

Drug Interactions: Scientific and Clinical Principles

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LEARNING OBJECTIVES

1. Assess patients on the basis of the incidence of drug interactions and their potential outcomes.
2. Distinguish the mechanisms behind various drug interactions and their impact on patients.
3. Develop strategies for identifying and mitigating potential drug interactions.
4. Evaluate the strengths and weaknesses of available drug interaction resources.

ABBREVIATIONS IN THIS CHAPTER

CDS	Clinical decision support
CMM	Comprehensive medication management
DART	Drug-Associated Risk Tool
DDI	Drug-drug interaction
OATP	Organic anion-transporting polypeptide

[Table of other common abbreviations.](#)

INTRODUCTION

Drug interactions occur when the concomitant administration of another drug or substance affects a drug's effect. The results of these interactions range on a scale of clinical importance, with some resulting in serious harm, some having no significant clinical impact, and some resulting in beneficial, synergistic effects. Although clinical pharmacists are familiar with the common underlying mechanisms of drug interactions, additional pharmacokinetic mechanisms have been elucidated in recent years, and interest has increased in the role of pharmacogenetics on the clinical significance of interactions. For example, the FDA first addressed interactions involving organic anion-transporting polypeptide (OATP) in its 2012 drug-drug interaction (DDI) guidance for industry, and since then, the number of known OATP substrates and inhibitors identified has increased (McFeely 2019). Genetic polymorphisms have also increasingly been studied to elucidate their impact on DDIs and drug-drug-gene interactions (Bahar 2017).

In addition to growing research and understanding in this area, increasing polypharmacy leads to an increased potential for interactions. According to the National Center for Health Statistics, 22.4% of American adults 40–79 years of age used five or more prescription medications in the prior month in 2015–2016 (Hales 2019). In addition, an analysis of the prevalence of medication use and subsequent risk of DDIs among older adults found that concurrent use of five or more prescription medications increased from 30.6% in 2005–2006 to 35.8% in 2010–2011, and use of dietary supplements increased from 51.8% to 63.7% during the same time (Qato 2016). Further analysis found that 15.1% of older adults in the 2010–2011 cohort were using drug combinations that could result in a major DDI, compared with 8.4% in 2005–2006. Thus, clinical pharmacists should be cognizant of recent research into new mechanisms, strategies for managing drug interactions, and available resources for identifying them.

Prevalence of DDIs

The true prevalence of drug interactions is difficult to define and quantify. First, prevalence depends on the types of drug interactions included in an analysis because many drug interactions are not clinically significant or are based only on theoretical data. Potential DDIs should be considered separately from clinically relevant DDIs because not all patients will experience an adverse event, even when taking a combination of drugs known to interact. Recent researchers in this area have tried to account for this issue by selecting only clinically relevant interactions, defined as those that lead to a clinical consequence such as adverse events. Despite these limitations, the prevalence of DDIs has been evaluated in several studies, particularly in the hospital setting, where patients may be exposed to more drugs and/or more complex regimens during their inpatient stay.

A systematic review of 10 observational studies that evaluated confirmed, clinically manifested DDIs found a wide

range of reported prevalence values, ranging from 1.2% in one cohort of internal medicine patients to 64% in a cohort of patients in the ICU (Gonzaga de Andrade Santos 2020). The pooled prevalence of clinically manifested DDIs was 9.2% (95% CI, 4.0–19.7). In another systematic review, the prevalence of potential DDIs in the inpatient setting was analyzed (Zheng 2018). Potential DDIs were defined as those detected on the basis of information in drug compendia regardless of clinical manifestations. Twenty-seven studies were included in the analysis, with 17 studies that were conducted in developing countries (e.g., India, Pakistan) and 18 studies that included general inpatients, excluding ICU patients. The pooled prevalence of patients with at least one potential DDI in the non-ICU population was 33% (95% CI, 17.3–51.3). In the ICU population, the pooled prevalence was 67% (95% CI, 52.7–79.1). The pooled data showed high heterogeneity (I^2 greater than 97%) across both populations.

Potential Outcomes of Drug Interactions

Because not all DDIs have clinically significant consequences, the epidemiologic impact of DDIs should be assessed through realized DDIs and their clinical outcomes. Clinical outcomes from DDIs have mainly been studied within the realm of hospital-related outcomes, including adverse drug events and risk of hospitalization or increased length of stay. Thus, the focus of most research has been on DDIs that result in adverse events, excluding therapeutic failures or synergistic interactions.

The proportion of hospital admissions that could be attributed to DDIs was evaluated in a systematic review of 13 studies (Dechanont 2014). From a pooled population of 47,976 hospital admissions, 1.1% (interquartile range [IQR] 0.4%–2.4%) were associated with DDIs. Looking more specifically at the 1683 hospitalizations associated with adverse drug reactions, 22.2% (IQR 16.6%–36.0%) were attributed to DDIs. In addition, five of the studies included in the review reported the interacting drugs; the most commonly reported DDIs were aspirin-NSAID or NSAID-NSAID interactions leading to GI bleeding, together with interactions of digoxin with other cardiovascular drugs (e.g., verapamil) leading to cardiovascular rhythm disturbances.

Drug-drug interactions are also associated with increased hospital length of stay. Data fully describing these outcomes are not very robust. However, one retrospective single-center evaluation found that the average length of stay in a cohort of patients with a potential severe or moderate DDI during hospitalization was 15 days compared with 8 days in patients who did not have a potential DDI identified during the same period (Moura 2009).

Drug-drug interactions can also result in a reduction or loss of efficacy for one of the involved drugs, which typically occurs when the metabolism of one drug is induced or if there are antagonizing effects of the two interacting drugs. Resulting therapeutic failure from actual DDIs has not been as well

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of the types of drug interactions (e.g., drug-drug, drug-food)
- The difference between pharmacokinetic and pharmacodynamic drug interactions
- Comprehensive medication management as a standard-of-care approach to ensuring each medication is safe, given patient comorbidities and concurrent medications
- The basic availability of drug interaction tertiary resources

[*Table of common laboratory reference values*](#)

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- U.S. Food and Drug Administration (FDA). [Tables for Substrates, Inducers, and Inhibitors](#).
- U.S. Food and Drug Administration (FDA). [Drug Interactions: What You Should Know](#).
- U.S. Food and Drug Administration (FDA). [CDER Conversation: Evaluating the Risk of Drug-Drug Interactions](#).
- U.S. Food and Drug Administration (FDA). [Preventable Adverse Drug Reactions: A Focus on Drug Interactions](#).
- Carpenter M, Berry H, Pelletier AL. [Clinically relevant drug-drug interactions in primary care](#). *Am Fam Physician* 2019;99:558-64.

characterized; some studies have reported that the percentage of adverse DDIs leading to failure of efficacy ranges from 8.6% to 11.6% (Magro 2012).

MECHANISMS OF DRUG INTERACTIONS

Many DDIs occur through common mechanisms related to the pharmacokinetics and pharmacodynamics of the interacting drugs. Although there are unique or unusual mechanisms for interactions for certain combinations, Table 1 summarizes

the most commonly documented DDI mechanisms. A discussion of several of these mechanisms follows to help characterize the varying incidence and relevance of DDIs.

Enzyme inhibition and induction mechanisms are well documented, with phase I oxidation by CYP isoenzymes being the most characterized and well understood. These interactions can further be classified by their degree of inhibition or induction (e.g., potent, moderate, weak). Enzyme inhibition is more common than enzyme induction. Inhibition also has faster onset than induction, which requires time to synthesize more

Table 1. Overview of Common DDI Mechanisms

Category	Type of Interaction	Overview	Example
Absorption	Changes in GI pH	Alterations in pH by one drug resulting in altered absorption of another drug	Decreased bioavailability of posaconazole oral suspension with administration of PPIs
	Adsorption, chelation, or complexing	Drug binding another drug to reduce absorption	Administration of antacids with tetracyclines leading to poorly soluble chelates, reducing tetracycline absorption
	Changes in GI motility	Changes in transit time affecting absorption	Increased cyclosporine exposure when given with metoclopramide because of enhanced gut motility by metoclopramide
	Modulation of drug transporter proteins	Changes in absorption of a drug from the GI tract because of inhibition or induction of drug transporter proteins	Induction of P-glycoprotein with rifampin leads to decreased absorption of digoxin because of decreased GI absorption and increased biliary excretion
Distribution	Protein binding	Competition for binding sites on serum proteins between drugs, resulting in displacement	Increased risk of supratherapeutic concentrations of warfarin with coadministration of valproic acid because of displacement of warfarin from protein binding sites (and CYP2C9-mediated warfarin metabolism inhibition)
	Modulation of drug transporter proteins	Changes in uptake of a drug to a site of action because of inhibition or induction of drug transporter proteins	Increased exposure of ritonavir in the CNS through ketoconazole induced–inhibition of P-glycoprotein leading to reduced transport out of the CNS
Metabolism	Changes in first-pass metabolism	Alteration of portal circulation flow by one drug affects the extent of first-pass metabolism of another drug	Increased dofetilide concentrations and risk of QT prolongation with administration of verapamil, which is thought to increase absorption through increased hepatic blood flow
	Enzyme induction	Increase in synthesis of an isoenzyme responsible for metabolism of a drug	Decreased simvastatin concentrations when administered with carbamazepine, an inducer of CYP3A4, which is the primary metabolizing enzyme for simvastatin
	Enzyme inhibition	Inhibition of an isoenzyme responsible for metabolism of a drug	Increased warfarin concentrations when administered with amiodarone, an inhibitor of CYP2C9, CYP3A4, and CYP1A2, which all contribute to the metabolism of warfarin

