Chapter 10
Drug-Drug Interactions and Psychiatric Medication

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Introduction

How many of us in clinical practice have heard the question: "Doctor, will this drug interact with any of my other medications?" This common question has been challenging to answer, often leading to using laborious drug interaction computer programs, smartphone-based programs, or a call to the pharmacist. The purpose of this chapter is to help address this question, assess the likelihood of a drug-drug interaction, and advise the patient on what to expect should they experience an adverse drug effect.

This chapter will discuss serotonin syndrome and other toxicity syndromes, adverse drug events (ADEs), drug-drug interactions (DDIs), the P450 enzymatic system, and the multiple inhibitors and inducers of drug metabolism. It will also address genetic variability of drug metabolism within certain populations and ethnic groups. Finally, we will develop a system for evaluating DDIs that includes a pocket-sized guide that can be used in the office or bedside to determine whether a patient may be at risk for a DDI.

Case Study

A 93-year-old woman presents with a 6-week history of recurrent syncopal events. She had been previously high functioning, living alone in her own home. One morning upon getting out of bed, she fell forward when bending for her slippers, falling

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to the floor without injury. She denied vertigo or loss of consciousness but felt "top heavy." Two weeks later, she had a second event while on the commode, felt suddenly unwell, and then fell off the commode, fracturing the left ankle. In the hospital, a carotid US showed a 90% stenosis of the left internal carotid artery. She underwent urgent endarterectomy and was discharged to short-term rehab. While there, she had a third event of dizziness, light-headedness, and loss of consciousness while on the commode, falling to the floor with confusion and slurred speech, lasting several minutes.

In the hospital, she had no orthostatic hypotension, and Dix-Hallpike testing was normal. She was found to have hypokalemia, hypocalcemia, and hypomagnesemia.

It was noted on her medication that she takes metoprolol. When asked, she admitted to taking nightly acetaminophen with diphenhydramine (Tylenol PM) for sleep.

Diphenhydramine, an antihistamine, is a common over-the-counter sleep aid. It is a substrate and an inhibitor of the P450 enzyme 2D6, which metabolizes 25% of all commercially available medications [1]. Metoprolol is also a substrate of 2D6. Coadministration of a substrate (metoprolol) and an inhibitor (diphenhydramine) of the same enzyme may increase serum concentrations of the substrate. In the case of metoprolol, an already active parent compound, this may lead to toxicity, resulting in bradycardia and hypotension [2]. It is suspected that the patient may have had syncope due to the interaction of diphenhydramine with metoprolol [3].

The converse is true in the case of a prodrug such as hydrocodone, which must be converted to its active metabolite, hydromorphone. When codeine cannot be converted to morphine due to P450 enzyme inhibition, the patient may have inadequate analgesia [4].

Pharmacogenomic differences may also contribute to drug-drug interactions. Five to 10% of Caucasians are poor metabolizers of CYP2D6, meaning they have fewer than two copies of the gene for the enzyme [5]. Metabolically active parent compounds like diphenhydramine and metoprolol will have higher concentrations in poor metabolizers, increasing the risk of toxicity [1]. Prodrugs such as hydrocodone and clopidogrel, metabolized by 2D6 and 2C19, respectively, lose efficacy in poor metabolizers, due to an inability to convert to the active metabolite [4].

The Impact of Libby Zion on Resident Education

In 1984, an 18-year-old college freshman died in New York Hospital. Few events have had as great an impact on medical resident education [6]. Libby Zion was admitted for agitation, confusion, and muscular twitching. She had a history of depression and was taking phenelzine, an MAO inhibitor. The house officers assigned to her care prescribed meperidine and haloperidol for sedation and placed restraints to prevent self-harm. By the following morning, she had a fever of 107F and died from a cardiac arrest. Her father Sidney Zion, a prominent journalist, brought charges against the hospital and the physicians, indicting the medical

training system for excessive work hours and poor supervision that, he argued, contributed to poor judgment and medical negligence [6, 7].

In 1995, the jury in the *Zion v. New York Hospital* trial returned a mixed verdict, finding that the doctors were partially responsible for Libby's death but that Libby was also responsible based on autopsy samples positive for cocaine metabolites. Later, the New York Supreme Court threw out the cocaine evidence. They upheld the damages against the doctors and found the hospital not guilty of negligent trainee supervision given the training standards of the time [6, 7].

