Chapter 3
Drug Interactions and Polypharmacy

Jessica L. Gören and Ashley Tewksbury

Abstract Over the past 20 years the number of psychotropic medications has increased dramatically. As a result, the use of psychotropic polypharmacy has rapidly expanded. One outcome of psychotropic polypharmacy has been an increase in the number of drug interactions that occur in routine clinical practice. Although drug interactions resulting in death are rare, the effects of drug interactions are often misinterpreted as drug inefficacy or toxicity. Therefore an understanding of pharmacodynamic and pharmacokinetic drug interactions is essential when using polypharmacy. This chapter reviews the mechanisms of drug interactions, describes the most commonly seen drug interactions and offers suggestions for addressing drug interactions in clinical practice. Given polypharmacy is common in psychiatry; clinicians must routinely assess which medication combinations are safe to prescribe, require dose adjustments and are best avoided. Future research should focus on the role of genetics and interventions to decrease adverse drug reactions related to drug interactions.

Keywords Drug-drug interactions • Adverse drug reactions • Psychotropics • Polypharmacy

J.L. Gören, PharmD, BCPP (✉)
Department of Pharmacy Practice, University of Rhode Island, Kingston, RI, USA

Department of Psychiatry, Harvard Medical School, Boston, MA, USA
e-mail: jgoren@challiance.org

A. Tewksbury, PharmD
Department of Pharmacy Practice, University of Rhode Island, Kingston, RI, USA

Community Health Network, Indianapolis, IN, USA

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Abbreviations

CNS	Central nervous system
CYP450	Cytochrome P450
EPS	Extrapyramidal side effects
GABA	Gamma-amino butyric acid
INR	International normalized ratio
MAOI	Monoamine oxidase inhibitor
NSAID	Non-steroidal anti-inflammatory drug
PD	Pharmacodynamic
P-gp	P-glycoprotein
PI	Prescribing information
PK	Pharmacokinetic
PPI	Proton pump inhibitor
QTc	Corrected QT interval
SNRI	Serotonin, norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant

3.1 Introduction

Drug interactions are defined as events in which the effects of a drug are altered by a second agent [1–3]. Often times, the second agent is a prescription medication. However, complementary and herbal supplements, over-the-counter medications, illicit drugs, alcohol, cigarette smoking and food can all impact the disposition of drugs. Given the number of patients exposed to multiple medications, the potential number of individuals affected by drug interactions is high [2].

There are two types of drug interactions, pharmacodynamic and pharmacokinetic. Both can be unilateral (drug A affects drug B) or bidirectional (drug A affects drug B and drug B affects drug A) [3]. Pharmacodynamic interactions occur when the effects of one drug are changed by another. Pharmacokinetic interactions result from alteration of a drug's pharmacokinetic properties leading to increased or decreased drug concentrations. Mixed types, both pharmacodynamic and pharmacokinetic, occur and may result in a net effect that can be difficult to predict.

Certain genetic polymorphisms, older age and polypharmacy all increase the risk of drug interactions. Drugs that undergo significant hepatic metabolism, alter hepatic metabolism and are prescribed for long periods of time are often involved in drug interactions. As such, patients receiving psychotropic polypharmacy are at an increased risk for drug interactions.

In clinical practice drug interactions can be advantageous or detrimental. For example, anticholinergic medications are often used to counteract the adverse effects of high potency first generation antipsychotics while combinations of highly anticholinergic drugs can lead to delirium. It is the later scenario, adverse drug events induced by drug interactions, that is a primary safety concern.

Approximately 5% of adverse drug events in the hospital are due to drug interactions though few result in significant morbidity or death [4]. More commonly drug interactions lead to adverse drug events or are misinterpreted as drug inefficacy [1, 2]. Therefore, assessment of potential drug interactions is relevant in daily clinical practice. This chapter focuses specifically on drug-drug interactions but the principles apply to drug interactions with other substances such as food or dietary supplements. While this chapter is not meant to provide an exhaustive list of psychotropic drug interactions, commonly encountered drug interactions are presented in the Appendix.

3.2 Pharmacodynamic Interactions

Pharmacodynamics (PD) refers to the biochemical and physiological effects of exogenous/pharmacological substances on the body. Put more simply, PDs refer to what a drug does to the body. Therefore, PD interactions can be predicted based on drugs' mechanisms of action. Clinically PD interactions magnify, diminish or antagonize the effects of drugs.

Drugs' primary mechanism of action can be associated with interactions. However, drugs have secondary effects that are often implicated in PD interactions. For instance, tricyclic antidepressants (TCAs) antagonize muscarinic and histaminic receptors, in addition to the therapeutic monoaminergic effects. Thus a wide array of side effects, often unrelated to the desired clinical effect, occur with TCAs. This lack of PD specificity also means TCAs are more likely to interact with multiple drugs.

The receptor binding profile of drugs differs across dose. Initially a drug will bind to its primary, highest affinity target but once saturated the drug will begin binding to lower affinity, secondary targets. This concept is helpful in contemplating the likelihood or extent of a drug interaction. For example, there is a theoretical drug interaction between multifunctional trazodone and other serotonergic agents. Trazodone has high binding affinity for serotonin-$_{2A}$, alpha-$_{1}$, and histamine-$_{1}$ receptors below 125 mg. Thus at lower doses trazodone acts primarily as a hypnotic. However, once this dose threshold is exceeded, trazodone acts on serotonin transporter proteins, inhibiting the reuptake of serotonin into the presynaptic membrane. Thus, a drug interaction resulting in serotonin toxicity is unlikely when a serotonergic agent is co-administered with low dose trazodone [5].

Another key concept in drug interactions is binding affinity of two drugs competing for binding sites at the same receptor. Consider a patient who is receiving a dopamine antagonist with a moderate binding affinity for dopamine-$_{2}$ receptors. Partial dopamine-$_{2}$ agonist aripiprazole is then added for dual antipsychotic therapy. Because aripiprazole has a stronger binding affinity for dopamine-$_{2}$ receptors, it will displace the original antipsychotic from its binding sites. In the patient's present neurological landscape of low dopamine (due to original dopamine-$_{2}$ antagonist), aripiprazole will exert agonist properties. Binding affinity and relative binding affinity (binding affinity of a drug in relation to its highest affinity site), are important

factors in PD interactions. Unfortunately, unequivocal translation of binding affinity (often in vitro) data into clinical practice is not currently feasible, and only rough estimations can be made. A direct comparison between drugs is an imperfect approach, as the binding affinities are derived from trials of disparate methodology and assessment techniques [6–9].

