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Methods for Studying the Health Effects of Drug–Drug Interactions

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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. In two-drug DDIs, the affected drug is called the **object** (or *victim*) and the affecting drug is called the **precipitant** (or *perpetrator*). The expected outcome of most hypothesized DDIs is an exaggeration of the major pharmacologic effect of the object, such as serious hypoglycemia from sulfonylurea antidiabetic agents or bleeding from anticoagulants. Other DDIs may result in reduced effectiveness of the object, such as the hypothesized reduced effectiveness of clopidogrel in lowering the risk of stroke resulting from the inhibition by proton pump inhibitors of the enzyme that converts clopidogrel to its active moiety. The precipitant of a DDI may or may not have an inherent effect on the health outcome in the absence of the object. For example, in a study of potential DDIs that involves warfarin as the object, nonsteroidal antiinflammatory drugs but not antibiotics as precipitants would be expected to increase the risk of bleeding in persons not taking warfarin.

Numerous pharmacokinetic and pharmacodynamic mechanisms are responsible for DDIs [1,2]. Because the pharmacokinetic pathways and pharmacodynamic effects of most drugs are not completely understood, 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 was hypothesized to reduce tamoxifen's effectiveness in lowering the frequency of breast cancer recurrence [3]. Although *in vitro* experiments, animal studies, and clinical trials are used to examine the effects of one drug on the pharmacokinetics of another drug, pharmacoepidemiologic studies are the principal way of studying the health effects of potential DDIs. This chapter focuses on methods for studying the health effects of potential DDIs.

Pharmacoepidemiology, Sixth Edition. Edited by Brian L. Strom, Stephen E. Kimmel and Sean Hennessy.

Clinical Problems to Be Addressed by Pharmacoepidemiologic Research

Drug–drug interactions are a large and growing clinical and public health problem, especially in older adults, 40% of whom take five or more prescription drugs in a given month [4]. Although the frequency with which DDIs cause adverse health outcomes is not well studied, in older adults known DDIs are estimated to cause 13% of adverse drug events (ADEs) [5] and 5% of hospital admissions [6]. As new drugs are developed, old drugs are repurposed, and per capita drug consumption continues to rise, the clinical and public health consequences of DDIs are likely to rise correspondingly.

There are many approaches to identifying novel potential DDIs, including physiologically based pharmacokinetic models (see Chapter 2) and data mining of spontaneous reporting databases, social media posts, and healthcare data (see Chapter 27). Potential DDIs, however, may not have observable effects on health outcomes, and relatively few studies have examined the health effects of specific potential DDIs in populations. This leaves critical knowledge gaps for clinicians, patients, caregivers, editors of DDI compendia, and those who manage clinical decision support systems. Recognizing these knowledge gaps, stakeholders attending a 2009 meeting on DDIs made the conduct of additional research on the health effects of DDIs their principal recommendation [7].

False warnings about DDIs that are sent to clinicians in the context of automated messaging in the healthcare setting, such as during prescribing or dispensing, can reduce the use of valuable combinations of medications because of unsubstantiated fears that they may interact detrimentally. Further, physicians and pharmacists who are subjected to frequent alerts about apparently inconsequential potential DDIs often become desensitized to them in a phenomenon known as "alert fatigue" [8]. This provides additional importance to conducting studies of the health effects of potential DDIs, as well as studies of better ways in which the healthcare system can avoid harmful DDIs.

It seems likely that some subgroups of people are more or less susceptible to the effects of a given DDI than other subgroups (see Chapter 30). Therefore, providing information about the health effects of potential DDIs that is relevant to identifiable subgroups is an important goal of DDI research.

Methodologic Problems to Be Addressed by Pharmacoepidemiologic Research

A number of methodologic problems are more prominent in pharmacoepidemiologic studies of DDIs than in those examining the effects of individual drugs. For example, pharmacoepidemiologic studies of DDIs usually require data from larger populations than those needed to study the effects of individual drugs. This is because, in any population, a small proportion of people will take any given drug, and a small proportion of those will concomitantly take the second drug of a drug–drug pair of interest. An additional problem is confounding by indication (see Chapters 3 and 43), which is regarded by many as the single biggest challenge in using the results from nonrandomized pharmacoepidemiologic studies to infer causation.