As a result of Libby's death, and her father Sidney Zion's considerable influence, the Bell Commission was convened in New York to address the issue of residency work hours [8]. In 2003, the ACGME adopted most of the Bell Commission's recommendations, restricting residency work hours at all US training programs to 80 h per week [9].

But would the current work hour restrictions have saved Libby Zion? Would a well-rested resident have recognized the signs and symptoms of serotonin syndrome that Libby Zion exhibited, namely, confusion, agitation, and muscular hyperactivity? Would the doctor have known that meperidine is associated with significant drug interactions that might worsen serotonin syndrome? Libby Zion's death was more likely due to a knowledge deficit than a sleep deficit.

An important lesson from Libby Zion's death is that drug-drug interactions (DDIs) and adverse drug events (ADEs) are common and under-recognized. Prescribers are often unaware of the potential for harm in many commonly prescribed medications.

Scope of the Problem

Adverse drug events (ADEs) are common. In an ambulatory setting, the rate of ADEs is 50 per 1000 person-years, of which 28% are considered preventable. Cardiovascular medications were the most common cause, followed by diuretics, nonopioid analgesics, hypoglycemics, and anticoagulants [10].

Almost 6.5% of all hospitalized patients are admitted due to ADEs, with a fatality rate of 0.15% [12]. Fear of receiving the wrong medication while in hospital is a common concern of patients [12]. High rates of hospitalization have been confirmed in multiple studies, of which two thirds are considered preventable [11, 13, 14].

Drug-drug interactions (DDIs) are a fraction of all ADEs [15]. However, most potential drug-drug interactions do not actually occur [16]. Despite the frequency of theoretically dangerous medication combinations, actual harm is relatively infrequent. Using a computerized interaction tool, Marino found 12,578 potential drug-drug interactions among 3473 emergency department patients, with 9% actually having the expected interaction [17].

Electronic medical records frequently flag potential drug interactions, but the relative infrequency of DDI may cause busy clinicians to ignore repetitive notifications when ordering medications, something known as alert fatigue [18].

Table 10.1 High Risk medications for side effects and interactions [22]

Amiodarone	Clonidine	Meprobamate
Amphetamine	Desmopressin	Metoclopramide
Anorexiants	Desiccated thyroid	Methyldopa
Anticholinergics	Disopyridine	Muscle relaxants
Antihistamines	Fluoxetine	Nifedipine
Antispasmodics	Indomethacin	Nitrofurantoin
Barbiturates	Ketoralac	Proton pump inhibitor
Benzodiazepines	Linezolid	Tricyclic antidepressants
Bisacodyl	Long-acting NSAIDs	Theophylline
Sulfonylureas	Meperidine	Typical antipsychotics

Despite the emphasis on detection and prevention of DDIs, the advent of computerized order entry has not substantially reduced the frequency of these events [19].

The adverse drug events reporting system of the FDA estimate roughly 15,000 deaths per year can be attributed to medication effects [20]. ADEs account for up to 6.5% of hospital admissions [11]. In 2011, there were an estimated 100,000 emergency visits for ADEs, 48% occurring over age 80 and two thirds due to unintentional overdose [21]. The most common medications were warfarin, insulin, antiplatelets, and oral hypoglycemic agents. Only 1.2% were due to a high-risk medication as listed in Beers list [22] (Table 10.1).

One third of all ED visits for ADRs involved just three medications: warfarin (17.3%), insulin (13.0%), and digoxin (3.2%) [21, 23].

It is no wonder that ADEs are so common. In 2006, the Slone Survey reported 82% of adults and 56% of children in the USA take at least one prescription or nonprescription medication or dietary supplement. Over age 65, 17% take ten or more medications in a given week [24].

Risk factors for ADEs and DDIs include age greater than 65, multiple medications and OTCs, genetic variability in drug metabolism, and medical comorbidity [13, 15]. Drug-drug interactions represented 3–5% of all in-hospital medication errors [16]. A lack of awareness of drug interactions by physicians also contributes to the problem [25].

Adverse drug reactions may occur by a variety of mechanisms as listed in Table 10.2 [26].

Clinical Syndromes of Drug Toxicity

There are many clinical syndromes relevant to neurologic practice that result from drug toxicity (Table 10.3).

Several are associated with acute confusional states, a common reason for neurologic consultation. Many of these agents are present on the Beers list of potentially inappropriate medications (Table 10.1).