3.2.1 Pharmacodynamic Drug Interaction Classification

Additive PD interactions occur when two or more drugs with similar properties are combined. Interactions involving single or multiple PD effects can lead to additive effects. For example, patients may experience increased somnolence when hydroxyzine is combined with chlorpromazine due to both drugs' antihistaminic properties or zolpidem due to combined gamma-aminobutyric acid (GABA) and antihistaminic effects. Synergistic interactions are additive interactions where a drug combination leads to extreme or exaggerated effects. This is exemplified by the increased rate of severe central nervous system (CNS) depression when benzodiazepines are co-ingested with alcohol compared with benzodiazepine use alone. Antagonism occurs when one drug prevents or decreases the effect of a second drug. These effects can occur due to direct effects at the receptor site or indirect effects. Direct effects occur when two drugs with opposing mechanisms compete for the same receptor site as seen when the dopamine antagonist haloperidol is given with levodopa. Indirect interactions involve more complex mechanisms. For example, mirtazapine increases norepinephrine within the synapse via pre-synaptic alpha-$_2$ blockade. Thus mirtazapine's antidepressant effect may be antagonized by the post synaptic alpha blocker, prazosin [9].

The magnitude of a PD interaction is based, in part by the tightness with which a drug binds to a receptor, relative concentrations of the drugs at the site of action and availability of target neurotransmitters within the synapse. Since these factors are unknown for any individual patient, prediction of the magnitude of a pharmacodynamic interaction is often based on patients' previous drug reactions. While significant morbidity or mortality resulting from pharmacodynamic interactions is uncommon, increased side effects or diminished treatment efficacy can be problematic. As shown in Table 3.1, notable exceptions include monoamine oxidase inhibitor (MAOI) interactions (serotonin syndrome, hypertensive crisis), antipsychotics (QTc prolongation) and CNS depressants [8–10].

3.2.2 Time Course of Pharmacodynamic Interactions

The time course for PD interactions can vary but typically effects are seen shortly after (1) starting a drug combination, (2) increasing or decreasing the dose of a drug, (3) discontinuation of a drug or (4) reaching steady state [3, 7]. While starting and increasing medications are obvious triggers for assessment of drug interactions,

Table 3.1 Potentially serious pharmacodynamic interactions [8–10, 16–23]

	SS	HTN	QTc	CNS
Antidepressants				
Selective serotonin reuptake inhibitors	X		X	
Tricyclic Antidepressants	X	X	X	
Serotonin, norepinephrine reuptake inhibitors	X	X		
Monoamine oxidase inhibitors	X	X		
Antipsychotics				
Second generation (except aripiprazole)			X	
Olanzapine IM (short and long acting)				X
Thioridazine			X	
Haloperidol (highest risk with IV)			X	
Anxiolytics				
Benzodiazepine				X
Analgesics				
Tramadol (unlikely)	X			X
Opioids	X			X
Methadone			X	
Herbal				
St. John's wort	X			
Illicit				
LSD	X			
Cocaine		X	X	
Anti-infectives				
linezolid	X	X		

SS serotonin syndrome; *HTN* hypertensive crisis; *QTc* prolongation; *CNS* central nervous system depression

achieving steady state, dose reduction and medication discontinuation may be overlooked. For example, methadone has a half-life of 60 h with repeat administration [11]. Due to this long half-life the full range of side effects may not be seen for weeks after initiating the medication. In other cases, medication discontinuation may result in changes such as intolerable insomnia with bupropion after a sedating antipsychotic is discontinued.

3.2.3 Serious Pharmacodynamic Interactions

3.2.3.1 Hypertension and Hypertensive Crisis

Norepinephrine plays a role in numerous physiologic processes through interactions with alpha and beta receptors [9, 12, 13]. Given the widespread distribution of alpha and beta receptors, drugs that affect the noradrenergic system lead to the diverse physiologic outcomes detailed in Fig. 3.1.

Clinical manifestations of excessive noradrenergic activity include tachycardia, vasoconstriction, diaphoresis, mydriasis, urinary retention, constipation, blurred

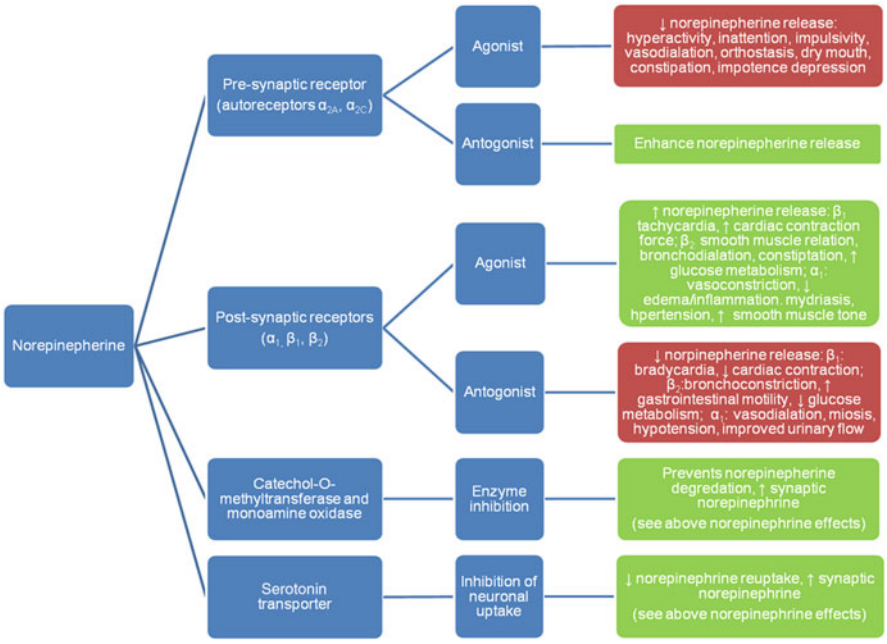

Fig. 3.1 Physiologic effects of norepinephrine

vision, dry mouth, anxiety, headache, and shortness of breath [9, 13]. While changes in blood pressure are typically limited, hypertensive crisis resulting in organ damage or stroke is possible with noradrenergic over stimulation. Few psychotropics are associated with hypertensive crisis but it is most likely to occur when MAOIs are co-prescribed with drugs that increase noradrenergic function [9]. High dietary tyramine intake can also cause hypertensive crisis in patients on MAOIs [9]. When hypertensive crisis does occur the offending drugs should be discontinued and supportive care should be initiated [9, 14].

More commonly seen in clinical practice are interactions involving antagonism of noradrenergic effects. For example, when mirtazapine, a presynaptic α-2 blocker, is added to clonidine, an alpha-2 agonist, patients may experience reemergence of hypertension despite continued use of clonidine [9].

