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Clinical Reference Guide

Drug-Drug Interactions

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Drug interactions are a major source of patient morbidity and mortality. Analytical evidence of drug or food ingestion and associated reports of potential interactions may help close existing gaps in the medication reconciliation process.

Drug-drug interactions (DDIs), which may occur due to use of multiple medications, may cause adverse drug events (ADEs). ADEs can lead to physical harm, mental harm, or loss of function.[1] Practitioners must therefore be vigilant in assessing patients at risk for DDIs when designing and monitoring pharmacotherapy regimens. Although DDIs are frequently considered in the context of prescription drugs, interactions with foods and supplements can also occur. Throughout this discussion, the abbreviation DDI will be used to address these multifactorial sources of interactions.

A. Mechanisms of Drug-Drug Interactions

There are two types of DDIs: pharmacokinetic and pharmacodynamic. Pharmacokinetics describes the body's actions on a drug, and includes the processes of absorption, distribution, metabolism, and excretion (ADME). When a pharmacokinetic DDI occurs, one or more of the aforementioned processes is affected. Many pharmacokinetic DDIs occur by disrupting Phase I metabolism, a group of processes carried out by the cytochrome P450 (CYP450) enzyme system, either by inhibition or induction. This is pertinent as CYP2C9, CYP2D6, and CYP3A4 enzymes in the CYP450 family are responsible for the metabolism of 18%, 25% and 53% of drugs, respectively.[2] Although interactions may also involve Phase II metabolism such as glucuronide conjugation, these are less prevalent. DDIs involving other kinetic mechanisms, including drug absorption, P-glycoprotein transporter activities, and alterations in plasma-protein binding, have also been described.[3-5]

Consequences of CYP450 inhibition are likely to occur quickly. In contrast, change in patient response to therapy due to enzyme induction occurs gradually over days to weeks.[6] Different enzyme types are susceptible to distinct interactions. For example, metabolic processes involving CYP2D6 enzymes are not inducible, but are capable of being inhibited. CYP3A4 enzymes, on the other hand, are able to be either induced or inhibited by multiple drugs.[6] Examples of inhibitors, inducers, and substrates of the CYP450 enzyme system can be found in literature and online. Some examples available online include the Indiana University's "Drug Interactions Flockhart TableTM" (https://drug-interactions.medicine.iu.edu/main-table) and the Food and Drug Administration's "Drug Development and Drug Interactions: Table of Substrates, Inhibitors, and Inducers" (https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers).[7,8]

Pharmacodynamics is a term that refers to a drug's effects after ingestion. During a pharmacodynamic interaction, one substance may mechanistically facilitate or antagonize the activity of another, leading to supratherapeutic or subtherapeutic effects of one or both substances involved.[6] Examples of this type of interaction include additive central nervous system (CNS) depression due to concurrent use of benzodiazepines and buprenorphine, or drug-induced torsade de pointes caused by taking multiple QT-prolonging medications.[9,10] Additional examples and case studies demonstrating the effects of kinetic and dynamic interactions are widely reported in the literature.

It is important to recognize that the risk for and severity of DDIs may be dependent on the dose of each substance involved and the chronicity of use of the offending agent. The relevance of effects caused by DDIs is highly variable and individualized. Clinical judgment should be utilized when evaluating the impact of DDIs and the risk to patients.

B. Cost and Prevalence of Interactions

According to the World Health Organization, adverse drug reactions are a leading cause of morbidity and mortality.[11] Drug interactions increase hospitalization rates and morbidity, prolong length of stay, and inflate economic burden on the healthcare system.[12-16] Medication-related morbidity and mortality continue

to impose a substantial economic burden on the U.S. healthcare system. A 2018 analysis estimated the annual cost of prescription drug-related morbidity and mortality at approximately $528.4 billion.[17] Studies of major potential drug-drug interactions have also demonstrated increased healthcare utilization and costs among affected patients.[18,19] Contemporary national surveillance further demonstrates that medication-related harm remains a significant contributor to emergency department utilization in the United States.[20]