(continued)

Table 1. Overview of Common DDI Mechanisms (*continued*)

Category	Type of Interaction	Overview	Example
Excretion	Changes in urinary pH	Alteration of urine pH by one drug leads to increased excretion or retention of another drug	Analgesic dose aspirin serum concentrations decrease with administration of antacids, which increases both urine pH and renal excretion
	Changes in active renal tubular excretion	Competition for active transport systems in renal tubules or alteration of drug transporter proteins in the kidney that affects elimination	Salicylates (e.g., aspirin) competitively inhibit the renal tubular elimination of methotrexate, leading to increased methotrexate exposure
	Enterohepatic shunt	Enterohepatic recirculation is affected by one drug leading to reduced recirculation of another drug, affecting its overall exposure	Cholestyramine reduces the enterohepatic recirculation of mycophenolate by binding free mycophenolic acid in the GI tract
Pharmacodynamic	Additive or synergistic interactions	Drugs with the same pharmacologic effect are given together, resulting in additive effects	Concomitant administration of opioids and benzodiazepines, leading to an increased risk of drowsiness, respiratory depression
	Antagonistic or opposing interactions	Drugs with opposite pharmacologic effects are given together, resulting in opposing effects	Blood glucose-lowering effects of antidiabetics are opposed by corticosteroid-induced hyperglycemia
Uptake	Drug or neurotransmitter uptake	Drugs occupy receptors on adrenergic neurons, leading to altered uptake, reuptake, or receptor interactions of drugs that are active at adrenergic neurons	Response to norepinephrine is greatly increased when given with TCAs, which inhibit reuptake of norepinephrine at adrenergic neurons, leading to hypertension

DDI = drug-drug interaction; PPI = proton pump inhibitor; TCA = tricyclic antidepressant.

Information from: Preston CL. Stockley's Drug Interactions, 12th ed. London: Pharmaceutical Press, 2019.

isoenzymes. The clinical impact of enzyme inhibition and induction depends on the therapeutic index of the affected substrate. For example, a drug with a wide therapeutic index that interacts with an enzyme inhibitor/inducer may not result in a clinically meaningful interaction, even if the serum concentrations of the drugs are decidedly altered. These interactions can also occur with prodrugs that require CYP metabolism to its active metabolite; these lead to an opposite result from the classic inhibition, leading to increased concentrations, with inhibition of an activating CYP enzyme leading to decreased active drug concentrations. Another challenge becoming more prominent with polypharmacy is the potential for multidrug interactions, in which several coadministered drugs are substrates/inducers/inhibitors of the same CYP enzyme, or more than one CYP metabolism pathway for a drug is affected by the presence of several inhibitors (Roughead 2015).

Other mechanisms, such as protein binding interactions, often do not result in clinically relevant interactions unless mediated by other factors. These interactions generally only affect drugs where most of the drug remains in the plasma, or those with a low apparent volume of distribution (Preston 2019). The impact of drug displacement of highly protein bound drugs can be muted through a compensatory increase in metabolism and clearance of the newly released, unbound active drug. Specifically, the interaction is unlikely to be clinically important if the affected drug has a low extraction ratio (i.e., minority of the drug is eliminated through a single mechanism of the eliminating organ). Many drugs that are highly protein bound also have low extraction ratios (e.g., warfarin, phenytoin), so the resulting drug exposure from DDIs is not highly affected by changes in protein binding. In addition, the clinical impact of protein binding interactions is tied to the distribution of the drug, where

drugs with a lower apparent volume of distribution are more likely to be affected.

Drug transporter proteins represent another mechanism for DDIs that can affect drug absorption, distribution, or elimination. These proteins can be classified into two groups: the ATP-binding cassette family and the solute carrier superfamily; the best-known examples of these groups are P-glycoprotein and OATP, respectively (Preston 2019). Drug transporter proteins affect the pharmacokinetics of drugs within the body through uptake and efflux actions (König 2013). The resulting action of P-glycoprotein inhibition depends on the site of the interaction. For instance, inhibition of P-glycoprotein in enterocytes leads to increased oral bioavailability, whereas inhibition of P-glycoprotein in the liver or kidney can result in reduced drug elimination. Hepatic uptake can be affected through OATP1B1 because it affects that amount of drug entering hepatocytes, the site of major metabolism pathways. The best-characterized DDIs related to OATP1B1 involve statins. Inhibition of OATP1B1, for instance, can lead to increased serum plasma concentrations of statins, increasing the risk of adverse effects.

Overall, however, these various mechanisms do not occur in a vacuum, and a particular DDI may be the result of more than one mechanism. Further complicating the understanding of DDIs is the overlap of drugs that affect both drug transporter proteins and the CYP system. In particular, many drugs are a substrate/inhibitor/inducer of P-glycoprotein together with CYP3A4 (Preston 2019).

Establishing Evidence for Drug Interactions

Inhibition and induction of specific CYP isoenzymes and drug transporter proteins are evaluated primarily through in vitro studies using specific probe substrates (FDA 2020b). Inhibition and induction are assessed during clinical development after characterizing the route of elimination and the impact of enzymes and transporters on the drug, together with the drug's effect on enzymes and transporters. This information combined with pharmacokinetic data informs the in vitro studies that should be conducted. Subsequently, the clinical impact of the interaction can further be assessed through clinical pharmacokinetic studies (FDA 2020a). Clinical DDI studies use drugs known to be reliable inducers, inhibitors, or substrates of the enzyme or drug transporter protein. The FDA provides a list of preferred substrates for these studies on its website and in the clinical guidance for industry; this guidance is currently limited to enzyme- and transporter-mediated interactions. Familiarity with the content of this list is imperative because it helps inform clinical pharmacists on the types of drug interactions likely to be known at the time of a drug's approval.

Some DDIs are not identified until the drug has been approved, and there are notable examples of drugs that were removed from the market because of DDIs leading to serious, potentially life-threatening adverse effects. For example,

major cardiac adverse effects of cisapride were identified in the postmarketing setting through adverse event reporting, where most reports occurred in patients taking interacting medications or having underlying conditions that increased the risk of ventricular arrhythmias, which led to discontinuation of the drug in the United States (Wysowski 2001). This example highlights the importance of continuous surveillance and the need for health care professionals to report adverse events in the postmarketing space. Potential clinically relevant DDIs can also be identified through case reports/series and other retrospective evaluations. Retrospective cohort studies can particularly help identify clinically relevant DDIs, given their ability to evaluate a large number of patients, typically through insurance claims data, where potential DDIs can further be analyzed to measure associations with resulting adverse events (Chang 2017).

However, the strength of evidence supporting a DDI can be poor. Of interest, in an analysis of 58 major or contraindicated DDIs for psychotropic drugs, only one-third of the interactions had supporting evidence from controlled studies showing an impact on drug plasma concentrations (Nguyen 2020). Even more limited data were available for controlled studies showing a clinical impact on the resulting DDI. Furthermore, only 7 of the 58 evaluated DDIs had underlying evidence from studies with at least 100 patients. This analysis highlights the need for clinical pharmacists to evaluate the supporting data for a potential DDI and understand the relative strengths and weaknesses of the available data.

Drug-Drug-Gene Interactions

The CYP isoenzymes and P-glycoprotein are associated with genetic polymorphisms that can affect their functional capacity. Genetic polymorphisms within the CYP system are well characterized, with CYP2C9, CYP2C19, and CYP2D6 being the best-understood isoenzymes. The metabolizing capacity of isoenzymes is categorized into different phenotypes, namely extensive or poor metabolizer or expressers or non-expressers.

The presence of genetic polymorphisms leads to some notable circumstances related to DDIs. First, in studying and identifying potential DDIs, data showing the difference in drug exposure among patients who have different phenotypes of an isoenzyme can help predict the potential for DDIs with drugs that inhibit these isoenzymes. For instance, if there is no significant difference in the serum concentrations of a drug in patients who are extensive versus poor metabolizers for a given isoenzyme, it is unlikely that a strong inhibitor of that isoenzyme will result in a clinically relevant DDI. Second, in evaluating a specific patient for potential DDIs, knowledge of the patient's polymorphisms can help identify whether a DDI is likely to be clinically relevant. For example, a patient who is a poor metabolizer of a CYP isoenzyme would be expected to be minimally affected by drugs that inhibit the CYP isoenzyme, so a clinically relevant DDI would not be expected.