3.2.3.2 Serotonin Syndrome

While low levels of serotonin may be implicated in some psychiatric disorders, the primary drug interaction of concern is serotonin syndrome from overstimulation of the serotonergic system (Fig. 3.2) [9, 13]. The clinical findings associated with serotonin syndrome are primarily neuromuscular in nature and include hyperreflexia, inducible clonus, spontaneous clonus, ocular clonus, myoclonus, peripheral hypertonicity, and

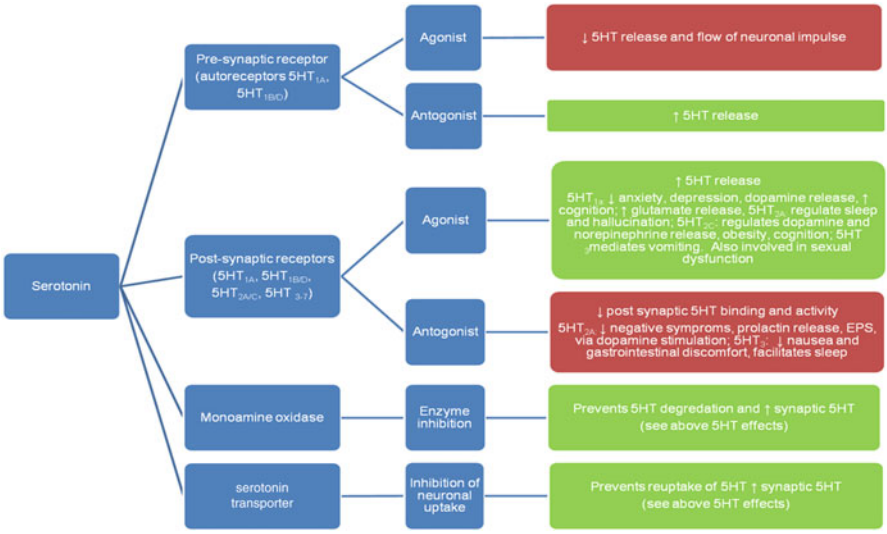

Fig. 3.2 Physiologic effects of serotonin. *5HT* serotonin; *EPS* extrapyramidal side effects

shivering (Table 3.2) [9, 13, 15–23]. Regardless of pharmacology, any combination of drugs, over-the-counter medications or herbal supplements that enhance serotonergic effects will trigger a serotonin syndrome alert on most drug interaction software programs. However, animal models suggest that serotonin syndrome is mediated through stimulation of serotonin-$_{1A}$ and serotonin-$_{2}$ receptors, particularly the latter [24]. Thus drugs that affect serotonin-$_{1A}$ and serotonin-$_{2}$ receptors are much more likely to result in serotonin syndrome compared with other mechanisms of increasing central serotonin activity [8, 14, 23, 24]. The primary exception to this would be utilization of drugs that increase total serotonin levels in the brain as serotonin itself acts on all serotonin receptors. This knowledge is important for assessing the clinical relevance of serotonin syndrome warnings since regulatory agencies have issued alerts for drug combinations unlikely to cause serotonin syndrome. For instance, a 2006 FDA alert based on 29 case reports cautioned health care providers about concomitant prescription of serotonin reuptake inhibitors (SSRIs) and the triptan class of anti-migraine medications. However, the validity of these cases has been called into question as only seven of the 29 case reports meet the Sternbach criteria for serotonin syndrome, while none fit the more rigorous Hunter criteria [19, 25]. Pharmacodynamically the interaction is implausible since triptans are agonists at serotonin-$_{1B}$, serotonin$_{-1D}$, and serotonin$_{-1F}$ receptors, which are distinct from the serotonin receptor subtypes implicated in the development of serotonin syndrome [19, 24]. Thus careful assessment of the mechanism of action at specific serotonergic receptors is necessary to discern which serotonin syndrome warnings are relevant in clinical practice. It is interesting also to note, data from the Hunter Area Toxicology Service indicate serotonin syndrome resulting in death is likely only when MAOIs are combined with drugs that decrease serotonin reuptake such as SSRIs, serotonin norephinephrine reuptake inhibitors (SNRIs) and TCAs [8, 16].

Table 3.2 Serotonin syndrome [9, 13, 16–23]

Onset	• Typically rapid • 60% of cases present within 6 h after initial use or dosage adjustment of medication and 75% within 24 h
Signs and symptoms	• Mild: tachycardia, shivering, diaphoresis, mydriasis, intermittent tremor, myoclonus or hyperreflexia • Moderate: mild symptoms plus hypertension, hyperthermia, hyperactive bowel sounds, diarrhea, hyperreflexia and clonus greater in lower extremities, mild agitation or hypervigilance, pressured speech • Severe: previous symptoms plus severe hypertension and tachycardia, agitated delirium, muscular rigidity, hypertonicity, rhabdomyolysis
Monitoring parameters	• Heart rate • Temperature (severe cases >40°C) • Blood pressure • Neurologic examination • Basic metabolic panel (increased serum creatinine and metabolic acidosis in severe cases)
Associated drugs	High risk: • Antibiotics: linezolid (*nonselectively inhibits MAO*) • Dietary supplements: Hypericum perforatum (St. John's Wort), tryptophan, S-adenosyl-methionine (SAMe) • Illicit Substances: methylenedioxymethamphetamine (MDMA), lysergic acid diethylamide (LSD), cocaine • MAOIs: tranylcypromine, phenelzine, moclobemide • SNRIs: venlafaxine • SSRIs: citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline • Serotonin releaser stimulants: amphetamine • TCAs: clomipramine, imipramine Low risk: • Anticonvulsants: carbamazepine, valproate • Antiemetics: ondansetron, metoclopramide • Antimigraine drugs: sumatriptan, dihydroergotamine • Cyclobenzaprine (*controversial*, *mimics TCA chemical structure*) • Lithium • Methylene blue (*inhibits MAO-A*) • Misc. Antidepressants: buspirone, trazodone • Opioid analgesics: fentanyl, meperidine, pentazocine, tramadol, dextromethorphan

If serotonin syndrome is suspected, all serotonergic medications should be promptly discontinued. When supportive therapy is necessary treatment may include stabilization of autonomic dysregulation and control of hyperthermia and agitation. In some cases benzodiazepine treatment may be necessary to treat agitation. In severe cases, limited data suggest administration of 12 mg of the $5HT_{2A}$ antagonist cyproheptadine followed by 4–8 mg every 6 h may be beneficial for some patients [8, 23, 26]. Most cases of serotonin syndrome subside within 24 h of discontinuing the offending agent [9].