Previous attempts to describe the prevalence of DDIs, in both general and specific patient populations, have yielded conflicting results. Studies that have attempted to assess occurrence of DDIs in patients often rely on information such as third-party payer claims and pharmacy fill data. Results are complicated by differences in content included in various drug interaction databases utilized when determining potential exposure to interactions. This has led to inconsistencies in reported rates of exposure to a DDI, as studies have concluded that interactions may affect as few as 5.4% of patients, or as many as 63% of patients.[12,16,18] This information may be troublesome for providers when attempting to determine what proportion of patients are actually at risk for ADEs associated with DDIs. More recent pharmacoepidemiologic guidance likewise emphasizes that many potential DDIs are based on pharmacologic predictions or case reports and that not every potential interaction produces a clinically important outcome.[21]

Although the actual prevalence of interactions has been difficult to capture, it is understood that polypharmacy is often the primary risk factor for drug interactions. Studies show that polypharmacy patients, defined as those taking ≥5 medications (or more medications than medically necessary) are at an increased risk for being exposed to a DDI.[22,23] Doan et al. further determined that there was a 12% increase in risk of exposure to a DDI associated with each additional drug added to a 5-medication treatment regimen after adjustment for age and sex.[23] It is increasingly important to understand that addition of medications to a drug regimen in patients with a complex medical history escalates the risk of adverse events, as the number of patients meeting polypharmacy criteria continues to climb.[24,25]
The risk of patients being exposed to interactions, and subsequent risk of suffering an ADE, is further compounded by the usage of over-the-counter (OTC) medications or supplements. Additionally, the potential for OTC medications and supplements to be involved in DDIs is often not appreciated by patients, who frequently omit these from their reported medication lists. In a study conducted by Qato et al., more than one-third of 57 to 85-year-olds reported recent use of more than five prescription medications.[25] Qato et al. also found 47% of older patients admitted to taking OTC medications, and 54% were currently using herbal supplements – these may also be causative factors in DDIs.[25]

C. Current Deficiencies in Identification of DDIs

It has been estimated that 50% of ADEs (which may be caused by DDIs) are preventable.[26] Assessment for DDIs can include the following:

- Medication reconciliation via obtaining subjectively reported home medication lists
- Pharmacy-based drug utilization review
- Reviewing findings of prescription drug monitoring programs (PDMPs)
- Use of automated DDI identification software

The Office of the National Coordinator for Health Information Technology (ONC) has emphasized the importance of identifying DDIs, yet electronic health records (EHR) and computerized provider order entry (CPOE) systems remain reliant on complete, accurate medication data to be of maximum benefit.[27] However, many of the methods currently in use depend on self-reported medication lists. Patients may be unable or unwilling to provide a comprehensive medication history, which can significantly reduce a provider's opportunity to identify DDIs. Providers may forego removing drugs that have been discontinued when reconciling a medication profile which may also contribute to errors. Automated software may be utilized in healthcare settings, but these systems can be circumvented if patients receive medications from multiple providers or pharmacies. PDMPs, while useful, are usually limited to controlled substances and have no nationally standardized method of reporting.

Studies have shown poor ability by providers to accurately identify DDIs consistently with current

methods.[27,28] Medication reconciliation is a common source of error. The results of one study showed that up to 85% of discrepancies in a patient's medication profile occurred due to incorrect self-reported histories.[29] According to Comer et al., of 609 patients evaluated based on pharmacy claims data, 77% had at least one medication discrepancy, and 229 discrepancies involved controlled substances.[30]

Another pitfall of current methods utilized to identify interactions is that use of supplements and OTC medications often go unrecognized or unreported. Healthcare professionals are frequently unaware of their patients' use of these products. Up to 48% of patients may have at least one medication reconciliation error at hospital admission when considering OTC and prescription medications.[31,32] In subjects undergoing orthopedic surgery, 43% were taking supplements, and 41% admitted their surgeons were not aware of their supplement use.[33] Although those receiving medical care may believe that supplements and food products are incapable of causing harmful DDIs, there is a plethora of literature that proves otherwise. St. John's wort, a supplement used for depression, is a known CYP3A4 inducer and can interact with multiple medications (including opioids).[34] Grapefruit, or dietary consumption of foods containing high levels of grapefruit juice, has also been implicated in clinically significant DDIs.[35] Omissions in reporting prescription medications, OTC medications, and herbal supplements can lead to DDIs that impact patient care.