Table 10.2 Types of adverse drug events

Type A – predictable based on drug concentration
Pt receives too much (benzos and confusion)
Pt metabolizes slowly, causing toxicity
Genetic variation (2D6 deficiency and venlafaxine)
Pharmacokinetic drug-drug interaction (fluvoxamine and clozapine- encephalopathy)
Pt metabolizes slowly, inactivating prodrug
Genetic variation (2D6 deficiency and codeine)
Pt has side effects at therapeutic levels (constipation w/ opioids)
Type B – aberrant reaction, not predictable
Drug allergy – rash with phenytoin
Idiosyncratic –Stevens-Johnson w/ carbamazepine

Table 10.3 Clinical syndromes related to medication toxicity

Clinical syndrome	Medication examples
Serotonin syndrome	SSRI, meperidine, MAOI, linezolid [27]
Neuroleptic malignant syndrome	Haloperidol, chlorpromazine [28]
Extrapyramidal syndromes	Metoclopramide, neuroleptics [29]
Myoclonus, falls, asterixis	Gabapentin [30]
Anticholinergic syndrome	TCA, trihexiphenadyl, atropine [31]
Stevens-Johnson syndrome	Carbamazepine, lamotrigine [32]
Drug-induced seizure	Bupropion, diphenhydramine, TCA [33]
Syncope from prolonged QT	Many SSRIs, TCAs, Haldol [34]
Reversible cerebral vasoconstriction syndrome (RCVS)	Sympathomimetic amines, marijuana, cocaine, fingolimod [35]
Posterior reversible encephalopathy syndrome (PRES)	Phentermine [36]

A number of commonly prescribed medications may induce neurotoxicity including confusion, myoclonus, asterixis, and increased risk of falls in patients with low creatinine clearance (<60 ml/min). The most common is gabapentin but also duloxetine, levetiracetam, pregabalin, and tramadol [22]. Gabapentin is a common cause of neurotoxicity in patients with low creatinine clearance [37, 38]. Patients may develop confusion, myoclonus, asterixis, and obtundation [30, 39]. They may present as recurrent falls due to asterixis of the legs, inducing unexpected knee buckling [40, 41].

The term serotonin syndrome was first coined by Sternbach in 1991 [42]. It is a potential complication of serotonergic drugs, especially when used in combination [43, 44].The incidence is unclear, since most cases are probably unrecognized. On occasion, cases are overestimated. An FDA alert warning of the risk of serotonin syndrome with the combination of SSRI and triptans was likely unwarranted based on poor documentation [45]. Toxicity occurs in 27% and deaths in 0.3% of patients overdosing on SSRIs [46]. For nefazodone, the incidence is 0.4 cases per 1000 patient-months [47].

Table 10.4 Clinical features of serotonin syndrome [48]

Cognitive dysfunction	Autonomic instability	Motor manifestations
Confusion	Tachycardia	Shivering
Disorientation	Hyperthermia	Multifocal myoclonus
Agitation	Diaphoresis	Tremor
Irritability	Hypertension	Asterixis
Euphoria	Mydriasis	Muscular rigidity
Hypomania	Hypotension	Hyperreflexia
Hallucinations	Pupillary dilatation	Ataxia
Coma	Diarrhea	Seizures
	Abdominal cramping	Clonus
		Nystagmus

Patients present with a clinical triad of mental status changes, autonomic instability, and motor hyperexcitability, usually within 24 h of a change in medication [43]. Most patients recover within 1–2 days after drug withdrawal; however some may develop respiratory failure, seizures, rhabdomyolysis, and cardiac arrest (Table 10.4). Mortality from serotonin syndrome was associated with use of MAO inhibitors but now is quite rare in recent series [27].

Some overlap of symptoms and signs exist for serotonin syndrome, neuroleptic malignant syndrome, and anticholinergic toxicity. They can generally be distinguished by the motor hyperexcitability, rapidity of onset, and recent addition or increase of a serotonergic medication [43].

Serotonergic drugs may act by increasing serotonin synthesis (tryptophan), decreasing serotonin metabolism (phenelzine, selegiline), increasing serotonin release (amphetamines, cocaine), and inhibiting reuptake (SSRIs, SNRIs, TCAs, meperidine, dextromethorphan). Some act directly on serotonin receptors (buspirone, triptans).