The problem of confounding by indication is more pronounced in DDI studies, which need to address confounding by the indications of two or more drugs. An additional problem is the inability of available healthcare data to validly identify all study outcomes of potential interest. In particular, while nonpharmacoepidemiologic studies of DDIs often examine serum drug

concentrations or other biomarkers such as the electrocardiographic QT interval or the international normalized ratio as outcome measures, pharmacoepidemiologic studies typically examine health outcomes such as clinically evident cardiac arrhythmias or serious bleeding. Further, some important outcomes of DDIs (e.g., serotonin syndrome) may not be validly identifiable using claims data. Thus, as in studies of the effects of individual drugs, 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 available healthcare data is essential. A further methodologic problem is that little attention has been given to optimizing pharmacoepidemiologic methods to perform well in screening for previously unanticipated associations (see Chapter 27), as may be desired when the goal is to identify hypotheses of novel potential DDIs. In addition to the need to increase the efficiency of such screening studies with regard to tasks performed by humans and by computers, screening large numbers of drug–drug pairs raises concerns that the conventionally accepted type I error rate of 5% may not be appropriate in such settings.

Currently Available Solutions

Available Research Designs for Studying the Health Effects of DDIs

Table 40.1 lists available pharmacoepidemiologic designs to study the health effects of DDIs using data derived from the provision of healthcare. 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 40.1, 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:

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

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 vs 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:

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

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 vs the neither-exposed were statistically different than the object-exposed vs 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 it 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

Table 40.1 Pharmacoepidemiologic designs used to study health effects of potential drug–drug interactions.

Design	Relative measure of association	Key assumptions	Comments	Example
1. Cohort study examining incidence rate (IR) of the outcome in: (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 use of either object or precipitant	While this 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 use of precipitant No effect of precipitant in absence of object	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 Use of a negative control object and/or negative control precipitant can help to assess validity of the key assumptions	Case–control study nested in person-time exposed to glyburide, examining the association between cotrimoxazole and serious hypoglycemia [9]
3. Cohort (or case–control) study nested within person-time exposed to the object, comparing person-time exposed to the precipitant vs the negative control precipitant	Incidence rate ratio (or odds ratio) associated with use of the precipitant vs control precipitant among persons receiving the object	No among-person unmeasured confounding by use of precipitant vs negative control precipitant No effect of precipitant in absence of object that is not shared by negative control precipitant No interaction between negative control precipitant and object	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 [13]

(*Continued*)

Table 40.1 (Continued)

Design	Relative measure of association	Key assumptions	Comments	Example
4. Cohort (or case–control) study nested within person-time exposed to either the object or the control object, comparing person-time exposed to the precipitant plus the object vs the precipitant plus the negative control object	Incidence rate ratio (or odds ratio) associated with use of the precipitant among users of the object vs use of the precipitant among users of the negative control object	No difference in direct effect of the object vs negative control object on the outcome No among-person unmeasured confounding by use of object vs negative control object No interaction between the precipitant and negative control object	Can help identify an inherent effect of the precipitant in the absence of the object	We are unaware of any published examples
5. 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 non-use of precipitant No effect of precipitant in absence of object	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 [16]

*IR_{11} is the incidence rate in person-time exposed to both the object and the precipitant; IR_{00} is the incidence rate in person-time exposed to neither the object nor the precipitant; IR_{10} is the incidence rate in person-time exposed to the object but not the precipitant; IR_{01} is the incidence rate in person-time exposed to the precipitant but not the object.