D. Comparison of DDIs and Pharmacogenetics

Pharmacogenetic polymorphisms and DDIs are capable of impacting the effects of a medication by altering either its bioactivity or metabolism. A patient's genetic makeup is static—that is, it will not change over a patient's lifetime. DDIs are dynamic and will fluctuate depending on co-ingestion of other drugs. Drug interactions have the potential to alter the phenotypic expression (observed effect) of a genotype (predicted effect), thus becoming an important consideration when predicting clinical response to a medication. For example, a patient's predicted phenotype following pharmacogenetic testing for CYP2D6 may reveal ultra-rapid metabolism, but if that patient ingests a strong CYP2D6 inhibitor, they may functionally exhibit the same impaired metabolism as an intermediate or poor CYP2D6 metabolizer.[36] This genotype-phenotype mismatch due to nongenetic factors is commonly termed phenoconversion.[37,38] Understanding the potential interplay of pharmacogenetics and DDIs while evaluating therapeutic efficacy or adverse effects associated with a medication regimen is essential. Lack of demonstrable clinical utility for pharmacogenetic testing in pain management should remain a consideration when determining the risks and benefits of pharmacogenetic testing in a given patient.[36]

E. InterACT Rx™: Drug Interaction Testing at Aegis

Due to gaps that currently exist in medication reconciliation processes, analytical testing to identify compounds ingested by patients may significantly improve recognition of potential DDIs. In a published study utilizing analytical testing of blood to determine medical record accuracy, 33% of detected medications in blood were not documented in medical records.[39] InterACT Rx was developed to include substances that primarily impact activity of the CYP2D6 and CYP3A4 pathways due to an understanding that numerous pain management and behavioral health medications are metabolized by these enzymes. InterACT Rx includes CYP2D6 inhibitors, CYP3A4 inhibitors, and CYP3A4 inducers which exhibit strong inhibitory or inductive effects, or that are commonly prescribed.[7,8,40-44] Definitive liquid chromatography/tandem mass spectrometry (LC/MS/MS) test results are reported qualitatively, and testing includes numerous substances (see Table 16.1). Interactions are only reported based on definitive findings in a submitted urine specimen, mitigating the need for providers to solely rely on subjective patient reports of recently ingested substances that may interact with prescribed medications. Interaction information is sourced from First Databank, Inc, and reported according to interaction severity (see Table 16.2).

Interaction descriptions based on positive urine test results are reported with the following limitations/ interpretations:

- Reported DDI test results reflect substances identified in a submitted urine sample through definitive LC/MS/MS testing. Each analyte included

in the profile is tested prior to release of a report. Those substances that are tested, but are not identified, are excluded from the report.