Characterizations of drug-drug-gene interactions have identified three main categories of interactions: inhibitory, induction, and phenoconversion (Malki 2020). Inhibitory and induction interactions occur when both a perpetrator drug and a genetic variant affect the pharmacokinetics of a victim drug. The inhibitory or induction effect can either affect the same isoenzyme or act in concert in two different routes of metabolism. For example, major metabolic pathways for voriconazole include CYP2C9 and CYP2C19, with some minor involvement from CYP3A4 (Preston 2019). Coadministration with ritonavir, a potent CYP2C19 inducer and CYP3A4 inhibitor, generally decreases voriconazole exposure because of CYP2C19 induction. However, in patients who are CYP2C19 poor metabolizers, voriconazole exposure may be increased as the inhibition of CYP3A4 from ritonavir dominates because these patients have little to no CYP2C19 activity. Phenoconversion interactions occur when the perpetrator drug and genetic variant oppose each other, resulting in change of phenotype temporarily. For instance, a patient who is an ultra-rapid CYP2C19 metabolizer can have a drug exposure similar to a poor metabolizer if given a CYP2C19 inhibitor (Malki 2020). Although drug-drug-gene interactions are less well understood for drug transporter proteins, some of these proteins are also subject to genetic polymorphisms; these interactions can also be grouped into the same three main categories. The Pharmacogenomics Knowledge Base is an accessible resource that characterizes some drug-drug-gene interactions.

Drug–Natural Product Interactions

Drug–natural product interactions are also important to note and evaluate because the percentage of adults who use both prescription medications and natural products has increased; a 2015 survey of over 26,000 U.S. adults found that 35% of respondents used at least one herbal supplement (Rashrash 2017). In addition, the survey showed that respondents with chronic diseases were more likely to use herbal supplements (e.g., prevalence of 43%, 41%, and 43% in patients with arthritis, diabetes, and heart disease, respectively). Pharmacokinetic enzyme- and transport-mediated interactions are the most common mechanisms, or at least the most frequently documented, for drug–natural product interactions (Rombola 2020).

However, the data available on natural products are more limited, with fewer *in vitro* studies and even fewer studies establishing clinically relevant DDIs. Further complicating the interpretation of DDI data with natural products is the greater variation between different products of the same herb, and it is sometimes not known which component of a supplement is contributing to the drug–natural product interaction, given that these products can be a complex mixture of active phytochemicals (Fasinu 2012). Clinical pharmacists can help increase the knowledge base for potential drug–natural product interactions by asking patients about their use of natural products and reporting any unexpected adverse events.

PREVENTION OF DRUG INTERACTIONS

Appropriate Prescribing and Risk Assessment

Clinical pharmacists should aim to prevent the potentially harmful effects of a drug interaction before it occurs. However, because clinical pharmacists are unlikely to recollect every potential drug interaction, use of a stepwise approach is key to preventing adverse reactions (FDA 2018). Essential elements of this stepwise approach include incorporating judicious prescribing concepts into patient care, identifying patients at high risk, obtaining a comprehensive medication (CMM) history, and consulting relevant general and specialized resources as necessary.

Although clinical pharmacists do not in many situations have prescriptive authority, application of judicious prescribing concepts can help clinical pharmacists develop a method that emphasizes harmful interaction prevention, translating to recommendations to prescribers with deterrence at the forefront. Appropriate application of selected judicious prescribing principles may prevent negative drug interactions using nondrug alternatives, encourage a focus on underlying causes of health concerns versus treatment of symptoms, help with mastery of a more limited personal formulary for prescribing, assist with patient education regarding potential adverse effects, enable greater collaboration with patients to optimize medication use, promote reassurance and close patient follow-up, and encourage consideration of the long-term risk-benefit of drug therapy over the short-term impact. Clinical pharmacists may also need to reflect on a patient's or caregiver's goals of therapy, the patient's estimated life expectancy, cognitive impairment and visual dexterity concerns, and adherence issues when considering the potential impact of drug interactions and recommendations to prescribers (Halli-Tierney 2019). Judicious prescribing, often called conservative or cautious prescribing, consists of six key principles that promote the effective and safe use of medications (Box 1) (Schiff 2011).

Clinical pharmacists should also assess patients for their potential drug interaction risk. In general, any patient with a medication regimen containing more than one drug or natural product is at risk of developing a drug interaction (FDA 2017). However, older adult patients who are more likely to receive several medications for chronic conditions and those who may be prescribed many medications as part of standard treatment regimens for certain disease states (e.g., heart failure, diabetes) are at higher risk. One way to potentially identify patients at risk of drug interactions is use of a screening tool such as the [Drug-Associated Risk Tool \(DART\)](#). The DART is a validated instrument consisting of 27 risk factors for developing drug-related problems. The DART is basically a patient questionnaire that contains queries regarding health status, medications, and adherence. Investigators conducted

Box 1. Principles of Judicious Prescribing

- Think beyond drugs
 - Seek nondrug alternative therapeutic options initially
 - Consider potentially treating the underlying cause of a health issue rather than prescribing a drug for symptom management
 - Look for prevention opportunities instead of focusing on treating symptoms or advanced disease
 - Use the test of time as a diagnostic and therapeutic trial, when possible, instead of reflexively prescribing a medication
- Practice more strategic prescribing
 - Use only a few drugs and learn to use them well
 - Avoid frequent changing to newly approved medications without clear, compelling evidence-based reasons
 - Be skeptical about “individualizing” therapy, which can often be a code word for “trial and error” medicine
 - When possible, initiate therapy with only one drug at a time
- Maintain heightened vigilance regarding adverse effects
 - Have a high index of suspicion for adverse drug effects
 - Educate patients about possible adverse effects to ensure early recognition
 - Be alert to clues that you may be treating or risking withdrawal symptoms
- Exercise caution and skepticism regarding new drugs
 - Educate yourself about new drugs and indications from trustworthy, unbiased sources
 - Do not rush to use newly marketed drugs
 - Be certain that the drug improves actual patient-centered clinical outcomes rather than a surrogate marker
 - Be vigilant about indications creep
 - Do not be seduced by elegant molecular pharmacology or drug physiology
 - Beware of selective reporting of studies
- Work with patients for a shared agenda
 - Do not hastily or uncritically succumb to patient requests for drugs, especially advertised medications
 - Avoid mistakenly prescribing additional drugs to patients with refractory symptoms, failing to appreciate the potential for patient nonadherence
 - Avoid repeating prescriptions for drugs that a patient has previously tried unsuccessfully or that caused an adverse reaction
 - Discontinue drugs that are not working or are no longer needed
 - Work with patients’ desires to be conservative with medications
- Consider long-term, broader impacts
 - Think beyond short-term beneficial effects to longer-term benefit-risk
 - Look for opportunities to improve prescribing systems in order to improve prescribing and make medication use safer

Information from: Schiff GD, Galanter WL, Duhig J, et al. Principles of conservative prescribing. JAMA 2011;171:1433-40.

a prospective validation study of DART in 195 hospitalized adults on orthopedic, geriatric, and internal medicine units in Switzerland (Kaufmann 2018). These patients completed the questionnaire, and answers were compared with objective patient data from medical records and laboratory results. Results showed that DART was associated with a satisfying feasibility and reliability, with the specificity of statements included in the questionnaire mostly high. The sensitivity of DART varied, with higher sensitivity in statements related to disease states requiring ongoing monitoring and attention to medication management. Overall, the authors concluded that querying patients regarding medications and related problems provides an uncomplicated rapid method of identifying those who may be at increased risk of drug-related problems, including drug interactions, allowing clinical pharmacists to target interventions to patients who may benefit the most.

Comprehensive Medication Management

Comprehensive medication management is the “standard of care that ensures each patient’s medications are individually assessed to determine that each medication is appropriate for the patient, effective for the medical condition, safe given the comorbidities and other medications being taken, and able to be taken by the patient as intended” (ACCP 2021). Obtaining a medication history as part of CMM is fundamental for preventing adverse reactions caused by drug interactions, and one approach for clinical pharmacists to recall components of an appropriate history is to use the “AVOID Mistakes” mnemonic (Box 2) (FDA 2018).

With respect to allergies, patients should be asked whether any medication should be avoided for any reason rather than simply asking whether a drug allergy exists. If a patient

Box 2. The “AVOID Mistakes” Mnemonic for Obtaining a Medication History

- **Allergies**
 - Identification of medications that should not be prescribed for any reason
- **Vitamins**
 - Including natural products or herbs
- **Old and new medications**
 - Including prescription and OTC medications
- **Interactions**
 - Initial assessment of potential interactions
- **Dependence**
 - Consider the need for a behavioral contract in the case of either drug dependence or adherence to a therapeutic regimen
- **Mendel**
 - Family history of beneficial or negative outcomes with medications

Information from: FDA. [Preventable Adverse Drug Reactions: A Focus on Drug Interactions.](#)

indicates an “allergy” is present, follow-up questions regarding associated symptoms should be used to delineate the severity of the reaction. Specific questions regarding natural product (e.g., vitamins, herbs, supplements) use should be asked because patients often do not consider these products as medications that might be subject to interactions. All prescription and OTC medications should be accounted for, including recently discontinued medications because some agents have relatively long-lasting effects. A unique aspect of the mnemonic is identification of patients with drug dependence or adherence issues, with the potential for establishing a behavioral contract to help the patient attain therapeutic goals. Finally, questioning the patient regarding familial responses to relevant medications, whether positive or negative, may determine whether a pharmacogenetic intervention is necessary in order to tailor drug therapy and avoid harmful effects of a drug interaction.