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 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 [9]. Their aim was to examine the association between use vs nonuse of cotrimoxazole and serious hypoglycemia. They found that the adjusted odds ratio (OR) for the association between cotrimoxazole use and serious 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 [10]. 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 such as 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. In the case of studies of DDIs, exposure may be said to begin with the onset of concomitant intake of the object and precipitant. However, many nested case–control studies assess potential confounders as of the index date, often defined as 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 (see Chapter 43) [11]. 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 40.1, Design 2) if there is no effect of the precipitant in persons not taking the object, and if there is no unmeasured confounding by the indication for the precipitant. Unfortunately, the assumption of no unmeasured confounding by the precipitant 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 or to have an inherent effect on the outcome in the absence of the object that is not shared by the precipitant. 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 serious 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 serious hypoglycemia (adjusted OR 1.5; 95% CI 0.8–2.9) helped provide reassurance that the association with cotrimoxazole (adjusted OR 6.6) was unlikely to be due primarily to confounding by the need for an antibiotic or a shared effect of all antibiotics [9].

To help distinguish a DDI from 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 object 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.* used metformin as a negative control object, which is not believed to interact with the precipitants [12]. In the setting of Design 2, the association with presence vs absence of the precipitant in users of the negative control object is used qualitatively to place into context and aid in the interpretation of the association measure of primary interest. For example, in the previously described study by Leonard *et al.* of sulfonylureas and antihyperlipidemics, the possibility of an association (although not quite statistically significant) between fenofibrate (a precipitant) and serious hypoglycemia among users of metformin (as a negative control object) suggested the possibility of an inherent hypoglycemic effect of fenofibrate in the absence of sulfonylureas [12].

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 [13]. Pantoprazole was selected as the negative control precipitant because it is not a potent inhibitor of the enzyme responsible for activating clopidogrel (cytochrome P450 2C19) and therefore is believed to have a low potential for interacting with clopidogrel. The multiplicative interaction parameter can be produced either through performing a single regression that estimates, among those exposed to the object drug, the association between the precipitant vs the negative control precipitant; or performing one regression that estimates the association between the presence vs absence of the precipitant in those receiving the object and one that estimates the association between the presence vs absence of the negative control precipitant in those receiving the object, and then calculating the ratio of ratios and the corresponding confidence limit from these two regressions using the delta method [14]. 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.

Similarly, Design 4 is just like Design 2 except that the association measure is the IRR (or OR) for the precipitant of interest in those receiving the object drug of interest vs the precipitant of interest in those receiving a negative control object drug. As with Design 3, this parameter can be calculated either through a single regression or by combining the results of two

regressions using the delta method [14]. We are unaware of any published examples that have used this design.

Although use of 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 negative 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 negative control precipitant does not have an unknown interaction with the object or an unknown inherent effect on the outcome. This may be particularly true for older drugs, for which pharmacokinetic pathways and pharmacodynamic effects may be 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 [15]. The case–crossover design is a self-controlled design that is analogous to the nested case–control study design [15].

Design 5 is a SCCS or case–crossover study nested within person-time exposed to the object, examining the IRR (for the SCCS design) or OR (for case–crossover design) 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 to the estimation of the drug interaction parameter, although they can contribute to the estimation of other model parameters such as time-varying confounders (if any) in 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 [16]. 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 observation that all antibiotics were associated with an increased rate of bleeding suggests either that all antibiotics share a mechanism for causing bleeding in persons taking warfarin (and possibly even in those not taking warfarin), or that the indication for antibiotics (acute infection) itself is associated

with bleeding in those taking warfarin (and possibly even in 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 that quantitatively employs a negative control precipitant (Design 3) may be useful in addition to or perhaps instead of a self-controlled study (Design 5), provided that a good negative control precipitant is available. In addition, one could use a negative control precipitant in a case-case-time-control study [17] (see Chapter 43), although we are unaware of any studies that have used this design to study DDIs. Further, 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 poor persistence, incomplete adherence, or other reasons. Therefore, self-controlled designs can sometimes be useful for studying precipitants that are intended to be used chronically, although they may be vulnerable to persistent user bias [18].