- Interaction severities subject to dose-dependency are reported as the most severe interaction identified as part of the analysis. Patients who are prescribed or taking different dosages of the medication may or may not be subject to the same effects of the interaction.
- Interactions which are variable depending on dosage form are reported only after considering the most commonly prescribed dosage form (usually oral). A patient utilizing a different route of administration (e.g., intravenous or topical) of the same medication may be more or less susceptible to the reported effects of the interaction, or subject to other possible adverse events not reported in the analysis.
- Certain opioids may be co-formulated with other medications for relief of cough/cold symptoms. Interaction severity may be further increased depending on which opioid formulation is ingested by a patient, and providers should determine the type of opioid formulation taken when interactions are identified to evaluate for additive risk of CNS depression.
- Clinical effects of interactions reported for medications which are present only in combination products (e.g., butalbital) may not include all potential interactions of other medications present in the formulation (e.g., acetaminophen, aspirin, caffeine, codeine). These interactions must be evaluated independently as they may present other adverse events/consequences.
- For medications which exist as isomers (e.g., citalopram/escitalopram or levomilnacipran), reported interactions are provided for both isomers.
- Drug interactions are not evaluated for illicit compounds or nicotine. These interactions must be evaluated independently.
- Concurrent ingestion of grapefruit juice and drugs metabolized via CYP3A4 has been extensively studied. Detection of the furanocoumarins bergaptol and dihydroxybergamottin may be indicative of recent grapefruit exposure.[45,46] Furanocoumarins in grapefruit can inhibit intestinal CYP3A4 and increase systemic exposure to some orally administered medications; the magnitude and clinical relevance vary by the drug, patient, and amount consumed.[47] Clinical judgment must be exercised in determining the original source of furanocoumarin exposure and the medication-specific significance of the finding.
- Some medications may be ordered as part of both healthcare adherence testing and DDI testing. If medications are tested in each testing scenario, any discrepancies found between the definitive-qualitative DDI and the definitive-quantitative healthcare adherence test will result in only the healthcare adherence test findings being utilized and reported.

F. Clinical Utility of Testing

Testing for potential DDIs may increase thoroughness and accuracy of the medication reconciliation process, as the results provide objective evidence of ingested medications. When DDIs are identified, InterACT Rx analysis provides clinically actionable information to support healthcare providers during the patient assessment process.

In a retrospective study of over 15,000 patients receiving treatment for chronic pain, addiction, and/or behavioral health conditions, InterACT Rx testing identified one or more drug interactions in 38% of patients; 11% of interactions were considered severe or contraindicated. Patients meeting polypharmacy criteria (5 or more detected substances) were four times more likely to have a DDI identified.[48] Furthermore, in a study assessing primary care physicians' recognition of DDIs, physicians showed a 26-fold improvement in identification of interacting substances utilizing InterACT Rx test results compared to not utilizing this test, and 40% more patients were correctly diagnosed with a DDI as the primary cause of their adverse health issues.[49]

The InterACT Rx test may also reduce outpatient visits and healthcare costs. In a study of 262 patients, the InterACT Rx test was associated with a 27% reduction in the average number of monthly outpatient visits and a 23% reduction in average monthly cost associated with pain-related outpatient visits. Additionally, 51% of identified severe or contraindicated DDIs were no longer present at follow-up after reported through the InterACT Rx test.[50]