After obtaining a complete medication history, clinical pharmacists may target patients who are prescribed several medications concurrently (i.e., polypharmacy) as a specific population of concern for drug interactions. Although no standard definition of polypharmacy exists, it is often applied when patients are routinely administered five or more medications (WHO 2019). Polypharmacy is a major and growing public health issue globally with negative consequences, including reduced quality of life and increased risk of adverse events, mortality, and health care use for patients; harmful effects on physician functionality and productivity; and proliferation of medication errors (Halli-Tierney 2019; WHO 2019). Many patient- and health care system-related risk factors for polypharmacy exist (Box 3). Clinical pharmacists should be aware of these factors when executing CMM, given that research has shown that patients experiencing polypharmacy

are at increased risk of medication-related harm because of drug interactions and that clinical pharmacist interventions (e.g., pharmacist-led protocols and prescriptive authority) have a significant positive impact (Kasper 2020).

Hand in hand with polypharmacy in the CMM process is the concept of deprescribing (Farrell 2019; Bembem 2016; Garfinkel 2015; Scott 2015). Deprescribing refers to the systematic identification, adjustment, and/or discontinuation of medications when existing or potential harms of medications outweigh benefits within the context of an individual patient's care goals, current level of functioning, life expectancy, values, and preferences (Farrell 2019; Scott 2015). Deprescribing is not a mechanism to deny effective treatment to eligible patients; rather, it is an essential component of the prescribing continuum. Clinical pharmacists can engage in deprescribing as a means to prevent and manage drug interactions. The deprescribing process involves (1) obtaining a complete medication list and determining an indication for each medication; (2) assessing each medication with respect to potential for drug-related harm; (3) weighing the current or future benefits against harms for each medication; (4) developing a plan to discontinue medications, with initial targets being those with the highest burden and lowest benefit; and (5) discontinuing medications and monitoring for improvement in patient outcomes or the development of adverse effects (Bembem 2016; Scott 2015). Clinical pharmacists should consider deprescribing another means of preventing and managing drug interactions in any older patient with a new symptom suggestive of an adverse drug reaction; in those receiving high-risk medications or drug combinations; in those manifesting advanced or end-stage disease, dementia, extreme frailty, terminal illness, or complete dependence on others for care; and in those administered preventive medications for clinical situations associated with no increased disease risk despite drug cessation (Scott 2015). Clinical pharmacists should also be aware of potential barriers to deprescribing, including clinical complexity, limited time for patient consultation, fragmented care involving multiple prescribers, inadequate information related to medication use (e.g., history of drug tolerance or indications for administration), ambiguous or changing goals of therapy, doubt about the benefits and harms of continuing or discontinuing specific medications, provider attitude that leans toward more rather than less drug use, fear of medication withdrawal effects, and pressure to prescribe medications because of evidence-based practice guidelines and recommendations. Despite these barriers, a variety of point-of-care resources are available for clinical pharmacists that can assist with successful deprescribing as a tool for avoiding the potentially negative effects of drug interactions (Table 2).

Box 3. Risk Factors for Polypharmacy

Patient-related

- Advanced age
- Cognitive impairment
- Developmental disability
- Frailty
- Lack of a primary care physician
- Mental health issues
- Several chronic medical conditions
- Receiving care from several subspecialists
- Residency in a long-term care facility

System-related

- Inadequate transitions of care
- Poor medical recordkeeping
- Prescription of medications in order to meet disease-specific quality metrics
- Use of automated refill systems

Information from: Halli-Tierney AD, Scarborough S, Carroll D. Polypharmacy: evaluating risks and deprescribing. *Am Fam Physician* 2019;100:32-8.

Communication and Patient Engagement

When counseling patients regarding the potential for drug interactions, clinical pharmacists should encourage patients

Table 2. Deprescribing Resources

Resources	General Resource Comments	Specific Deprescribing Impact
American Geriatric Society Beers Criteria MedStopper STOPP/START criteria	Clinical pharmacists can use these resources at the point of care to identify potentially inappropriate medications	<ul style="list-style-type: none">• Beers Criteria: List of medications that pose the highest harm to older adult patients; provides potential alternatives to reduce risk• MedStopper: Sequences a patient's medications from "more likely to stop" to "less likely to stop" according to the drug's potential to improve symptoms and reduce the risk of future illness and its likelihood of causing harm; tapering recommendations are also provided, if needed• STOPP/START criteria: Tool used to review potentially inappropriate medications in older adults; application of these criteria may improve medication appropriateness, reduce polypharmacy and adverse drug reactions, and lower medication costs
Deprescribing.org: Guidelines and algorithms Informational pamphlets Shared decision-making in deprescribing	These resources can help the clinical pharmacist engage patients regarding deprescribing and determining potential deprescribing options and provide ongoing support and monitoring	<ul style="list-style-type: none">• This website contains evidence-based deprescribing guidelines and informational pamphlets for PPIs, antihyperglycemics, antipsychotics, benzodiazepine receptor agonists, and cholinesterase inhibitors and memantine. In addition, the site contains a process guide for improving shared decision-making with patients regarding medication management in long-term care facilities

Information from: Halli-Tierney AD, Scarborough S, Carroll D. Polypharmacy: evaluating risks and deprescribing. *Am Fam Physician* 2019;100:32-8; Farrell B, Mangin D. Deprescribing is an essential part of good prescribing. *Am Fam Physician* 2019;99:7-9.

to always read labels carefully and learn about any warnings or major drug interactions associated with their medications (FDA 2008). Clinical pharmacists should explain to patients that there are varying types of drug interactions (e.g., drug-drug; drug-food; drug-condition; drug-laboratory) and that interactions may result in differing effects, including a reduction in therapeutic efficacy of a medication, unexpected adverse effects, an increase in the action of a particular drug, and potentially beneficial effects on a disease state (FDA 2004). To promote safe medication use and reduce the potential for harmful effects related to drug interactions, patients should be advised to store medications in their original container for easy identification; visit a single pharmacy location for all medication-related needs; maintain a listing of all current and recently discontinued prescription, OTC, and natural products; and inform all health care providers about all medicinal products they may be taking (FDA 2008). Encouraging patients to ask questions about potential signs of a drug interaction, useful patient-friendly resources, and any prescription and OTC medications, natural products, food products, and beverages that may need to be avoided when initiating a new medication is also essential.

Over-the-counter medications are of particular concern because they are easily acquired by patients, and the nonprescription Drug Facts label has either limited or nonexistent information on drug interactions. The FDA has developed a

web-based application that provides a full-text search of FDA-approved product labeling documents for prescription drugs and biological products, OTC medications, and animal drug products. This application contains the Drug Facts label information for over 87,000 human OTC drugs as of December 30, 2020 (FDA 2021). Clinical pharmacists can use the Drug Facts label information as a quick resource to determine what drug interaction-related information is available on an OTC label and supplement this information for the patient as necessary.

DRUG INTERACTION RESOURCES

Many general and specialty tertiary resources are available to help clinical pharmacists evaluate and manage drug interactions. These resources may discuss the mechanism of the interaction, rate its significance (including likelihood of occurrence) and severity, discuss factors that may increase risk, explain the quality and clinical relevance of the primary literature supporting the interaction, and provide recommendations for management. Some of these resources are freely available in various formats or exist as a component of a subscription database (e.g., *Clinical Pharmacology, Facts and Comparisons*). This chapter primarily focuses on the drug interaction resources available in electronic formats and does not describe in depth those that may be available in print format. Clinical pharmacists should be aware that all

Patient Care Scenario

A 75-year-old man with hypertension, heart failure, type 2 diabetes, and chronic kidney disease comes to your medication therapy management clinic with his daughter for his initial visit and brings his medications. These include a daily aspirin, enalapril, metoprolol, hydrochlorothiazide, furosemide, glyburide, and ibuprofen. He also mentions that he takes some natural products; however, he did not bring them and cannot recall their names currently. He

ANSWER

Any patient with a medication regimen containing more than one drug or natural product is at risk of developing a drug interaction. However, older adult patients who are more likely to receive several medications for chronic conditions are at higher risk. This patient is an older adult, has several chronic disease states, and is experiencing polypharmacy, given that he is routinely receiving five or more medications. All of these factors increase this patient's drug interaction risk.

There are a variety of steps that you could take to prevent a potential drug interaction beyond identifying high-risk patients. These include incorporating judicious prescribing concepts into patient care, obtaining a comprehensive medication history, and implementing deprescribing principles. For this patient, you can query him (or his daughter) further regarding his current

states that he "generally feels good" except he seems "not to remember a lot of stuff" lately. You are concerned that this patient may be at increased risk of drug interactions and want to intervene to prevent any negative adverse effects. Explain why this patient may be at an increased drug interaction risk and steps you could take to prevent a potential interaction.

prescription, OTC, and natural product use—including dosage regimens and duration of use, medication history (including discontinued products), and allergies—to achieve a more complete picture of his medication profile. After obtaining a complete medication list, you should determine an indication for each product; assess each product for potential drug-related harm; weigh the current or future benefits against harms for each product; develop an appropriate plan for discontinuing medications, if necessary; and monitor the patient for improved outcomes or potential adverse effects if treatment discontinuation occurs. You can use deprescribing resources at the point of care, such as the Beers Criteria and the STOPP/START criteria, to help identify potentially dangerous or ineffective medications for this patient.