One could consider performing a SCCS (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, with amoxicillin as a negative control precipitant. A self-controlled study of this question would include only persons who experienced bleeding while treated 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 such persons are likely to exist even in a large population database, this design seems unlikely to be of practical use. However, one could quantitatively incorporate a negative control precipitant in a self-controlled study by fitting one regression that estimates the association with the precipitant in users of the object, fitting a second regression that estimates the association with the negative control precipitant in users of the object, and calculating the ratio of these ratios (with the corresponding confidence limits) using the delta method [14]. Similarly, one could quantitatively incorporate a negative control object using a self-controlled design by fitting one regression that estimates the association with the precipitant in users of the object, fitting a second regression that estimates the association with the precipitant in users of the negative control object, and calculating the ratio of these ratios (with the corresponding confidence limits) using the delta method [14]. For example, Han *et al*. used this approach to examine the association between numerous potential precipitants and serious hypoglycemia in users of sulfonylureas as objects, using metformin quantitatively as a negative control object [19].

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 Assessment Methods

Many studies have used review of medical records to examine the validity and performance characteristics of algorithms to identify outcomes using administrative healthcare data [20]. 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 that occurred on October 1, 2015, researchers using administrative data from this date or later in 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 antihyperlipidemic pravastatin [21] and between proton pump inhibitors and metformin [22]. Compared to studies that rely on binary outcomes such as the occurrence of serious hypoglycemia, studies examining a continuous measure such as serum glucose require much smaller sample sizes and may raise fewer concerns about outcome validity, assuming that the laboratory value is accurately measured and recorded. 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 precipitant and negative 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. While this can be helpful, the investigator should consider the possibility that confounding might be different for the precipitant and positive control such that replicating the known association for the positive control is no guarantee that the study will yield the truth for the precipitant. In addition, other considerations such as sample size may negate the ability of a precipitant to serve as a reliable positive control.

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 be 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 may be titrated to produce its desired effect in a patient who is not receiving the precipitant, and this titration is later followed by initiation of the precipitant. For example, if warfarin is started and cotrimoxazole is later added, the prescriber may be unaware of the need to retitrate the dose of warfarin, and overanticoagulation and bleeding may result. In contrast, if warfarin and cotrimoxazole are started simultaneously or if warfarin is started in a patient already receiving cotrimoxazole, the warfarin dose will be titrated to the desired level of laboratory-measured anticoagulation in the presence of cotrimoxazole, avoiding clinical consequences of the DDI in that patient, provided that the patient continues to take cotrimoxazole. Naturally, if the cotrimoxazole is later discontinued, the patient may be at risk of the effects of underanticoagulation, that is, 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 (see Chapter 43). 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 (precipitants), 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 90 days after the clopidogrel initiation date. Thus, patients who qualified for 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 three 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 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 supratherapeutic 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 metabolic inhibition [28]. 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.

Figure 40.1A 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 40.1A 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 rate of the adverse event, even if the precipitant has a large but transient effect. This is because, as illustrated in Figure 40.1A, 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 40.1B.

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 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 unexposed to the precipitant was shortly after corticosteroid initiation, and the majority of time concomitantly exposed to the precipitant was longer after corticosteroid initiation, then there would be a lower baseline risk of avascular necrosis during unexposed time than in exposed time, even if there were no effect of the precipitant.