Table 16.1: *Compounds Included in InterACT Rx**

ANTIARRHYTHMICS Amiodarone Quinidine Ranolazine ANTIDEPRESSANTS AND ANTIPSYCHOTICS Amitriptyline Aripiprazole Asenapine Bupropion Chlorpromazine Citalopram/Escitalopram Clomipramine Desipramine Desvenlafaxine Doxepin Duloxetine Fluoxetine Fluphenazine Fluvoxamine Haloperidol Iloperidone Nefazodone Nortriptyline Olanzapine Paliperidone Paroxetine Perphenazine Quetiapine Risperidone Sertraline Thioridazine Trazodone Venlafaxine ANTIEMETICS AND GASTRIC REFLUX Cimetidine Esomeprazole/Omeprazole Famotidine Lansoprazole Metoclopramide Ondansetron Promethazine Ranitidine ANTIEPILEPTICS Carbamazepine Clobazam Lamotrigine Oxcarbazepine Phenobarbital Phenytoin Primidone	ANTIHYPERTENSIVES Amlodipine Atenolol Carvedilol Diltiazem Labetalol Metoprolol Nebivolol Nifedipine Propranolol Timolol Verapamil ANTIMICROBIALS AND ANTIRETROVIRALS Acyclovir Atazanavir Azithromycin Chloroquine Ciprofloxacin Clarithromycin Cobicistat Darunavir Delavirdine Efavirenz Erythromycin Etravirine Fluconazole Fosamprenavir Indinavir Itraconazole Ketoconazole Levofloxacin/Ofloxacin Metronidazole Nelfinavir Nevirapine Posaconazole Quinine Rifabutin Rifampin Rifapentine Ritonavir Saquinavir Terbinafine Tipranavir Valacyclovir Voriconazole ANTI-PARKINSON AGENTS Carbidopa/Levodopa Ropinirole ANTITHROMBOTICS Apixaban Clopidogrel Rivaroxaban Warfarin	CHEMOTHERAPEUTIC AGENTS Abiraterone Anastrozole Doxorubicin Enzalutamide Nilotinib Pazopanib COGNITIVE ENHANCEMENT Atomoxetine Donepezil Guanfacine Memantine FOODS AND SUPPLEMENTS Grapefruit Furanocoumarins Kava St. John's Wort INHALED CORTICOSTEROIDS AND BETA AGONISTS Albuterol Formoterol Salmeterol MISCELLANEOUS Atorvastatin Avanafil Baclofen Butalbital Canagliflozin Cyclobenzaprine Hydroxyzine Linagliptin Lorcaserin Methadone Methocarbamol Methotrexate Mirabegron Pioglitazone Sumatriptan Tizanidine Zileuton STEROIDS AND HORMONES Dexamethasone Methylprednisolone Prednisone

**Composition and number of analytes in testing profile subject to periodic updates.*

Table 16.2: *Interaction Severity*

DRUG-DRUG INTERACTIONS	
Contraindicated	Generally should not be administered to the same patient.
Severe	Action is required to reduce the risk of severe interaction.
Moderate	Assess the risk to the patient and take action as needed.
Undetermined	Evidence may be insufficient to assign level of severity (used for supplements).
DRUG-FOOD INTERACTIONS	
Most Significant	Documented; (more clinical data may be needed). Action to reduce risk of adverse interaction usually required.
More Significant	Documented; (more clinical data may be needed). Assess risk to patient and take action as needed.
Significant	Documented; (more clinical data may be needed). Conservative measures are recommended until more is known.

Patients with multiple disease states or those who receive care from more than one practitioner may be at risk for polypharmacy and DDIs. Patients with a genetic polymorphism predicting impaired metabolism (e.g., CYP2D6 poor metabolizer) may also be at risk for increased effects from DDIs. Others with risks for DDI-related morbidity and mortality, such as elderly patients or those with abnormal organ function, may be candidates for testing.

Clinical circumstances which raise suspicion for a DDI include patients presenting with adverse effects or intolerance to prescribed therapy, clinical non-response, unusual or atypical dose escalation patterns, or other changes in clinical presentation/condition in a previously stable patient. Unexpected laboratory results may also warrant further investigation. For example, a urine test result for parent drug with no metabolites present may indicate tampering (e.g., direct addition of drug to urine to appear adherent with prescribed therapy) or may occur secondary to an excretion pattern affected by a DDI. In cases of very high parent drug concentrations (particularly when multiple metabolites are absent), the chances of adulteration likely exceed that of an interaction, but clinical judgment should be utilized in discerning the cause of a high drug concentration. Furthermore, DDIs may contribute to unexpected negative immunoassay tests due to a failure to detect metabolites, particularly for opioids and benzodiazepines.[51-53]

G. Conclusions

DDIs may strongly influence patient response, alter pharmacokinetic parameters, contribute to adverse effects and morbidity, increase healthcare costs, and impact toxicology results. Complete assessments for medication history are difficult to perform, and DDIs are frequently overlooked. An analytical DDI test may not identify every possible interaction, but it can isolate common causes of DDIs impacting pain management and behavioral health medications. InterACT Rx provides objective information that can facilitate intervention prior to the patient suffering serious adverse effects, and providers can utilize this tool as an important element of patient care.

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