1. FDA. [CDER Conversation: Evaluating the Risk of Drug-Drug Interactions](#). 2017.

2. WHO. Medication Safety in Polypharmacy. [Technical Report](#). 2019.

3. Bembien NM. Deprescribing: an application to medication management in older adults. *Pharmacotherapy* 2016;36:774-80.

4. Scott IA, Hilmer SN, Reeve E, et al. Reducing inappropriate polypharmacy. The process of deprescribing. *JAMA Intern Med* 2015;175:827-34.

tertiary resources have innate limitations, including the lag time associated with updating information, most notably for those available in print formats only, and that information within a tertiary resource may be incomplete for various reasons (e.g., space limitations, inadequate searches of the biomedical literature by the author).

Drug Interaction Tools in Tertiary References

Clinical pharmacists are often familiar with tertiary subscription databases if they work in health care settings that provide employees with access to support the optimal provision of patient care. Beyond the general drug information within these resources, these databases contain specific drug interaction tools. The Facts and Comparisons interaction tool allows clinical pharmacists to search for interactions involving various drugs, allergies, and diseases/conditions (Facts and Comparisons 2021). Results from a search provide an analysis of potential drug-allergy, drug-drug, drug-food, and drug-alcohol interactions as well as data regarding pregnancy and lactation concerns, precautions in certain patient populations, and duplicate therapy, if existing. For a specific DDI monograph, the Facts and Comparisons tool rates interaction severity (major, moderate, or minor), documentation

level (established, probable, suspected, possible, doubtful/unknown), and onset (delayed or rapid). The Facts and Comparisons resource provides a short description of the interaction, its mechanism, and the management approach and discusses the primary literature evaluating the interaction with references (if available).

Lexicomp contains the Lexi-Interact tool, which allows users to enter a single medication and observe all potential interactions or enter several medications and run an interaction report (Lexicomp 2021). Patient allergy data can be added, when appropriate, as well. Each interaction monograph is assigned a risk rating (A = no known interaction; B = no action needed; C = monitor therapy; D = consider therapy modification; X = avoid combination), with the progression from A to X associated with an increased urgency for clinical intervention. The monograph also contains a summary statement qualifying the nature of the interaction(s) and an indication of outcome severity and/or onset for an unmanaged interaction. The severity of interaction may be classified as minor (effects tolerable in most situations; medical intervention is not necessary), moderate (medical intervention is necessary to manage effects of the interaction), and major (serious effects may occur with the interaction, including

death, hospitalization, permanent injury, or therapeutic failure). Regarding onset, the tool classifies the time from interaction to occurrence of related adverse events as immediate (0–12 hours), rapid (12–72 hours), or delayed (more than 72 hours). Lexi-Interact also provides clinical pharmacists with recommended action steps for preventing potential interaction-related adverse outcomes and a brief referenced discussion of published literature on the documented or presumed interaction. A unique aspect of Lexi-Interact is the use of “interacting category members.” This section lists all the medications within a specific interacting category and marks with an asterisk those that have specifically been identified in the published literature as being involved in an interaction.

Clinical Pharmacology contains a tool called the Drug Interaction Report (Clinical Pharmacology 2021). Within this tool, clinical pharmacists can add various medications to a drug list and then perform an interaction search. Clinical pharmacists can also check for alcohol, food, caffeine, grapefruit juice, enteral feeding, and tobacco interactions with medications, if necessary, and assess for duplicate therapy. The Drug Interaction Report itself classifies interactions into various severity categories—level 1 (contraindicated; avoid concomitant use), level 2 (major; an intervention should be performed before the drugs are coadministered or at the time of initiation), level 3 (moderate; a preemptive intervention is usually not necessary; however, patients should be monitored closely and counseled regarding potential adverse effects), and level 4 (minor; a clinically significant interaction does not usually occur with concomitant use). The findings within the report are not as in depth as those in Facts and Comparisons and Lexicomp, with the provision of a basic interaction summary statement and an unreferenced paragraph discussing the mechanism of the interaction and management approach. A novel aspect of the drug interaction tool within Clinical Pharmacology is the ability to provide a professional- or consumer-focused report of an interaction, with the consumer report written in patient language and detailing potential interaction-related symptoms.

Micromedex is a widely available database in hospital settings; its drug interaction tool allows clinical pharmacists to enter several prescription, OTC, and natural products; add allergy data, if necessary; and subsequently run a drug interaction report (Micromedex 2021). The report itself details information related to drug-drug, drug-allergy, drug-food, drug-ethanol, drug-laboratory, drug-tobacco, drug-pregnancy, and drug-lactation interactions. The interaction detail is generally more thorough than that in other tools and includes an overall warning statement, an overview of clinical management, a severity level, a documentation rating, probable mechanism and time to onset of the interaction, and a referenced summary and overview of the published literature of the interaction. Interaction severity categories include unknown, minor (the interaction has limited clinical effects), moderate (the interaction may exacerbate the patient's

condition and/or require a therapy alteration), major (the interaction is life threatening and/or requires medical intervention), and contraindicated. A unique aspect of the Micromedex interaction report is a documentation rating system, which ranges from excellent (the interaction is clearly established by results from controlled studies) to fair (available data for the interaction are poor) and unknown.

With the increasing availability of natural products, clinical pharmacists need a reliable source of information specific for drug–natural product interactions. Natural Medicines (formerly known as the Natural Medicines Comprehensive Database) contains such a tool (Natural Medicines 2021). The Natural Medicines interaction checker contains individual natural products as well as brand products that contain several vitamins and herbs. Results from the interaction checker consist of an interaction rating, severity, likelihood of occurrence, and level of evidence. The interaction rating is color coded and may be minor (chance of an interaction occurring is possible, and patients should be made aware of it), moderate (the combination should be avoided or used with caution, and patients should be counseled regarding potential adverse outcomes), or major (concurrent use is contraindicated, and patients should be advised to avoid the combination). The likelihood of the interaction occurring ranges from unlikely (the interaction has only been shown in animal or in vitro research) to likely (well-controlled studies of humans have shown that the interaction occurs). Similar to other databases, the Natural Medicines interaction checker also determines a severity level for the interaction: insignificant, mild, moderate, or high; however, in contrast to others, this checker also uses a level of evidence that shows the types of evidence supporting the occurrence of the interaction. The level of evidence key is classified from A to D, with each level defined as follows:

- A: high-quality randomized controlled trials and high-quality meta-analyses/quantitative systematic reviews
- B: nonrandomized clinical trials, nonquantitative systematic reviews, lower-quality randomized controlled trials, clinical cohort and case-control studies, historical controls, and epidemiologic studies
- C: consensus and expert opinion
- D: anecdotal evidence, in vitro or animal studies, and theoretical effects on the basis of pharmacology

Of note, the checker does not evaluate for the presence of natural product–natural product interactions but only for the existence of drug–natural product interactions.

Specialty Drug Interaction Resources

Some tertiary resources specifically focus on the mechanism, effects, prevention, and management of drug interactions. These include Hansten and Horn's *Drug Interactions* and Stockley's *Drug Interactions*. Hansten and Horn wrote the well-known *Drug Interactions, Analysis and Management* textbook, which used to be printed annually but is now out of print. Their website contains a variety of information on

current topics in drug interactions and clinical decision support (CDS). Hansten and Horn, both pharmacists, are currently the authors of *The Top 100 Drug Interactions: A Guide to Patient Management* (Hansten 2019). The book's 2019 edition contains individual monographs for the top 100 interactions, with comments on the effects observed, management considerations, and patient monitoring recommendations. In addition, the text includes a table of CYP and transporter substrates, inhibitors, and inducers; a section on the effects of antibiotics on warfarin; drug interactions with drugs that prolong the QTc interval; genetic polymorphisms of CYP enzymes; drug interactions with natural products; and a drug interaction probability scale. A unique feature of this resource is use of the Operational Classification (ORCA) system (Hansten 2001), which assigns drug interactions to categories on the basis of management of the interaction as follows:

Class 1: Avoid combination (risk of combination outweighs benefit)

Class 2: Usually avoid combination (use only under special circumstances)

- Interactions for which there are clearly preferable alternatives to one or both drugs
- Interactions to avoid using an alternative drug or other therapy unless the benefit is judged to outweigh the increased risk

Class 3: Minimize risk (assess risk and take one or more of the following actions, if needed)

- Consider alternatives: alternatives may be available that are less likely to interact
- Circumvent: take action to minimize the interaction (without avoiding combination)
- Monitor: early detection can minimize the risk of an adverse outcome

Class 4: No special precautions (risk of adverse outcomes appears small)

Class 5: Ignore (evidence suggests the drugs do not interact)

Stockley's Drug Interactions has been described as the most comprehensive and authoritative reference on drug interactions (Preston 2019). *Stockley's Drug Interactions* is available as an annual textbook and online through Medicines complete with an interaction checker. The text includes interactions between medications, natural products, foods, drinks, and drugs of abuse, with each interaction monograph including the mechanism and clinical evidence for the interaction, an evaluation of its clinical importance, guidance on management, and references. The most recent edition of *Stockley's* contains over 4800 interaction monographs.

Open Access Databases/Websites with Drug Interaction Checkers

Beyond subscription-based resources, there are several open access databases and websites that clinical pharmacists can use for information related to drug interactions (Table 3).