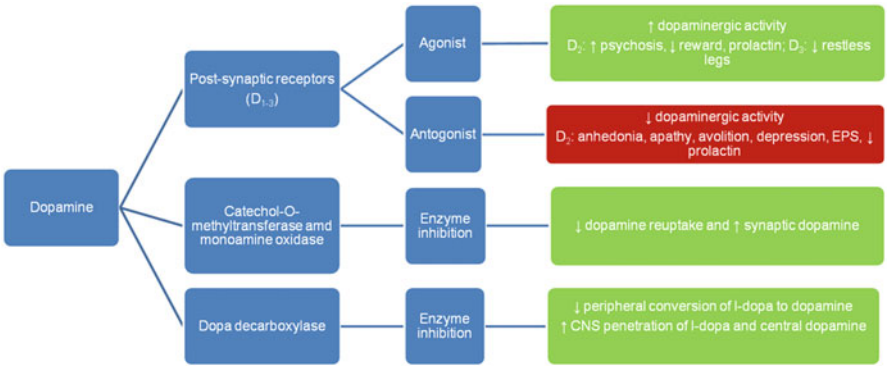

Fig. 3.3 Physiologic effects of dopamine. *EPS* extrapyramidal side effects; *CNS* central nervous system

3.2.3.3 Bleeding

Increased risk of bleeding is another potential adverse effect of drug interactions involving SSRIs and SNRIs. Reduced serotonin uptake into platelets with SSRIs and SNRIs decreases platelet aggregation which can lead to increased risk of bleeding when combined with anticoagulants. The risk is highest with fluoxetine, paroxetine, and sertraline, as they inhibit serotonin reuptake to the greatest degree [14].

Although the absolute risk of bleeding with SSRI monotherapy is low, observational studies indicate concomitant use with nonsteroidal anti-inflammatory drugs (NSAIDs) increases the absolute risk of bleeding three to 15-fold while co-administration of SSRIs and warfarin increases the risk of hospitalization due to non-gastrointestinal bleeding [27–29]. Risk reduction strategies include using (1) acetaminophen, (2) NSAIDs with less gastrointestinal effects, such as ibuprofen and cyclo-oxygenase 2 inhibitors, (3) the lowest effective dosage, and (4) a proton pump inhibitor (PPI) to protect against gastrointestinal bleeding [27, 28]. Caution should be taken when using PPIs with citalopram, as PPIs inhibit citalopram metabolism and could result in prolonged corrected QT interval (QTc) [30].

Due to the mechanism by which SSRIs and SNRIs affect platelets, the international normalized ratio (INR) would not reflect the increased bleeding risk. However, INR monitoring should be considered when starting an SSRI/SNRI in a patient on warfarin to ensure they are not at an elevated risk of bleeding due to a supratherapeutic INR [9, 27, 28].

3.2.3.4 Psychosis and Extrapyramidal Side Effects

In rare cases, elevated dopamine levels may lead to life threatening changes in cardiovascular function (Fig. 3.3) [9, 13]. More commonly, excessive dopaminergic activity causes symptoms of impulsiveness and psychosis, including cognitive impairment,

agitation, hallucinations, paranoia, and delusions [31]. Dopamine antagonists, such as antipsychotics, may inhibit the effects of drugs increasing dopamine levels, including MAOIs, dopamine agonists (ex. ropinirole, pramipexole), bupropion, and illicit substances such as cocaine. This effect is bidirectional, with dopaminergic medications markedly exacerbating psychotic symptoms in schizophrenia, and potentially aggravating dyskinesias in Huntington's disease [31]. Drugs effecting some serotonin receptors influence dopamine release and should be incorporated into assessments of net dopamine function. For example, serotonin-$_{2A}$ receptors serve as a break on dopamine function, whereas serotonin-$_{1A}$ receptors stimulate dopamine release [6, 9, 14].

3.2.3.5 CNS Depression

Substances that enhance the inhibitory neurotransmitter GABA, including benzodiazepines, barbiturates, anticonvulsants, alcohol, and non-benzodiazepine hypnotics (e.g. zaleplon, zolpidem, eszoplicone), can have additive or synergistic effects on sedation and motor impairment when used in combination [9]. Other sedating medications that work through alternate mechanisms may also enhance sedation and motor impairment. These include opioids, antihistamines, trazodone, mirtazapine and antipsychotics, particularly quetiapine and chlorpromazine [9, 13]. This adverse effect is of particular concern in elderly patients, as increased drowsiness and motor impairment elevate the risk for debilitating falls [6, 14]. Combinations of intramuscular olanzapine and benzodiazepines are particularly concerning for all patients as the peak olanzapine blood concentration is five times higher than with the oral formulation and deaths from cardiorespiratory depression have been reported with the combination [32].

When there is clinical concern of excessive CNS depression, signs and symptoms of sedation, lethargy, gait/motor impairment, slurred speech, cognitive dulling, and respiratory depression should be monitored while anxiety, panic attacks, dysphoria, and seizures may occur with rapid reversal of benzodiazepine induced CNS depression seen with administration of flumazenil [6, 9, 33].

3.2.3.6 Anticholinergic Effects

Numerous psychiatric medications antagonize acetylcholine at muscarinic and nicotinic receptors, often to a much lesser extent than their primary mechanism of action. Combinations of anticholinergic agents, including those used to treat urinary incontinence (e.g. oxybutynin, tolterodine, darifenacin), can lead to PD drug interactions. Additive anticholinergic activity manifests as confusion, orthostatic hypotension, dizziness, blurred vision, constipation, dry mouth, and urinary retention [9, 13]. Excessive or synergistic anticholinergic activity can lead to tachycardia, tachypnea, fecal impaction, anuria, increased body temperature, diplopia, mydriasis resulting in photophobia, cognitive impairment/delirium, xerostomia, and impaired coordination [6, 9, 13].

Anticholinergics exacerbate many symptoms that may already be present in the elderly population, including urinary retention and constipation. Additive

Table 3.3 Medications that may induce anticholinergic delirium [9, 36–38]

- Antiparkinsonian agents (e.g. trihexyphenidyl, benztropine)
- Antipsychotics
  Lower potency first generation (e.g. thioridazone, chlorpromazine)
  second generation/atypical (ex. clozapine, olanzapine)
- Antispasmodics for urinary incontinence (e.g. oxybutynin)
- Histamine (H_1) antagonists (particularly first generation, such as diphenhydramine)
- Histamine (H_2) antagonists (GI agents, such as cimetidine, ranitidine)
- Muscle Relaxants: cyclobenzaprine pancuronium
- Tricyclic Antidepressants (particularly tertiary)
- Tropane Alkaloids: scopolamine, hyoscyamine, atropine

anticholinergic effects such as orthostatic hypotension can lead to falls and therefore are important in elderly patients [34]. This is partially due to receptor changes that occur with aging, which heightens the brain's sensitivity to anticholinergic effects [35].

Due to decreased cholinergic reserve patients with Alzheimer's disease are particularly sensitive to polypharmacy induced anticholinergic delirium [9]. However, even in elderly patients without Alzheimer's disease, high anticholinergic load from polypharmacy has been associated with cognitive decline and delirium [36, 37]. Deficits noted include decreased processing speed, attention/concentration, psychomotor performance and disorganized thinking with wavering alertness [29].

