow BK, Addiego JE, et al. Risk of rehospitalization for patients using clopidogrel with a proton pump inhibitor. *Arch Intern Med.* 2010 Apr 26; 170(8):704–710. [PubMed: 20421557]
25. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. *Am J Epidemiol.* 2003 Nov 1; 158(9):915–920. [PubMed: 14585769]
26. Moride Y, Abenhaim L. Evidence of the depletion of susceptibles effect in non-experimental pharmacoepidemiologic research. *J Clin Epidemiol.* 1994 Jul; 47(7):731–737. [PubMed: 7722586]
27. Guess HA. Behavior of the exposure odds ratio in a case-control study when the hazard function is not constant over time. *J Clin Epidemiol.* 1989; 42(12):1179–1184. [PubMed: 2585009]
28. Amin M, Suksomboon N. Pharmacotherapy of type 2 diabetes mellitus: an update on drug-drug interactions. *Drug Saf.* 2014 Nov; 37(11):903–919. [PubMed: 25249046]
29. Schelleman H, Han X, Brensinger CM, Quinney SK, Bilker WB, Flockhart DA, et al. Pharmacoepidemiologic and in vitro evaluation of potential drug-drug interactions of sulfonylureas with fibrates and statins. *Br J Clin Pharmacol.* 2014 Sep; 78(3):639–648. [PubMed: 24548191]
30. Han, X.; Chiang, C.; Leonard, C.; Bilker, W.; Brensinger, C.; Hennessy, S. Bioinformatics approaches to identifying drug-drug interactions: Application to insulin secretagogues. Submitted

Figure 1.
Schematic depiction the two different potential time-courses of a precipitant-triggered drug-drug interaction.

Table 1
Pharmacoepidemiologic designs used to study health effects of potential drug-drug interactions.

Design	Relative measure of association	Key assumptions	Key Limitations	Comments	Example
1. Cohort study examining incidence rate (IR) of outcome in 4 groups: 1) those taking the object with the precipitant (IR ₁₁) 2) those taking the object without the precipitant (IR ₁₀); 3) those taking the precipitant without the object (IR ₀₁), and 4) those taking neither the object nor the precipitant (IR ₀₀)	Incidence rate ratio due to interaction (IRR _I), defined as $IRR_I = (IR_{11} / IR_{00}) / [(IR_{10} / IR_{00}) \times (IR_{01} / IR_{00})]^*$	No among-person unmeasured confounding by either object or precipitant	In most scenarios, it is implausible that there is no confounding by the indication for either the object or the precipitant	While this is the design yields the theoretically correct overall relative measure of association, the key assumption is implausible for most drug pairs	We are unaware of any published examples.
2. Cohort (or case-control) study nested within person-time exposed to the object, comparing persons exposed vs. unexposed to the precipitant	Incidence rate ratio (or odds ratio) associated with use of the precipitant among persons receiving the object	No among-person unmeasured confounding by precipitant No effect of precipitant in absence of object	Subject to confounding by the indication for the precipitant or an inherent effect of the precipitant on the outcome	Key assumptions are more likely to hold than that for Design 1. Will show association if precipitant has inherent effect on outcome apart from interaction mechanism. May be useful for precipitants with a chronic indication that is unlikely to be associated with outcome. Even if control precipitant isn't used as a direct comparator as in design 3, association with control precipitant can help to assess validity of key assumption.	Case-control study nested in person-time exposed to glyburide, examining the association between cotrimoxazole and severe hypoglycemia(12)
3. Cohort (or case-control) study nested within person-time exposed to the object, comparing person-time exposed to the precipitant vs. control precipitant	Incidence rate ratio (or odds ratio) ratio associated with use of the precipitant vs. control precipitant among persons receiving the object	No among-person unmeasured confounding by precipitant vs. control precipitant No effect of precipitant that is not shared by control precipitant in absence of object No interaction between control precipitant and object	A valid control precipitant may not exist	Preferable to Design 2 because use of a valid control precipitant reduces susceptibility to confounding by indication for the precipitant. It can be difficult to know for certain that the control precipitant does not interact with the object or otherwise affect the rate of the outcome	Cohort study within person-time exposed to clopidogrel, examining the rate of ischemic stroke associated with individual proton pump inhibitors, each vs. pantoprazole (16)

Design	Relative measure of association	Key assumptions	Key Limitations	Comments	Example
4. Self-controlled case series (or case-crossover study) nested within person-time exposed to the object, comparing person-time exposed vs. unexposed to the precipitant	Incidence rate ratio (or odds ratio) associated with use of the precipitant vs. no exposure among persons receiving the object	No within-person unmeasured confounding by precipitant vs. no exposure No effect of precipitant in absence of object	Subject to within-person confounding by the indication for the precipitant, especially for precipitants used for acute indications	Self-controlled design inherently eliminates confounding by factors that remain constant within the individual over the study period. Necessitates within-person variability in exposure to precipitant and accurate knowledge of onset and offset of exposure to precipitant. For precipitants with an acute indication (e.g., antibiotics), Design 3 may be preferred if a valid control precipitant. Results can be affected by secular or within-person trends in exposure to the precipitant.	Case-crossover study nested within person-time exposed to warfarin examining within-person odds ratio for exposure to antimicrobial agents (18)
5. Self-controlled case series (or case-crossover study) nested within person-time exposed to the object, comparing person-time exposed to precipitant vs. control precipitant	Incidence rate ratio (or odds ratio) associated with use of the precipitant vs. the control precipitant among persons receiving the object	No within-person unmeasured confounding by precipitant vs. control precipitant No effect of precipitant vs. control precipitant in absence of object No interaction between control precipitant and object	Only includes subjects who were exposed to both the precipitant and the control precipitant concomitantly with object and in whom the event occurred during exposure to the object plus either the precipitant or the control precipitant. In most scenarios, few if any such subjects are likely to exist	Self-controlled design inherently eliminates confounding by factors that remain constant within the individual over the study period. Necessitates within-person variability in exposure to precipitant and accurate knowledge of onset and offset of exposure to precipitant. Only includes subjects who were exposed to both the precipitant and the control precipitant concomitantly with object.	We are unaware of any published examples.

* IR₁₁ is the incidence rate in person-time exposed to both the object and the precipitant; IR₀₀ is the incidence rate in person-time exposed to neither the object nor the precipitant; IR₁₀ is the incidence rate in person-time exposed to the object but not the precipitant; IR₀₁ is the incidence rate in person-time exposed to the precipitant but not the object.