The type and extent of information vary significantly within each resource, with Drugs.com providing a health care professional–focused interaction report that contains the most thorough reference data on the mechanism and clinical management of the interaction. Gold Standard is also notable for its consumer focus and ability to check for interactions with caffeine, enteral feedings, ethanol, food, grapefruit juice, and tobacco. Clinical pharmacists may find this open access site useful when describing the potential effects of an interaction to patients. Clinical pharmacists should also be aware that an interaction may not appear across all of these databases; it may thus be worth validating any interaction concerns by checking two databases if these are the only interaction checkers available.

Evaluation of Drug Interaction Resources

Publications have evaluated, analyzed, and/or compared drug interaction resources. Investigators completed a cross-sectional study of seven drug information resources—Lexicomp, Micromedex, Clinical Pharmacology, Facts and Comparisons, *Stockley's Drug Interactions*, Drug Interactions Analysis and Management (print version no longer available), and Drug Interaction Facts (print version no longer available) (Patel 2016). The authors analyzed the information provided by these resources for 100 drug-drug (n=82) and drug–dietary supplement (n=18) clinically relevant interactions. Two independent reviewers gathered mechanism, severity, clinical effect, level of documentation, and course of action data (if available) from each of the seven resources using a common form. The reviewers also documented the time required to locate and gather the necessary information within the resource. Results showed that, compared with all other resources, Lexicomp (97%), Clinical Pharmacology (97%), and Micromedex (93%) had higher scope scores (i.e., does the resource contain an entry for the interaction?; $p<0.05$) for each comparison. Micromedex had a higher overall completeness score than the other resources ($p<0.01$ for each comparison). Lexicomp, Facts and Comparisons, and Drug Interaction Facts also had higher completeness scores than all the other resources (except for Micromedex) ($p<0.05$ for each comparison). Micromedex had higher consistency scores than all other resources ($p<0.05$ for each comparison). Lexicomp also had significantly higher consistency scores than Clinical Pharmacology ($p=0.021$). All resources were similar regarding time to locate and gather information on the interactions.

Investigators compared the ability of five common DDI software programs (i.e., Lexicomp, Micromedex, iFacts [Drug Interaction Facts], Medscape, and Epocrates) to detect clinically important interactions (Kheshti 2016). The accuracy of these resources was assessed using 360 unknown interaction pairs (taken randomly from prescriptions) and 40 known clinically important interaction pairs. Comprehensiveness was assessed by identifying the presence of the

Table 3. Overview of Open Access Databases/Websites for Drug Interactions

Open Access Resource	Comments	Interaction Example
Epocrates	<ul style="list-style-type: none">• Family of resources about drugs and disease states available online and as a mobile application• Need to register online (for free) before gaining access• Tool: Interaction MultiCheck• Checks for interactions between up to 30 prescription or OTC products at a time• Minimal information provided on the interaction and its management• Information is not referenced	Fluvoxamine + Theophylline Monitor/modify treatment Monitor theophylline concentrations; decrease theophylline to one-third the usual dose; combination may increase theophylline concentrations; risk of toxicity (hepatic metabolism inhibited)
Drugs.com	<ul style="list-style-type: none">• Online and mobile resource that provides drug monographs, a drug identifier, and news related to medication approvals or recalls; contains both a consumer and a professional “edition”• Limitation: Each page of the site contains commercial advertisements• Tool: Drug Interactions Checker• More in-depth interaction information is provided compared with Epocrates with respect to the mechanism of the interaction and clinical management• Searches drug-drug, drug-food interactions as well as therapeutic duplications and provides interaction information focused toward health care professionals and consumers (can change between a professional and consumer drug interaction report)• Classifies the interaction severity as major, moderate, or minor• References for statements in the drug interaction summary are provided in the health care professional report	Fluvoxamine + Theophylline Major interaction: Generally avoid Coadministration with fluvoxamine may significantly increase the serum concentrations of theophylline and the associated risk of toxicity. The mechanism is fluvoxamine inhibition of theophylline metabolism by CYP1A2. Case reports and pharmacokinetic studies indicate that fluvoxamine 50–100 mg/day can reduce the clearance of theophylline by 50%–70%, resulting in toxic theophylline concentrations and/or clinical toxicity in some patients. Two- to 4-fold increases in theophylline serum concentrations or systemic exposure (AUC) and half-life have been reported, with onset of clinical toxicity as early as 2 or 3 days and typically within 1 wk of initiating fluvoxamine. Patients with liver dysfunction may be less susceptible to the interaction. In a study of 10 healthy subjects, 10 subjects with mild hepatic impairment (Child-Pugh class A), and 10 subjects with severe hepatic impairment (Child-Pugh class C), fluvoxamine-induced inhibition of theophylline clearance was reduced from 62% in healthy subjects to 52% and 12% in subjects with mild and severe cirrhosis, respectively. These differences may be the result of reduced hepatic uptake of fluvoxamine as well as reduced hepatic expression of CYP1A2 in the cirrhotic liver Management: Use of theophylline or its salts in combination with fluvoxamine should generally be avoided. If coadministration is required, a reduction in theophylline dosage by one-half to two-thirds should be considered. Pharmacologic response and serum concentrations should be closely monitored after initiation, discontinuation, or change of dosage of fluvoxamine, with the theophylline dosage adjusted accordingly. Patients should be advised to contact their physician if they experience signs and symptoms suggestive of theophylline toxicity such as nausea, vomiting, diarrhea, anorexia, headache, tremor, irritability, confusion, insomnia, seizure, palpitation, and arrhythmia. Other selective serotonin reuptake inhibitors including citalopram, escitalopram, fluoxetine, paroxetine, and sertraline do not significantly inhibit CYP1A2 and may be safer alternatives in theophylline-treated patients

(continued)

Table 3. Overview of Open Access Databases/Websites for Drug Interactions (*continued*)

Open Access Resource	Comments	Interaction Example
Medscape	<ul style="list-style-type: none">• Online and mobile clinical resource that provides clinicians with information on diseases, procedures, and medications; the resource also contains formulary information, medical calculators, and image collections of various disease states• Tool: Drug Interaction Checker• Searches for interactions involving prescription and OTC medications and supplements• Provides an interaction severity classification• Minimal information is provided regarding the interaction; information is not referenced	Fluvoxamine + Theophylline Serious: Use alternative Fluvoxamine will increase the concentration or effect of theophylline by affecting hepatic enzyme CYP1A2 metabolism. Avoid or use alternative drug
WebMD	<ul style="list-style-type: none">• Online and mobile resource that contains information on health, drugs and supplements, living healthy, family and pregnancy, and medical news• Tool: Drug Interaction Checker• Checks for interactions between two or more prescription and OTC medications and supplements• Interaction severity rating classification: Don't use together, serious, monitor closely, minor• Minimal information related to the interaction provided; information is not referenced	Fluvoxamine + Theophylline Serious Potential for serious interaction; regular monitoring by your physician required Fluvoxamine oral will increase the concentration or effect of theophylline oral by altering drug metabolism
Gold Standard	<ul style="list-style-type: none">• Online resource that evaluates potential prescription, OTC, herbal, and vitamin products for interactions• Tool: Drug Interactions• Beyond drug interactions, the database checks for interactions with caffeine, enteral feedings, ethanol, food, grapefruit juice, and tobacco• Links the interaction to the various brand names of the products involved• Includes an interaction severity classification of high, moderate, and low• Information provided is in consumer language; information is not referenced• Interface is minimalist in nature and somewhat clumsy to use	Fluvoxamine + Theophylline Severity: High Fluvoxamine can increase the amount of theophylline in the blood if you are taking either theophylline or aminophylline. Adverse effects from theophylline, aminophylline may become worse. Too much theophylline or aminophylline can cause nausea, nervousness, or sleeplessness and occasionally other effects like rapid heartbeat, tremor, or seizures. Notify your prescriber if any of these effects occur. Your prescriber may need to closely monitor the blood concentration of theophylline
RxList	<ul style="list-style-type: none">• Online resource that is part of the WebMD Consumer Network• Tool: Drug Interaction Checker	Fluvoxamine + Theophylline Serious: Use alternative

(continued)

Table 3. Overview of Open Access Databases/Websites for Drug Interactions (*continued*)

Open Access Resource	Comments	Interaction Example
	<ul style="list-style-type: none">• Classifies drug interactions as contraindicated, serious, significant, or minor• Introductory webpage contains an overview of drug interactions• Contains a “patients and caregivers” and “clinician explanation” of the interaction• Minimal information related to the interaction provided; information is not referenced	Possible serious or life-threatening interaction. Monitor closely. Use alternatives, if available. Fluvoxamine oral will increase the concentration or effect of theophylline oral by affecting hepatic/intestinal CYP3A4 metabolism

Patient Care Scenario

A 65-year-old man presents to the ED with concerns of muscle weakness, stiffness, and dark urine for the past day. He has a history of hyperlipidemia and has been prescribed atorvastatin 40 mg once daily for 2 years. Recently, the patient was initiated on verapamil therapy

for hypertension. No other medications are on his medication list. Explain the process for determining whether the patient's adverse effects are because of a potential DDI, and counsel him regarding what to be aware of regarding drug interactions.