Polypharmacy is an important cause of cognitive impairment as cognitive impairments are believed to be due to anticholinergic polypharmacy rather than a single medication with strong anticholinergic effects [36, 37]. Tools such as the anticholinergic drug scale and drug burden index, which incorporates anticholinergic and sedative drug load, have been utilized in clinical trials and may be applied to individual patients [38]. Common medications associated with anticholinergic delirium are listed in Table 3.3 [9, 36–38].

3.2.3.7 Arrhythmias/QTc Prolongation

Various psychotropic medications have potential cardio-toxic effects. Prolonged QTc is typically associated with drugs that block the sodium and potassium channels [10]. The risk is greatest with medications that block potassium channels but in vulnerable patients sodium channel blockade can also be associated with QTc prolongation [39]. The risk of QTc prolongation increases with the number of QTc prolonging drugs prescribed (Table 3.4) [40]. Selective serotonin reuptake inhibitors, SNRIs, TCAs and antipsychotics have all been reported to prolong the QTc. Citalopram, ziprasidone, thioridazine, mesoridazine, pimozide and haloperidol (particularly when used in high doses intravenously) are all labeled in the USA with boxed warnings for QTc prolongation [10, 25, 40–42].

Table 3.4 Drug which may prolong QTc [40]

Moderate or high risk of torsades	Torsades under some conditions[a]	QTc prolongation but rare torsades
Antipsychotics		
Chlorpromazine		
Haloperidol[b]		Asenapine
Pimozide		Clozapine
Thioridazine		Iloperidone
Ziprasidone		Paliperidone
		Quetiapine
		Risperidone
Antidepressants		
	Amitriptyline	Desvenlafaxine
	Citalopram	Mirtazapine
	Clomipramine	Venlafaxine
	Desipramine	
	Escitalopram	
	Fluoxetine	
	Imipramine	
	Nortriptyline	
	Paroxetine	
	Protriptyline	
	Sertraline	
	Trazodone	
	Trimipramine	
Miscellaneous		
Methadone		Amantadine
		Amphetamine
		Atomoxetine
		Chloral Hydrate
		Lithium

Excerpted with permission from PL Detail-Document, Drug-induced Long QT Interval. Pharmacist's Letter/Prescriber's Letter. January 2012. www.pharmacistsletter.com

[a]The drug may cause torsades under certain conditions (e.g. high dose, overdose, drug interactions, patients with long QT syndrome or other risk factors) but otherwise unlikely to cause torsades

[b]Highest with IV administration

QTc prolongation can be dose related as seen with thioridazine, ziprasidone and citalopram [9, 43, 44]. Therefore, PK interactions which increase the concentration of these drugs are particularly concerning and will be discussed later in the chapter.

In relation to psychotropic polypharmacy, two small studies reported no statistically significant differences in QTc prolongation in patients on antipsychotic/antidepressant polypharmacy versus monotherapy with either class alone [43]. However, combinations of QTc prolonging medications should be used with

caution, as other studies have found an increased risk of death when QTc prolonging drugs were used in combination [45].

Prior to initiating combinations of QTc-prolonging psychotropics any electrolyte abnormalities should be corrected. Potential causes of electrolyte abnormalities should be followed during polypharmacy with QTc prolonging drugs (e.g. vomiting, diarrhea, malnourishment, alcohol abuse, and diuretic therapy). For patients with multiple risk factors, consider obtaining an ECG recording prior to drug initiation and after steady state has been achieved. Monitoring parameters include ECG, serum potassium, and signs/symptoms of dizziness, palpitations, convulsions, or syncope [9].

Combinations of QTc prolonging medications should be used with caution in women, patients over the age of 60, those with a history of myocardial infarction or ischemic heart disease, persistent or recurrent bradycardia, previous episode of drug-induced QTc prolongation or electrolyte abnormalities (or a predisposition to abnormalities resulting from eating disorders or diuretic use) [9, 46].

Typically QTc prolongation occurs early in treatment (90 days) and in patients with other risk factors [10, 45]. Patients who have been maintained on a combination of QTc prolonging medications for extended periods of time are at a lower risk of adverse cardiovascular outcomes than patients initiating or increasing QTc prolonging drugs [10, 45].

3.3 Pharmacokinetic Drug Interactions

The effects of pharmacokinetic (PK) drug interactions are directly attributable to changes in drug concentrations [3]. Therefore PK interactions produce a quantitative rather a qualitative change in the response. Pharmacokinetic interactions can result in drug concentrations that are either sub-therapeutic or toxic. Often, they present as a "sensitivity" or "resistance/lose of efficacy" problem that may be incorrectly attributed to administration of a drug rather than a drug interaction [1, 14]. Pharmacokinetic interactions can occur as a result of changes in the absorption, distribution, metabolism or excretion of a drug.

Absorption. Absorption is the movement of a drug from its site of administration into the body. Absorption of a drug from the gastrointestinal tract is governed by multiple factors such as surface area for absorption, blood flow to the site of absorption, dosage form (e.g. solution, suspension or tablet/capsule), water solubility and drug concentration at the site of absorption [3]. Drug interactions involving absorption occur through both direct and indirect effects affects on the gastrointestinal tract. The absorption of drugs can be altered through changes in gastric acidity, chelation or altered gastrointestinal motility rate. Typically absorption interactions result in decreased or delayed drug absorption, although there are psychotropic medications that require ingestion with food to maximize absorption (e.g. ziprasidone) [9].

Alterations in pH. Many drugs are weak acids or bases whose absorption is influenced by the pH of the gastrointestinal contents. Since the non-ionized form of a drug is

more lipid soluble, acidic drugs are more readily absorbed from the upper GI tract, where they are primarily in a non-ionized form [3]. Thus changes in the pH of the gastric contents will influence drug absorption. While separating administration of the medications by several hours may improve absorption in some cases, drugs that consistently alter the stomach acidity (e.g. proton pump inhibitors) will cause interactions that cannot be avoided with separation of medication administration. However, these types of interactions are not common with psychotropic medications [47].

Complexation/Adsorption. Drugs can combine with other substances such as calcium, magnesium, aluminum, and iron in the GI tract to form insoluble complexes. Certain foods, vitamins and drugs can significantly decrease the absorption of drugs via this mechanism. Typically complexation interactions can be avoided by altering the timing of medication administration. Clinically significant interactions are possible but uncommon with psychotropic medications [47].

Alterations in Motility. The majority of drugs are absorbed in the intestine rather than the stomach. Any acceleration in gastric emptying will likely increase the rate of absorption, while the converse is true for drugs that decrease gastric emptying. In addition, medications that decrease gastrointestinal motility may alter drug absorption via changes in dissolution secondary to slowed gastric emptying or increases in a drugs' presence at the site of absorption. It is important to remember gastrointestinal motility effects may vary between with specific dosage forms. For example, enteric coating or sustained release dosage forms may be more susceptible to motility interactions [3, 47]. However, alterations in gastrointestinal motility are not a common source of psychotropic drug interactions.