The treatment of serotonin syndrome is supportive care, with no randomized trials of any specific therapy. Most respond to withdrawal of the offending agent, intravenous fluids, benzodiazepines for agitation and myoclonus, anticonvulsants for seizures, critical care monitoring for autonomic instability, and airway protection. Cyproheptadine, a nonspecific serotonin receptor blocker, may be used in doses of 4–24 mg/day administered by nasogastric tube. Other agents have been tried anecdotally including dantrolene, propranolol, mirtazapine, and atypical antipsychotics. Bromocriptine, an agent commonly used for neuroleptic malignant syndrome, may exacerbate serotonin syndrome due to its indirect effect on serotonin metabolism and should be avoided [43].

P450 Metabolism

Over 95% of commercially available drugs are metabolized by the P450 system. Most are metabolized by just five enzymes: CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4.

The p450 enzyme system is an important determinant of drug interactions. With the exception of renal failure, alterations in protein binding are less clinically relevant than the P450 system [49, 50]. Even highly protein-bound drugs such as phenytoin and warfarin quickly alter binding ratios when coadministered and achieve a new steady state. Less well appreciated by practicing physicians is that medications may compete with, inhibit, or induce the metabolism of other drugs. Further, some of these enzymes are subject to genetic variation, making affected patients susceptible to toxicity at lower than expected doses [5, 51].

Drugs undergo phase I, II, and III metabolism. Phase I is carried out by the P450 system, primarily in the liver, and includes oxidation, hydroxylation, acetylation, and methylation [52].

Monamine oxidation, also phase I, is not part of the P450 system.

Phase II prepares the drug for elimination. Glucuronidation and sulfation increase water solubility, enhancing elimination in the urine or stool. Important drug interactions occur during phase II metabolism, such as the interaction of lamotrigine with valproate leading to Stevens-Johnson syndrome [53]. Further discussion of phase II metabolism may be found in Sirot et al. [26].

Phase III refers to the action of P-glycoprotein and other intracellular transporters. They account for the blood-brain barrier. Inhibitors of P-glycoprotein increase the permeability of the blood-brain barrier, allowing certain compounds to penetrate the CNS. An example is the combination of quinidine, a P-glycoprotein inhibitor, with loperamide, a peripherally acting opioid used for diarrhea. Patients on both may experience a central narcotic effect of loperamide in the presence of quinidine [54, 55].

P450 Enzyme System (Fig. 10.1)

These enzymes are located primarily in the liver, kidney, intestine, lungs, and brain. Six enzymes metabolize over 80% of all medications [2, 52]. They are CYP1A2, 2B6, 2C9, 2C19, 2D6, and 3A4.

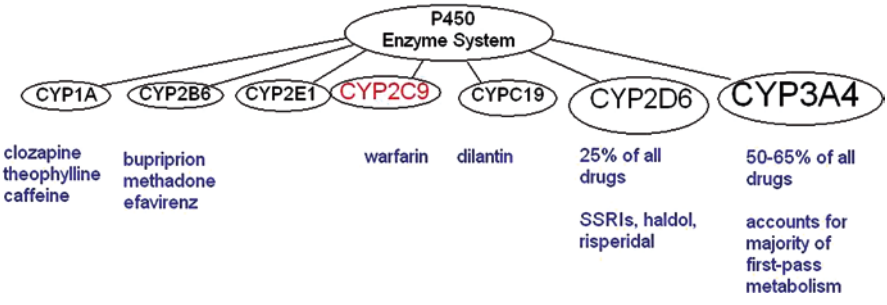

Fig. 10.1 P450 enzymes and some examples of representative drugs

CYP2D6, 2C19, and 2C9 are especially prone to genetic variability. Depending upon the number of gene copies of a particular allele, patients may be poor metabolizers (no functioning alleles), intermediate metabolizers (1 copy), extensive metabolizers (2 copies – the normal state), or ultrametabolizers (3–13 copies).

Substrates/Inducers/Inhibitors

Drugs may be substrates (requiring the enzyme for its metabolism/activation), inhibitors (preventing the metabolism of other substrates of the enzyme), or inducers of enzymatic activity, leading to accelerated metabolism/activation of another drug. Some drugs such as fluoxetine may be both a substrate of 2D6 at low concentrations and an inhibitor at higher concentrations [2]. The pharmacokinetic mechanism of drug interactions may be enzyme competition from two substrates [4], enzyme inhibition of a substrate by an inhibitor [4, 56], or enzyme hyper- or hypometabolism of a substrate medication due to pharmacogenetic variants of P450 enzymes [5, 57, 58].