ANSWER

If a drug interaction is suspected in this patient, there are a variety of subscription and open access, general, and specialty tertiary resources (e.g., Facts and Comparisons, Epocrates, *Stockley's Drug Interactions*) that you can consult as a clinical pharmacist for further information. The content within each resource varies; therefore, it is important to check at least two resources to collect as much information as possible before proposing a clinical intervention. The interaction checker in Facts and Comparisons states that atorvastatin/verapamil is a moderately severe interaction with a delayed onset for potential adverse effects. Inhibition of CYP3A4 by verapamil may reduce the metabolic elimination of atorvastatin, leading to an increase in atorvastatin concentrations and subsequent muscle weakness and symptoms of rhabdomyolysis, as in this patient. The interaction checker concludes that the documentation level for this interaction is “probable,” with references provided to support its potential occurrence. The Epocrates Interaction Check provides minimal information compared with Facts and Comparisons and generally states that the combination may result in increased atorvastatin concentrations and subsequent myotoxicity. Neither of these references provides recommendations for clinical management; however, the drug interactions tool in Micromedex supplies such information. Micromedex states that if coadministration of atorvastatin with verapamil is necessary, lower starting and maintenance doses of atorvastatin may be required.

Atorvastatin should be discontinued if the patient has markedly elevated CPK concentrations or if severe myopathy/rhabdomyolysis is diagnosed or suspected. Because this patient appears to have symptoms of myopathy/rhabdomyolysis, discontinuation of atorvastatin in this situation seems warranted.

When counseling a patient regarding drug interactions, clinical pharmacists should explain the varying types of interactions, encourage patients to read labels carefully, be cognizant of warnings or major drug interactions associated with their medications, and be aware that interactions may result in differing effects that are not always negative. To reduce the potential for harmful drug interaction-related outcomes, patients should also be advised to store medications in their original container for easy identification, visit a single pharmacy location for all medication-related needs, maintain a listing of all current and recently discontinued medications and natural products, and inform every health care provider about all medicinal products they may be taking. For this patient, you should explain that adding verapamil for high blood pressure to the existing atorvastatin for high cholesterol led to an increase in the amount of atorvastatin in his blood and the harmful effects he is experiencing. To avoid these effects in the future, different medications may be prescribed to treat his blood pressure and cholesterol issues without the negative muscle effects.

1. Facts and Comparisons [online database]. St. Louis: Wolters Kluwer, 2021.
2. Micromedex [online database]. Ann Arbor, MI: Truven Health Analytics, 2021.
3. FDA. [Avoiding Drug Interactions](#). 2008.
4. FDA. [Drug Interactions: What You Should Know](#). 2004.

following elements within the drug interaction monograph of each resource: severity, onset, mechanism, level of interaction, documentation, management, clinical manifestations, case discussion, related drugs, and reference availability. A total score for each software program was calculated on the basis of the sum of accuracy (75% of the total score) and comprehensiveness (25% of the total score). Lexicomp and Epocrates had the highest accuracy scores, followed by Micromedex, Medscape, and iFacts. The most comprehensive resource was iFacts, followed by Lexicomp. Overall, Lexicomp and Micromedex were determined to provide the most complete, accurate, and user-friendly applications.

Investigators compared the severity categorization of potential psychiatric DDIs provided by six drug interaction databases (i.e., Clinical Pharmacology, Lexicomp, Micromedex, Drugs.com, Medscape, and Epocrates) (Monteith 2019). The authors selected 100 drug interaction pairs for analysis; 67 pairs included a psychiatric and nonpsychiatric drug and 33 included two psychiatric medications. The existing category of each potential DDI provided by the six databases was converted into five categories for analysis: severe (contraindicated), major, moderate, minor, and none. If more than one category for the potential interaction was found for an interaction pair, the more serious category was selected for classification. Results showed that the overall percent agreement regarding the severity categorization for the 100 potential psychiatric drug interaction pairs was 66% and that categorization often differed among the drug interaction databases. The authors recommended that clinicians check more than one drug interaction database in clinical practice because of the differences observed among the databases.

A systematic review of DDI software in clinical practice evaluated the usability and appropriateness of various commercially available electronic databases (Roblek 2015). After performing a systematic literature search, 38 publications were included in the analysis, with most studies (n=26) using a single software for the evaluation of potential drug interactions. Results showed that the most commonly used DDI software in the studies was Micromedex, followed by Facts and Comparisons and Lexicomp. Among studies that compared a database with clinician assessment of a DDI, there was a large discrepancy in the number and relevance of detected interactions, with an overlap as low as 11% in some cases.

Overall, published evidence evaluating available drug interaction resources has generally found subscription-based databases such as Micromedex, Lexicomp, and Facts and Comparisons to be fairly comprehensive in scope, with one analysis concluding that Lexicomp and Micromedex provided the most complete, accurate, and user-friendly applications (Kheshti 2016). However, clinical pharmacists should check more than one drug interaction database in practice, if possible, because differences in interaction severity, documentation, and management may occur among resources.

CDS Tools for Drug Interactions

A chapter on drug interactions would not be complete without a brief mention of the CDS tools used widely in hospitals, pharmacies, and other health care institutions. Because drug interactions may result in patient harm, several electronic prescribing and medication information systems include interruptive alerts and non-interruptive information, either during prescriber order entry or during dispensing/verification, as forms of CDS to warn clinicians of potential interactions (Tilson 2016). In addition, health care institutions may have access to more than one CDS tool with a drug interaction checker; therefore, clinical pharmacists should be aware of the potential for information mismatch regarding drug interactions from CDS tools within their institution.

The Centers for Medicare & Medicaid Services guidelines for achieving meaningful use of electronic health records include drug interaction screening, emphasizing the importance of CDS in this arena. However, issues surrounding the quality of drug interaction alerts and subsequent clinician frustration and alert overrides remain prevalent (Edrees 2020; Poly 2020; Wong 2017; Bryant 2014). To address these concerns, a workgroup was convened to develop recommendations for selecting DDIs for CDS. Members of the workgroup addressed four key questions (Table 4).

Beyond this workgroup, other recommendations focusing on improving the usability of CDS drug interaction alerts were published in 2015 (Payne 2015). The individuals involved in this workgroup achieved consensus through drafting recommendations, collecting verbal or written comments from workgroup members, and revising documents until no additional substantive comments were provided. This group focused on addressing three key questions. (1) What, how, where, and when do we display decision support? (2) Should presentation of DDI decision support vary by clinicians? (3) How should effectiveness of DDI decision support be measured?

Similar to the prior workgroup, members of the 2015 group recommended that each DDI alert should include the drugs involved, a seriousness category, clinical consequences (and frequency), the mechanism of the interaction, contextual information/modifying factors, recommended actions to mitigate potential harm, and information on the underlying evidence for the interaction. The group also recommended that alerts be presented with a consistent use of color, visual cues, terminology, and brevity with minimal impact on clinician workflow. In addition, the most critical information related to the DDI alert should be presented on the top-level screen of the alert, with linked information accessible on demand as necessary, at the point of decision-making. Regarding the presentation of interaction decision support for various clinicians, the workgroup recommended that general alert content be consistent regardless of the clinician; however, the alert message may be altered on the basis of context or function of the health care professional (e.g., recommendations

Table 4. Recommendations for the Selection of DDIs for CDS Systems

Key Questions	Recommendations
What process should be used to develop and maintain a standard set of DDIs?	<ul style="list-style-type: none">• Form a national consensus expert panel to develop and maintain a standard set of clinically relevant DDIs for CDS systems, with oversight by a national organization• Use a systematic process for assembling DDI evidence• Grade recommendations for risk management• Develop a web-based tool to solicit community feedback on recommendations• Ensure periodic and timely updates of the standard DDI set
What information should be included in a knowledgebase of standard DDIs?	<ul style="list-style-type: none">• Each DDI should include:<ul style="list-style-type: none">◦ Severity classification◦ Clinical consequences◦ Frequency of harm and exposure◦ Modifying factors◦ Mechanism of the interaction◦ Recommended actions, with strength of recommendation◦ Evidence, with quality ratings
Can/should a list of contraindicated drug pairs be established?	<ul style="list-style-type: none">• Classifying an interaction as “contraindicated” should occur infrequently and should be reserved for drug pairs where coadministration should not be permitted under any circumstances
How can DDI alerts be more intelligently filtered?	<ul style="list-style-type: none">• Health care institutions should convene an interdisciplinary committee to periodically review commonly overridden alerts and suggest ways to either suppress alerts of minimal value or change their presentation format• Allow users to provide feedback on alerts as part of continuous quality improvement• Do not indiscriminately “turn off” alerts• Modifications to DDI alerts should be done cautiously, with careful evaluation to ensure that patient safety is not compromised• Strategies to actively monitor for signs of harm for patients receiving concurrent medications that may result in a DDI should be incorporated into CDS systems

CDS = clinical decision support.

Information from: Tilson H, Hines LE, McEvoy G, et al. Recommendations for selecting drug-drug interactions for clinical decision support. *Am J Health Syst Pharm* 2016;73:576-85.

Practice Points

Even though pharmacists are experts in managing DDIs and are familiar with their underlying mechanisms, they must stay abreast with research identifying other pharmacokinetic considerations, such as the influence of genetic polymorphisms on DDIs and strategies on how best to treat patients with potential DDIs. Particularly important for patients, pharmacists should engage in CMM to evaluate a patient's full medication profile and seek efforts not only to mitigate DDIs but also to find opportunities to deprescribe.