Distribution. Within the blood drugs can bind to multiple plasma proteins. Albumin is the primary protein carrier for drugs although nonspecific binding to other plasma proteins can occur [3]. As there are limited binding sites available, drugs compete for protein binding sites [3, 48]. Since only unbound drug is active, displacing a drug from its protein binding site may alter the level of active drug without altering the total blood concentration. In low extraction drugs (i.e. minimal first pass metabolism) displacement usually leads to transient increases in free drug concentration that is offset by compensatory increases in drug clearance [3, 48]. Thus while there is a potential for increased adverse reactions with protein displacement, the risk is usually transient as the amount of drug available to be metabolized will increase correspondingly. Displacement interactions warrant less concern for high extraction drugs (e.g. antidepressants and antipsychotics) because they are highly cleared by the liver [47, 48]. In any case, displacement interactions are primarily a concern only for drugs with a narrow therapeutic window that are >90% protein bound [3, 9].

The most common protein binding interactions in psychiatry involve valproate, which can be displaced by medications such as aspirin or can saturate its own protein binding sites at higher concentrations. As plasma valproate concentrations increase more valproate is free or active. Thus the total valproate concentration will not change but the amount of unbound or active drug is increased. So at higher blood concentrations, small increases in plasma concentrations may lead to significant changes in clinical effects.

Metabolism. For an orally administered drug to enter into systemic circulation, it must first be absorbed through the gut wall and transported to the liver via the hepatic portal system [3, 9]. During this process a drug can be metabolized by enzymes in the gut and/or the liver before entering systemic circulation. The degree to which a drug is metabolized prior to entry into systemic circulation directly affects the plasma concentration of the drug [3, 9]. Drugs that reach systemic circulation with little to no metabolism are considered highly bioavailable. Conversely, drugs that are metabolized significantly in the gut or liver prior to entering systemic circulation are considered to have poor bioavailability [3]. The primary drivers of psychotropic drug bioavailability are the cytochrome P450 (CYP450) enzymes, a large super-family of proteins involved in the metabolism of a wide variety of both exogenous and endogenous compounds [9, 47, 49].

The CYP450 enzymes are located on the smooth endoplasmic reticulum of cells predominately in the liver and, to a lesser extent, the small intestine. These enzymes are responsible for the metabolism of many psychotropic medications to both active and inactive metabolites [47]. While metabolites can be less active than the parent compound, many psychotropics form metabolites with significant activity that differs from the parent compound. For example, the carbamazepine 10-, 11-epoxide metabolite is associated with seizure efficacy but can also lead to neurotoxicity and exacerbate seizures [50, 51]. Thus care should be taken to assess CYP450 effects not only on drug clearance but also generation of specific metabolites.

The CYP450 enzymes are divided into families based on amino acid sequence similarities and are designated by an Arabic number (e.g. CYP1). In humans more than 18 families of CYP450 enzymes have been identified [49]. Each family is further divided into subfamilies, which are designated by capital letters following the family designation (e.g. CYP1A). Individual enzymes are designated by the Arabic numeral following the subfamily designation (e.g. CYP1A2). The CYP450 enzymes most commonly involved in psychotropic metabolism are CYP450 1A2, 2C9, 2C19, 2D6, and 3A4 (Table 3.5) [9, 49, 52]. CYP450 3A4 is the predominant CYP450 enzyme in the human liver and intestine, thus accounting for a large number of drug interactions [9, 49, 52].

An individual enzyme of CYP450 is capable of metabolizing many different drugs while a large, intermediary, or small percentage of a single drug can be metabolized by a specific enzyme or multiple enzymes. Clinically significant interactions are more likely to occur when one enzyme is a major or moderate contributor to a drug's metabolism, while drugs with only minor metabolism via this pathway are less likely to result in clinically significant interactions [53].

Metabolism via CYP450 enzymes is partially dependent on genetics with clinically significant genetic polymorphisms (i.e. genotype) noted in CYP450 1A2, 2C9, 2C19 and 2D6 enzymes [47, 54]. The amount of drug exposure resulting from CYP450 genotype (i.e. phenotype) has direct implications for drug dosing (Fig. 3.4) [54]. For example, people unable to manufacture fully functional enzymes due to genetic polymorphisms do not efficiently metabolize specific drugs, have greatly increased levels of drug exposure and require lower doses than extensive metabolizers. Poor 2D6 metabolizers may also experience extreme increases in plasma drug

Table 3.5 Human CYP enzymes involved in drug metabolism [9, 49, 52]

1A1	2A6	3A3/4[a]	4A11	7A1	11A1	17A1	19A1	21A2	27A1	39A1	46A1	51A1
1A2[a]	2A7	3A5	4A22	7B1	11B1				27B1			
1B1	2A13	3A7	4B1		11B2				27C1			
	2B6	3A43	4F2									
	2C8		4F3									
	2C9[a]		4F8									
	2C18		4F11									
	2C19[a]		4F12									
	2D6[a]		4F22									
	2E1		4V2									
	2F1		4X1									
	2J2		4Z1									
	2R1											
	2S1											
	2U1											
	2W1											