Genetic Variants and Pharmacogenomics

Pharmacogenomics is the study of the variability in drug metabolism in individuals. Most P450 enzymes have two gene copies. However, an individual may have none, one, or more than two copies, thus increasing or reducing the rate of metabolism of the substrate medication. The multiple variants of the enzymes are termed polymorphisms. Screening tests are available from commercial laboratories that assess the likelihood of genetic susceptibility to drug interaction. Phillips reviewed 18 studies of ADEs related to genetic variations of CYP enzymes. Two thirds of the 27 drugs most commonly identified are metabolized by an enzyme with genetic variants [59].

Although 2D6 polymorphisms are present in 7% of the population, 14% of hospitalized psychiatric patients have 2D6 variants, suggesting a far greater risk of adverse drug events requiring hospitalization [60] (Table 10.5).

Table 10.5 Genetic polymorphisms and clinical relevance [26]

Polymorphism	Frequency	Drugs affected
CYP2C9 poor metabolizer	6–10% Caucasian	Phenytoin, warfarin, tolbutamide or glipizide
CYP2C19 poor metabolizer	13–23% Asian	Barbiturate, benzodiazepine
CYP2D6 poor metabolizer	1–10% Caucasians 1–4% African	Toxicity with TCAs, typical antipsychotics
CYP2D6 ultra metabolizer	25% Ethiopians 5–20% Turks, Southern European, Saudi Arabia	Opioid intoxication with codeine

Prodrugs

Some agents like hydrocodone and clopidogrel are prodrugs. They must be converted by 2D6 or 2C19, respectively, to the active compound. Other agents like metoprolol are metabolically active prior to 2D6 metabolism. Therefore coadministration of codeine and an inhibitor of 2D6 such as diphenhydramine or paroxetine may lead to inadequate analgesia due to lack of conversion of codeine to its active metabolite, morphine. Conversely, coadministration of metoprolol with an inhibitor of 2D6 such as amiodarone may lead to metoprolol toxicity with hypotension and bradycardia [4, 56].

P450 Enzyme Subtypes

CYP1A2 metabolizes 15% of all drugs, including caffeine, benzodiazepines, SSRIs, haloperidol, and clozapine [61]. Activity of metabolism is induced by tobacco [62] and inhibited by fluvoxamine, quinolones, and cimetidine. There is mild genetic variability.

CYP2C9 metabolizes 20% of the most commonly prescribed drugs, most importantly warfarin. Other "substrates" include phenytoin, tolbutamide, glipizide, losartan, fluvastatin, and NSAIDs. It is inhibited by fluconazole and induced by phenobarbital and rifampin. Up to 10% of Caucasians may be 2C9 deficient and may develop bleeding on usual doses of warfarin due to an inability to metabolize the drug. An FDA alert encourages physicians to consider genetic screening in patients whose anticoagulation is difficult to manage [63].

CYP2C19 metabolizes citalopram, diazepam, and omeprazole. It is inhibited by fluoxetine, fluvoxamine, omeprazole, and certain HIV drugs. It is induced by phenobarbital and rifampin. Up to 20% of Asians may be 2C19 poor metabolizers and are susceptible to toxicity on standard doses of diazepam [52, 63].

CYP2D6 is responsible for 25% of P450 drug metabolism, particularly the SSRIs, TCAs, phenothiazines, risperidone, and codeine. It is inhibited by amiodarone, fluoxetine, paroxetine, cimetidine, and quinidine. It may be induced by dexamethasone. 2D6 has significant polymorphisms. One in 10–14 Caucasians and 4% of African Americans are poor metabolizers. Because codeine must be converted to morphine to have an analgesic effect, these patients experience no analgesia with codeine. A small percentage are ultrametabolizers (1–7% of Caucasians, 25% of Ethiopians), leading to excessive narcosis on standard doses of codeine [51]. Conversely, patients deficient in 2D6 may develop toxicity on standard doses of active compounds such as haloperidol, due to inability to convert to inactive metabolites [64, 65].

CYP3A4 metabolizes 60% of currently available medications, including calcium channel blockers, HIV drugs, statins, cyclosporin, antihistamines, and cisapride. It is present in the intestinal mucosa and liver and accounts for the majority of first-pass metabolism. The enzyme lining the intestine is strongly inhibited by grapefruit juice [66]. The furanocoumarins in the fruit inactivate the enzyme in the gut, reduc-

ing first-pass metabolism, and allows for higher concentrations of drug leading to toxicity [52]. Other inhibitors include ketoconazole, metronidazole, AZT, omeprazole, erythromycin, and verapamil. The enzyme is induced by *Hypericum* (St John's-wort), carbamazepine, phenobarbital, and phenytoin [67].