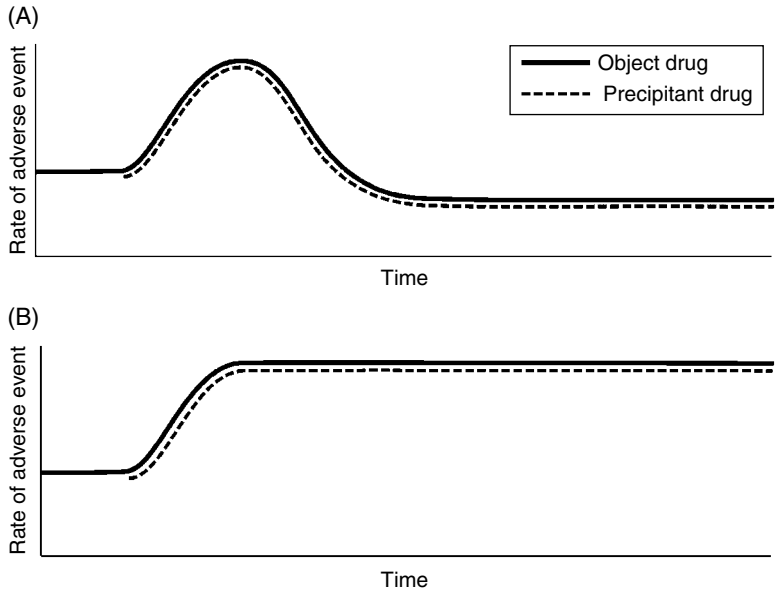

Figure 40.1 Schematic depiction of the two different potential time-courses of a precipitant-triggered drug–drug interaction. In (A), the rate of the adverse event rises transiently, while in (B), the rate of the adverse event rises and remains persistently elevated.

Given that, as illustrated in Figure 40.1A, 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 low 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 associated with multiplicity-adjusted estimates, provided that such association measures are interpreted as exploratory in light of their corresponding higher-than-nominal type I error rate. The issue of multiple testing can be mitigated in settings where the pharmacologic mechanism of

the potential DDI is sufficiently well characterized so that the time course of the interaction can confidently be predicted *a priori*, and analyses within specific time windows considered primary, with other time windows considered secondary.

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 serious hypoglycemia in persons taking insulin secretagogues (Design 5) [19]. 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 for multiple comparisons adjustment [30], an approach that limits the variability of the resulting measures of association and controls the type I error rate.

The Future

Given the continued development of new drugs, repurposing of old drugs, the rising frequency of polypharmacy, and the aging of the population, the clinical and public health importance of DDIs will continue to grow. The increasing use of healthcare data from larger populations, including data accessed using distributed data models (see Chapter 25), that characterizes pharmacoepidemiology in general promises to be particularly important for studying the health effect of DDIs. This is because studying the effects of multiple drugs in combination necessitates larger population databases than does studying the effects of individual drugs. The settings in which the health effects of DDIs are characterized are likely to expand from the current predominance of studies of community-dwelling persons to those set in hospitals, nursing homes, and other settings.

A wide variety of data and approaches are now being used to screen for potentially clinically important DDIs, including animal models, healthcare data, spontaneous reporting data (see Chapter 10), physiologically based pharmacokinetic models (see Chapter 2), physiologic and pharmacologic networks (see Chapter 2), and social media (see Chapter 27). As the use of screening increases, the number of hypothesized DDIs whose health effects need to be confirmed or refuted in etiologic studies will rise. Perhaps the most urgent need is to develop and test approaches to better incorporate the knowledge gained through studies of the health effects of DDIs into the healthcare system, thereby reducing the frequency of harmful effects of DDIs while allowing and perhaps even encouraging use of combinations that had been predicted to be harmful but were actually found to be safe. However, given the fragmented market for DDI knowledge bases and the surprising degree of lack of agreement among them [31], addressing this problem will be challenging.

Acknowledgments

The authors thank Mary A. Leonard for preparing Figure 40.1 and Maria Kalai for assistance with manuscript preparation. Writing of this chapter 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.

Portions of this chapter have been previously published as Hennessy S, Leonard CE, Gagne JJ, Flory JH, Han X, Brensinger CM, Bilker WB. Pharmacoepidemiologic methods for studying the health effects of drug–drug interactions. *Clinical Pharmacology & Therapeutics* 2016; **99**(1): 92–100. Copyright © 2015, American Society for Clinical Pharmacology and Therapeutics, John Wiley & Sons (http://onlinelibrary.wiley.com/wol1/doi/10.1002/cpt.277/full)

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