[a]Denotes CYP450 enzymes most commonly involved in psychotropic drug

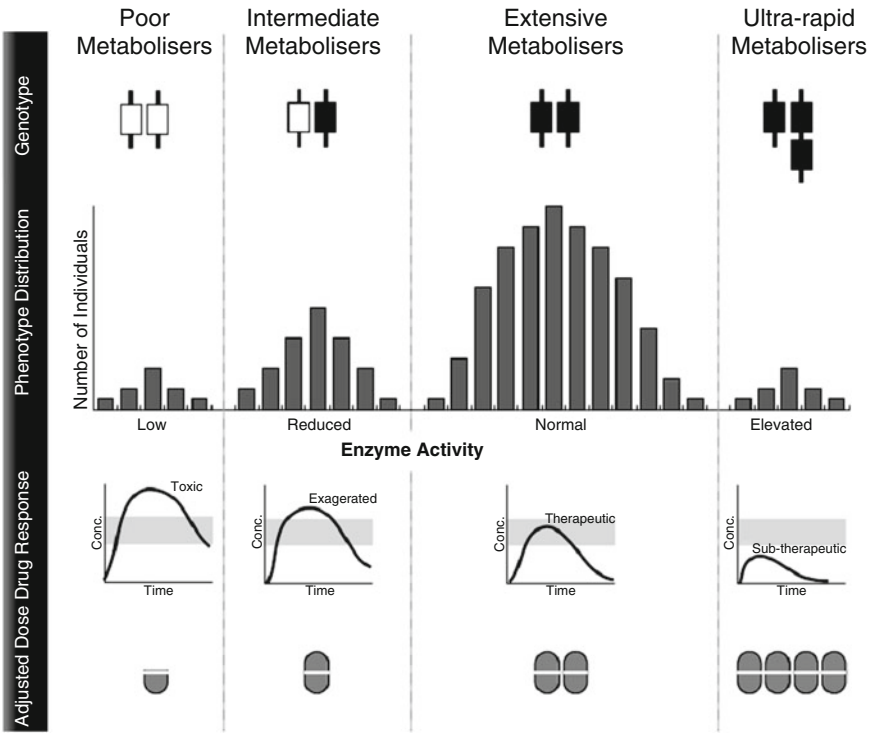

Fig. 3.4 Relationship between genetic variation, enzyme activity, drug response and optimized drug dose. Genetic variation as indicated by genotype (*white boxes* defective allele, *black boxes* functional allele) can produce four different levels of enzyme activity [54] (Reprinted with permission)

concentrations when given a 2D6 inhibitor. Conversely, ultra rapid metabolizers (those with genetic amplification of CYP450 enzymes) will have much lower drug exposure and require increased doses for clinical effect. These genetic polymorphisms are also important in transformation of pro-drugs into the active moiety. For example, poor 2D6 metabolizers are unable to convert codeine into morphine, its pharmacologically active metabolite. Thus they do not experience clinically significant pain relief with codeine and could be labeled as drug seeking patients rather than treated with a more appropriate opiate for their pain [47, 49]. The likelihood of being a poor metabolizer varies between ethnic groups, with 20% of Asians and 3–5% of Caucasians being poor CYP2C19 metabolizers. Conversely, Caucasians are more likely to be poor 2D6 metabolizers (5–10%) than Asians (0–1%). Approximately 29% of black Ethiopians and 1% of Caucasians are CYP450 2D6 ultra-rapid metabolizers [9, 47, 54].

The relationship between psychiatric medications and CYP450 enzymes is bidirectional. While CYP450 enzymes metabolize psychiatric medications, psychiatric medications can also increase (i.e. inducers) or decrease (i.e. inhibitors) the activity of CYP450 enzymes (Table 3.6) [1, 9, 47, 52, 53, 55–58]. Hence medications can be the target and the cause of PK interactions. In addition, a single drug can both be the target and cause of drug interactions. Psychotropic medications are particularly prone to drug interactions since they are commonly CYP450 substrates, often affect the activity of CYP450 enzymes and are frequently used in combination.

Induction. Induction is an increased synthesis of CYP450 enzymes which increases the metabolism of substrates of that CYP450 enzyme, ultimately leading to decreased blood concentrations of the substrate. Due to the need to synthesize new enzymes, the maximal effect of induction takes several weeks to occur. Conversely, when an inducer is discontinued, it takes time for the extra CYP450 enzyme to die off [53]. Thus reversal of induction is dependent on the half-life of the induced CYP450 enzyme and can take up to 4 weeks [53]. This delay between drug initiation or discontinuation and induction is the key to understanding the timing of clinical effects seen with CYP450 enzyme interactions involving induction. For example, carbamazepine is a potent inducer of CYP450 3A4. Since CYP450 3A4 is responsible for carbamazepine's metabolism and maximal induction takes approximately 4 weeks, carbamazepine's dose must be increased 1 month after achieving steady state to maintain a therapeutic concentration. Non-drug induced induction also has the potential to effect metabolism of psychotropic drugs. For example, cigarette smoking induces CYP450 1A2. Therefore, changes in smoking should be factored in when dosing drugs that are predominately metabolized by CYP1A2 (e.g. olanzapine, clozapine). This interaction is due to compounds contained in the cigarette smoke (i.e. polycyclic aromatic hydrocarbons) and not due to the effects of nicotine [55, 56].

Inhibition. Competitive inhibition is the most common mechanism of inhibition and occurs when a drug prevents another drug from binding to a specific CYP450 enzyme [57]. Competitive inhibitors can be but are not always substrates for the inhibited enzyme. For example, bupropion is an inhibitor but not a substrate of CYP450 2D6 while fluvoxamine is both an inhibitor and a substrate for CYP450 1A2 [9, 53]. The clinical significance of inhibition depends on the relative

Table 3.6 CYP450 enzymes commonly involved in drug interactions [1, 9, 47, 52, 53, 55–58]

			Inducer		Inhibitor	
Enzyme	Substrate		Psychotropic	Other	Psychotropic	Other
CYP1A2	Amitriptyline	Haloperidol	Phenobarbital	**Cigarette smoking**	**Fluvoxamine**	Amiodarone
	Caffeine	Imipramine		Insulin		Cimetidine
	Clomipramine	Mirtazapine		Modafinil		**Ciprofloxacin**
	Clozapine	Olanzapine		Omperazole		Fluorquinolones
	Fluvoxamine	Tacrine		Rifampin		
CYP2C9	Amitriptyline		**Phenobarbital**		Fluvoxamine	Amiodarone
	Fluoxetine					Fluconazole
	Phenytoin					Fluvastatin
	Sertraline					Isoniazide
						Lovastatin
						Sulfamethoxazole
						Rifampin
CYP2C19	Amitriptyline	Fluoxetine	Carbamazepine	Prednisone	**Fluvoxamine**	Cimetidine
	Citalopram	Imipramine		Rifampin	Modafinil	Indomethacin
	Clomipramine	Phenytoin				Ketoconazole
	Diazepam	Propranolol				Lansoprazole
	Escitalopram	Sertraline				Modafanil
						Omperazole
						Oxcarbazepine
						Topiramate

CYP2D6	Amitriptyline	Duloxetine		Dexamethasone	Bupropion	Cimetidine
	Amphetamine	Escitalopram		Rifampin	Chlorpromazine	Diphenhydramine
	Aripiprazole	Fluoxetine			Clomipramine	Hydroxyzine
	Atomoxetine	Haloperidol			Duloxetine	Ritonavir
	Chlorpromazine	Imipramine			**Fluoxetine**	
	Citalopram	Mirtazapine			Fluvoxamine	
	Clomipramine	Paroxetine			Methadone	
	Desipramine	Thiordiazine			**Paroxetine**	
		Venlafaxine			**Perphenazine**	
					Thioridazine	
CYP3A4	Alprazolam	Methadone	Barbiturates	Rifabutin	Fluvoxamine	Amiodarone
	Amitriptyline	Mirtazapine	**Carbamazepine**	Rafampin	**Nefazodone**	Cimetidine
	Aripiprazole	Nefazodone	**Oxcarbazepine**		**Paroxetine**	Ciprofloxacin
	Benzodiazepines	Paroxetine	Modafanil			**Clarithromycin**
		Quetiapine				
	Buspirone	Risperidone	**Phenobarbital**			Diltiazem
	Carbamazepine					
	Citalopram	Sertraline	**Phenytoin**			Erythromycin
	Clomipramine	Trazodone				Fluconzaole
	Clozapine	Triazolam				Grapefruit juice
	Diazepam	Venlafaxine				**Protease inhibitors**
	Escitalopram					
	Fluoxetine	Zaleplom				**Itraconazole**
	Haloperidol	Ziprasidone				**Ketoconazole**
	Imipramine	Zolpidem				Macrolide antibiotics
						Norfloxain
						Verapamil