Substrates/Inducers/Inhibitors

The majority of clinically useful medications are P450 substrates, meaning that they are metabolized by one or more P450 enzymes [52]. Medications may also be inhibitors or inducers (activators) of enzyme metabolism. Inducers are medications that increase the activity of enzyme. Inhibitors reduce enzyme activity. An agent may be both a substrate at low concentrations, and an inhibitor at higher levels, thus providing a potential check on toxicity. Some medications may be metabolized preferentially by one P450 enzyme at lower concentrations and by one or more others enzymes at higher concentrations. An example is codeine, a prodrug, which is a substrate of 2D6 but also 3A4 [51] (Table 10.6).

Prodrugs

Tamoxifen, a common antihormonal agent for the treatment of breast cancer, is a substrate of both 3A4 and 2D6. If taken with potent inhibitors of 2D6 metabolism such as fluoxetine, duloxetine, or diphenhydramine, tamoxifen is unable to be converted to its active form endoxifen, rendering it ineffective (Table 10.7).

Table 10.6 Significant P450 enzymes and clinically relevant drug-drug interactions [2]

Drug 1	Enzyme inhibitor or inducer	Drug 2	Metabolizing enzyme	Clinical effects
Fluoxetine, paroxetine	CYP2D6 inhibitor	Risperidone, tramadol	CYP2D6	Risperidone toxicity, inadequate pain relief
Grapefruit juice	CYP3A4 inhibitor	Buspirone	CYP3A4	Toxicity, serotonin syndrome
Diphenhydramine	CYP2D6 inhibitor	Amitriptyline	CYP2D6	Dry mouth, cardiac arrhythmia [68]

Table 10.7 Common prodrugs

Common prodrugs in clinical practice
Hydrocodone
Tramadol
Clopidogrel
Tamoxifen
Midodrine
Losartan
Azathioprine

Table 10.8 A top ten list of potential DDIs

Substrate	Inhibitor or inducer	Toxicity
Risperidone	Fluoxetine, paroxetine	Inhibits 2D6, leading to risperidone excess, sedation
Buspirone	Grapefruit juice	Increased absorption of buspirone due to 3A4 inhibition in the gut, leading to somnolence
Hydrocodone	Amiodarone, SSRIs	Lack of pain relief due to 2D6 inhibition
Metoprolol	Diphenhydramine	2D6 inhibition leading to bradycardia, hypotension
Meperidine	SSRIs, MAOIs	Serotonin syndrome
Oral contraceptives	Carbamazepine, phenytoin	3A4 induction, possible pregnancy
Clopidogrel	Omeprazole	2C19 inhibition, loss of prodrug clopidogrel efficacy
Amitriptyline	Fluvoxamine	2D6 inhibition
Theophylline	Fluoroquinolone	Seizures related to 1A2 inhibition
Marijuana	Fluvoxamine	Increased marijuana levels due to 2C9 inhibition

A Top Ten List of DDIs: Table 10.8

A Top Ten list would include commonly prescribed medications in combination with known P450 enzyme inhibitors or inducers or enzymes with marked pharmacogenomic variation. That list might include combinations of diphenhydramine, metoprolol, fluoxetine, SSRIs, first-generation anticonvulsants, oral contraceptives, meperidine and other opioids, amiodarone, fluoroquinolone, omeprazole, theophylline, antifungals, and clopidogrel.

Combining risperidone with carbamazepine, commonly used as a mood stabilizer, may lead to reduced therapeutic levels of risperidone due to enzyme induction [69].

Prevention/Recognition (Table 10.9)

Prevention of DDIs begins with a careful assessment of the patients medications and dietary supplements. A mnemonic such as AVOID MISTAKES serves as a helpful reminder of risk factors for drug interactions.

Table 10.9 A stepwise approach to drug-drug interactions

1. Take a medication history
Mnemonic **– Avoid m**istakes
Allergies?
Vitamins and dietary supplements
That is, grapefruit juice, St John's-wort (*Hypericum*)
Old drugs and **OTC**?
Interactions risk?
Dependence?
Mendel: any family history of drug sensitivity
2. Identify high-risk patients
>3 medications
Red flag drugs – anticonvulsants, antibiotics, digoxin, warfarin, amiodarone
3. Check pocket reference card
4. Consult pharmacist/drug specialist
5. Check computer programs
www.epocrates.com
Medical letter drug interaction program

www.fda.gov/cder-archived lecture

DDI Card

Patients frequently want to know whether the medication we are about to prescribe is likely to interact with others on their list. The tables listed below may be reprinted for use in the patient exam rooms and serve as a guide when counselling on potential drug interactions.