For DDIs, pharmacists should:

- Understand the underlying mechanisms and clinical data supporting potential DDIs. The strength of evidence should be scrutinized on whether it is supported by data showing clinically relevant outcomes.
- Remain cognizant of patient-specific factors that can enhance the risk of clinically relevant DDIs, such as genetic polymorphisms, polypharmacy, or impaired organ function.
- Obtain comprehensive medication histories, including any OTC or herbal products, to provide a complete DDI assessment.
- Evaluate strategies for mitigating DDIs, which may include monitoring plans or alterations in dose when avoiding interacting combinations is not feasible.
- Consider deprescribing as a means to prevent and manage drug interactions.
- Identify the general and specialty tertiary resources available at a practice site to help evaluate and manage drug interactions and advocate for additional resources if gaps are identified.

for prescribers may focus on monitoring values to order regarding the interaction, whereas pharmacists may require notification to ensure that monitoring orders were placed and the results reviewed). The workgroup also recommended the formation of a professional group or trusted agency to standardize the collection and analysis of DDI decision support/alert data submitted in a de-identified manner to a central repository to help measure the effectiveness of drug interaction CDS tools. Alert override rates alone may not be a good measure of effectiveness.

CONCLUSION

Although the true prevalence of clinically relevant DDIs is difficult to define, clinical pharmacists should be aware of potential mechanisms for interactions and apply available data to an individual scenario. Prevention of adverse events associated with DDIs requires a systematic approach that involves applying concepts of judicious prescribing and CMM, implementing deprescribing principles, identifying patient-specific risk factors, and consulting DDI resources.

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Self-Assessment Questions

1. A pharmacist is tasked with estimating the prevalence of realized drug-drug interactions (DDIs) within hospitalized patients at a tertiary health system. Over the past year, 3145 individual patient encounters are identified. Which one of the following would be the best approach in collecting additional data to estimate the prevalence of clinically relevant DDIs?
 - A. Screen patient medication profiles through Micromedex to identify major interactions.
 - B. Quantify the number of potential drug interaction alerts that appeared in the clinical decision support (CDS) system.
 - C. Evaluate the adverse events reported and their relation to potential DDIs.
 - D. Conduct a Drug-Associated Risk Tool (DART) evaluation for a representative set of the patient encounters.
2. Which one of the following scenarios best represents a clinically relevant DDI?
 - A. Patient recently prescribed oral prednisone currently taking metformin with no significant changes in blood glucose concentrations
 - B. Patient taking furosemide who uses an intermittent albuterol inhaler for asthma symptoms
 - C. Patient taking an antidepressant who experiences diaphoresis and tremor after linezolid is initiated for an infection
 - D. Patient taking omeprazole 20 mg daily who is given fluconazole, resulting in a 2-fold increase in omeprazole AUC
3. A 45-year-old man takes atorvastatin 40 mg once daily for hypercholesterolemia management. His medical history also includes plaque psoriasis, which recently became unresponsive to usual systemic treatments. His physician has prescribed cyclosporine, and the patient presents the prescription to you at the pharmacy. You are concerned about the potential for a DDI between atorvastatin and cyclosporine. Which one of the following monitoring parameters would be best to recommend for this patient if this combination is used?
 - A. Creatinine phosphokinase
 - B. Cyclosporine trough concentrations
 - C. Liver function tests
 - D. Serum creatinine
4. A transplant recipient taking cyclosporine has started taking St. John's wort. Which one of the following adverse effects is best to monitor for in this patient?
 - A. Increased triglycerides
 - B. Renal toxicity
 - C. Sexual dysfunction
 - D. Transplant rejection
5. A pharmacist providing transition of care services reviews a patient whose medical history is significant only for acute coronary syndrome and diabetes who was recently discharged from the hospital after receiving percutaneous coronary intervention. The patient's current medication list consists of aspirin, clopidogrel, lisinopril, metformin, metoprolol, omeprazole, pioglitazone, and simvastatin. Which one of the following is best to recommend for this patient to mitigate potential DDIs?
 - A. Change clopidogrel to prasugrel.
 - B. Discontinue omeprazole.
 - C. Educate the patient on the potential for decreased symptoms of hyperglycemia.
 - D. Change pioglitazone to empagliflozin.
6. A pharmacist is involved in direct patient care at an outpatient clinic where a newly hired provider routinely "individualizes" therapy through trial and error, particularly with recently approved medications. The pharmacist is concerned that this approach to prescribing may increase the risk of medication errors, including drug interactions, and plans to discuss the principles of judicious prescribing with the provider in order to improve the provider's prescribing patterns. Which one of the following principles of judicious prescribing would be best for the pharmacist to prioritize in discussion with the provider?
 - A. Think beyond drugs.
 - B. Maintain heightened vigilance regarding adverse effects.
 - C. Consider long-term, broader impacts.
 - D. Practice more strategic prescribing.

7. A provider at a long-term care facility has asked for the pharmacist's assistance in identifying residents who may be at increased risk of drug interactions in order to target interventions to the residents who may benefit the most. Which one of the following residents is most likely to be at an increased risk of drug interactions?
 - A. Patient A, who has hypertension, diabetes, and heart failure and receives several prescription medications for disease state management
 - B. Patient B, who only takes an aspirin daily for cardiovascular prevention and ginkgo for memory
 - C. Patient C, who currently takes simvastatin for hyperlipidemia and various natural products to promote general health
 - D. Patient D, who recently had a broken leg and is receiving only intravenous morphine as needed for pain
10. K.W. is experiencing polypharmacy, which may increase her risk of drug interactions. The pharmacist obtains a medication list and assesses each medication with respect to potential harm. Which one of the following is the best next step to take for K.W. in the deprescribing process?
 - A. Develop a plan to discontinue medications.
 - B. Discontinue medications and monitor patient outcomes.
 - C. Weigh the current or future benefits against the harms for each medication.
 - D. Seek nondrug alternative therapeutic options for the patient.
11. A patient approaches the pharmacist with concerns related to a potential drug interaction between amiodarone and warfarin. She is aware that an interaction may occur but wonders about the degree to which documentation exists regarding the interaction. Which one of the following resources would be best to consult with respect to the documentation rating of the interaction?
 - A. Micromedex
 - B. Facts and Comparisons
 - C. Clinical Pharmacology
 - D. Lexicomp

Questions 8-10 pertain to the following case.

K.W., a 72-year-old woman, is referred to a pharmacist's comprehensive medication management (CMM) clinic by her new primary care provider. Her home drugs include enalapril, warfarin, aspirin, paroxetine, simvastatin, and ezetimibe. On further discussion, K.W. also admits starting garlic and turmeric a few days ago because she had read these supplements might be beneficial for her.

8. Given her medication/natural product profile, which one of the following potential drug interactions is most important to monitor for in K.W.?
 - A. Concurrent use of aspirin and enalapril, which could increase the effectiveness of enalapril and reduce blood pressure.
 - B. Concurrent use of warfarin with simvastatin, which could increase bleeding risk.
 - C. Concurrent use of warfarin with ezetimibe, which could decrease PT or INR.
 - D. Concurrent use of warfarin and garlic, which could decrease the anticoagulant effects of warfarin.
9. Because of her concurrent use of aspirin and paroxetine, which one of the following is best to recommend for K.W.?
 - A. No additional clinical management
 - B. Close monitoring for signs of bleeding
 - C. Changing aspirin to ibuprofen
 - D. Adding misoprostol
12. A physician stops you in the clinic to ask about open access electronic resources for drug interactions. He is interested in a resource that provides not only an interaction severity rating, description of the interaction mechanism, and recommendations for clinical management for him, but also consumer-focused information that he can potentially share with his patients. Which one of the following information sources is best to share with this colleague?
 - A. Epocrates
 - B. Drugs.com
 - C. Medscape
 - D. WebMD

13. A nurse practitioner calls the pharmacy regarding a potential interaction between atorvastatin and cyclosporine. You consult Hansten and Horn's *Top 100 Drug Interactions* and discover that cyclosporine is likely to increase systemic exposure to atorvastatin, which is a class 2 interaction using the ORCA system. Which one of the following is best to recommend for managing this interaction?
- A. There is no need to avoid this combination; however, monitor the patient closely for signs of myopathy.
 - B. This combination should always be avoided because the risks of therapy outweigh the benefits.
 - C. This combination should generally be avoided and used only under special circumstances; a careful risk-benefit analysis and consideration of alternative drug therapies should inform the decision.
 - D. There is no need to avoid this combination; however, the prescriber can consider alternatives that are less likely to interact, if desired.
14. A nurse approaches you in the hallway seeking your advice. She works part-time in a neighborhood clinic and wonders whether there is an easily accessible online drug interaction resource that she can refer patients to if they have interaction questions. Which one of the following would best provide this colleague with patient-friendly information?
- A. Gold Standard
 - B. Micromedex
 - C. WebMD
 - D. Epocrates
15. A pharmacist is working with the clinical informatics team to update CDS tools to address the recent FDA communication about serious, life-threatening respiratory depression with gabapentinoids, particularly with coadministration with other CNS depressants. Which one of the following strategies would be best to use for DDI alerts to reduce this risk?
- A. Classify the interaction between gabapentin and opioids as contraindicated.
 - B. Include comprehensive, detailed information about the interaction on the top-level screen of the alert.
 - C. Highlight the need to monitor for respiratory depression symptoms for alerts targeted to prescribers.
 - D. Track alert override rates of the message as the sole measure of effectiveness.