The most common mechanism of DDI is the coadministration of a substrate with an inhibitor or inducer of the same P450 enzyme. The tables below list common and clinically relevant drugs likely to interact.

First, determine whether there are any inhibitors on the patient's medication list. Next, identify any substrates of the inhibited or induced enzyme in question. Finally, discuss the symptoms and warning signs of possible interactions and whether the drug should be abruptly discontinued or weaned in the event of an interaction.

Cytochrome P450 drug interactions		
CYP1A2		
Substrates		
Acetaminophen	Frovatriptan	Quinine
Amitriptyline	**Haloperidol**	Ranitidine
Bupropion	**Imipramine**	**Rasagiline**
Caffeine	Melatonin	
Clomipramine	Metoclopramide	**Theophylline**
Clozapine	**Mexiletine**	**Tizanidine**
	Mirtazapine	**R-warfarin**
Cyclobenzaprine	Naproxen	
Doxepin	**Olanzapine**	Zolmitriptan
Duloxetine		
	Propranolol	
Fluvoxamine		
Inhibitors		
Amiodarone	Fluphenazine	Paroxetine
Amlodipine	Fluoxetine	Perphenazine
Caffeine	**Fluvoxamine**	**Refecoxib**
Cimetidine	**Levofloxacin**	Sertraline
	Lidocaine	
	Mexiletine	**Verapamil**
Ciprofloxacin	Nifedipine	
Diclofenac	Norfloxacin	**Herbal tea**
Duloxetine		Peppermint, Chamomile Teas
	Olanzapine	
	Oral contraceptives	
Inducers		
Brussels sprouts	Phenobarbital	
Cruciferous veggies	Rifampin	
Carbamazepine	**Tobacco smoke**	Marijuana
Char-grilled meats	**St. John's Wort**	
	Paclitaxol	
Key- **bold=** common drug interactions, or dominant pathway		
MAO, Phase II and Phase III (P-glycoprotein) drug interactions are not included		
Important Prodrugs*		
Codeine		**Tramadol**
Clopidogrel	**Tamoxifen**	**Azathioprine**
Midodrine		**Mycophenolate**

CYP3A4			
Substrates			
Alprazolam	Doxepin	Methadone	**Quetiapine**
Amiodarone		**Midazolam**	Quinidine
Amlodipine	Erythromycin	Mirtazapine	
	Esomeprazole	Marijuana	**Sildenafil**
Atorvastatin		Modafinil	**Simvastatin**
Bromocriptine	Ethosuximide	Nefazodone	**Tacrolimus**
Bupropion	Felbamate	**Nicardipine**	**Tamoxifen**
Buspirone	Felodipine		
Caffeine		Omeprazole	Tiagabine
Carbamazepine	Fentanyl	Ondansetron	
	Fluconazole	**Oral contraceptives**	Ttramadol
Clarithromycin	Fluvoxamine	Oxcarbazepine	
Cocaine	**Haloperidol**		Trazodone
Cyclophosphamide			Venlafaxine
Cyclosporine	Hydrocortisone	Pravastatin	**Verapamil**
	Ketoconazole		
Dexamethasone	**Lansoprazole**	**Prednisone**	Warfarin
Diazepam	Lidocaine	**Progesterone**	
Diltiazem	Losartan		Zolpidem
	Lovastatin		
Inhibitors			
Amiodarone	Fentanyl	**Ketoconazole**	
Atorvastatin	**Fluconazole**	Lovastatin	**Saquinavir**
Cimetidine	Fluoxetine	Nicardipine	Simvastatin
Ciprofloxacin	Fluvoxamine		
Clarithromycin		Nifedipine	Sertraline
Cyclosporine	**Grapefruit juice (functional inducer)**	**Nefazodone**	Tacrolimus
Diltiazem			
Erythromycin		Omeprazole	Valproic acid
	Isoniazid		
		Paroxetine	Verapamil
		Quinidine	**Voriconazole**
Inducers			
Carbamazepine	**Oxcarbazepine**	**Prednisone**	**St. John's Wort**
Dexamethasone	**Phenobarbital**	**Primidone**	**Topiramate (>200 mg)**
Modafinil	**Phenytoin**	**Rifampin**	

Important notice: These tables are not all-inclusive. New information is continually identified

CYP2D6		
Substrates		
Poor metabolizers- 7–10% of Caucasians, 4% African Americans		
Ultrarapid metabolizers- 1–7% Caucasians, 25% of Ethiopians		
Amitriptyline	Duloxetine	Nortriptyline
Bupropion	**Fluoxetine**	**Oxycodone**
Carvedilol	Fluphenazine	Paroxetine
Codeine*	Fluvoxamine	Propafenone
Desipramine	Haloperidol	**Propranolol**
Dextromethorphan	Hydrocodone	**Risperidone**
Donepezil	Imipramine	Sertraline
Doxepin	Lidocaine	**Tamoxifen***
Doxorubicin	Methadone	Thioridazine
	Metoclopramide	**Timolol**
	Metoprolol	**Tramadol***
	Mexiletine	Venlafaxine
	Mirtazapine	
Inhibitors		
Amiodarone	**Duloxetine**	Nortriptyline
Amitriptyline	**Fluoxetine**	**Paroxetine**
Atorvastatin	Fluvoxamine	**Pimozide**
Bupropion	**Haloperidol**	Pioglitazone
Celecoxib	Isoniazid	**Quinidine**
Clozapine	Lansoprazole	Risperidone
Cocaine	Methadone	**Ritonavir**
Desipramine		Sertraline
Diclofenac		Thioridazine
Diphenhydramine		Trazodone
		Venlafaxine
Inducers		
Probably none		

CYP2C9			
Substrates			
2C9 Impaired in 1–10% Caucasians			
Bupropion	**Glipizide**	**Naproxen**	Valproic acid
Carvedilol	**Ibuprofen**	Phenobarbital	Voriconazole
Celecoxib	**Indomethacin**	Phenytoin	**S-warfarin**
Cyclophosphamide	**Irbesartan**	**Piroxicam**	Marijuana
Dapsone	**Losartan***	Sildenafil	
Diclofenac	**Meloxicam**	SMX/TMP	
Fluoxetine	Methadone	Tamoxifen	
Inhibitors			
Amiodarone	**Fluvoxamine**	**Metronidazole** nicardipine	Sertraline
Cimetidine	**Ginkgo Biloba**	Pantoprazole	Simvastatin
Fluconazole	Ibuprofen	**Paroxetine**	**Valproic acid**
Fluoxetine	Indomethacin	Piroxicam	**Zafirlukast**
Fluvastatin	**Ketoconazole**	Quinine	
	Losartan	Ritonavir	
Inducers			
Carbamazepine	**Phenobarbital**	Primidone	Ritonavir
Dexamethasone	**Phenytoin**	**Rifampin**	**St. John's Wort**
Oxcarbazepine			

CYP2C19			
Substrates			
2C19 impaired in 15–30% of Asians			
Amitriptyline	**Diazepam**	**Omeprazole**	Progesterone
Carisoprodol	**Esomeprazole**	Pantoprazole	Sertraline
Clomipramine	**Fluoxetine**	Phenobarbital	Voriconazole
Citalopram	**Imipramine**	**Phenytoin**	Warfarin
Clopidogrel*	Indomethacin		
Cyclophosphamide	**Lansoprazole**		
Dapsone	Methadone		
Inhibitors			
Amiodarone	**Fluoxetine**	**Isoniazid**	**Oral contraceptive** paroxetine
Amitriptyline	**Fluvoxamine**	**Ketoconazole**	Sertraline
Cimetidine	Imipramine	**Lansoprazole**	**Topiramate**
Felbamate	Indomethacin	Modafinil	**Valproic acid**
Fluconazole		Nicardipine	
		Omeprazole	
Inducers			
Carbamazepine	Pentobarbital	**Rifampin**	**St. John's Wort**
Oxcarbazepine	Phenytoin		**Glucocorticoids**

Prevention/Recognition

An effective means of preventing adverse drug reactions and drug-drug interactions is rounding with a hospital-based clinical pharmacist. Rivkin found that rounding with a pharmacist who screened ICU patients for potential drug interactions reduced ADEs by 65% and reduced length of stay and mortality [70]

DDI Websites

http://medicine.iupui.edu/CLINPHARM/DDIS
https://www.drugs.com/drug_interactions.html
www.themedicalletter.com [17]
www.druginteractioninfo.org
www.pharmvar.org
www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm080499.htm

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