Bolded potent

concentrations, binding affinities and inhibition potency of the drugs involved as well as the degree to which the substrate is metabolized by the CYP450 enzyme [52]. Typically a moderate to high amount of a drug must be metabolized by the inhibited CYP450 enzyme to produce clinically significant effects. Inhibition of CYP450 enzymes is particularly concerning for drugs with narrow therapeutic windows, as small increases in blood concentrations may lead to severe potentially life threatening reactions [53].

Unlike induction, enzyme inhibition usually begins with the first dose of the inhibitor. Since inhibition is dependent on drug concentration, maximal inhibition is typically not seen until a drug reaches steady state [57, 58]. Reversal of inhibition is dependent on the half-life of the drugs involved with full resolution occurring only after five half lives have elapsed since discontinuation of the inhibitor. Less commonly, drugs may irreversibly inhibit a specific CYP450 enzyme and require synthesis of new enzymes, which may take several days [53, 54].

It is important to know which drugs are predominately or moderately metabolized by specific enzymes. Given the large number of drugs involved, memorization of the inducers and inhibitors is time consuming. Therefore it is useful to be aware of the most common, clinically significant interactions and the drug classes most prone to drug interactions. In this way, one is alerted to either a common significant interaction or to a medication that is often involved in drug interactions and should be reviewed.

Excretion. Urinary pH influences the ionization of weak acids and bases and thus affects their reabsorption and excretion. A non-ionized drug more readily diffuses from the glomerular filtrate into the blood. More of an acidic drug is non-ionized in acidic urine than in alkaline urine, where it primarily exists as an ionized salt. Thus, an acidic drug (e.g. a salicylate) diffuses back into the blood from acidic urine, resulting in prolonged and perhaps intensified activity [3]. The risk of a significant interaction is greatest in patients who are taking large doses of salicylates (e.g. for arthritis). Opposite effects are seen for a basic drug like dextroamphetamine. Such interactions are not commonly seen with psychotropic medications.

Some drugs are excreted through the kidney without undergoing significant metabolism. While uncommon for psychotropic medications, lithium and gabapentin, are notable exceptions. Given gabapentin's large therapeutic window, it is not subject to clinically significant elimination interactions. However, lithium excretion is highly sensitive to changes in sodium, hydration status and use of certain medications such as nonsteroidal anti-inflammatory agents and diuretics [47].

Drug Transport. Transport proteins are membrane bound proteins that control the influx of essential nutrients and ions and the efflux of cellular waste and toxins. P-glycoproteins (P-gp) are the most widely studied transport proteins [51]. P-gp is the main transport protein involved in movement of drugs across biological membranes [9, 47, 59]. P-gp is present in many organs associated with drug metabolism, such as the gastrointestinal tract, liver and kidney, but plays no role in a drug's metabolism. P-gp can play an indirect role in the removal of a drug from the body via transport of a drug from the blood into the bile or urine. Alternately, a drug which has already been absorbed into the body may be transported back into the

Table 3.7 P-glycoprotein substrates and inhibitors [9, 39, 59]

Substrates	Inhibitors	Inducers
Bupropion	Carbamazepine	Amitriptyline
Chlorpromazine	Chlorpromazine	Nefazodone
Clozapine	Citalopram	Phenobarbital
Fluoxetine	Nortriptyline	Phenothiazines
Haloperidol	Olanazpine	Phenytoin
Mirtazapine	Paroxetine	Prazosin
	Phenobarbital	St. John's Wort
	Phenytoin	Trazodone
	Quetiapine	
	Risperidone	
	Sertraline	
	Topiramate	
	Trimipramine	
	Venlafaxine	

gastrointestinal tract by P-gps. P-gp transport is important for psychotropic medications as P-gps are located at the blood brain barrier to prevent potentially toxic substances from entering the brain [9, 47, 59].

P-gp binds to a wide range of drugs and there is considerable overlap of substrates of P-gp and CYP450 2D6 and 3A4 [9, 39, 47, 59]. Similar to CYP450 nomenclature, drugs can be classified as substrates, inducers or inhibitors of P-gp (Table 3.7) [9, 39, 59]. Substrates are actively expelled from cells by P-gp, thus limiting a cells' exposure to the substrate. Inhibitors decrease P-gp activity while inducers increase P-gp activity. A drug can be both a substrate and inducer or inhibitor of P-gp.

Drug interactions can occur when two drugs compete for P-gp or when a drug is an inducer or inhibitor of P-gp [39, 47]. Drug interactions with P-gp can have multiple effects depending on the site of action [59]. For example, inhibition of P-gp can prevent a drug's removal from the body via decreased transfer from the blood to the kidney or bile. Alternately, a drug may not be transported back into the gastrointestinal tract due to P-gp inhibition, leading to increased drug concentrations [47].

3.4 Clinical Effects of Drug Interactions

The incidence of life threatening drug interactions is low. Rates of death secondary to drug interactions were reported to be less than 1% in two studies [60, 61]. However, drug interactions reportedly account for up to 20% of adverse drug reactions and can lead to severe adverse drug events [2, 62]. Drug interactions are also implicated in hospital admissions and readmissions [2]. In one retrospective study, 47.7% of avoidable adverse drug reactions were attributed to drug interactions with

Table 3.8 Risk factors for experiencing a drug interaction [60–67]

Patient	Age
	Genetic polymorphism
Drug	Narrow therapeutic window
	Dose
	Major CYP450 substrate
	Strong CYP450 inducer/inhibitor
	Polypharmacy
Other	Number of prescribers

67% reported as life threatening, permanently disabling or requiring transfer for medical care [63]. More commonly, patients may experience increased side effects or lack of benefit secondary to drug interactions. These problems can be incorrectly attributed to drug toxicity or inefficacy [47, 53]. While this may seem relatively minor, particularly with psychotropics that are dosed based on observed effects, it can lead to clinically significant problems. For example, many patients are considered unresponsive to treatment and receive polypharmacy for "treatment resistant" disease. However, if the patient's lack of response was due to drug interactions resulting in low drug concentrations, a patient may be overmedicated or treated with drugs reserved for treatment resistance, which often have significant side effects. Conversely, patients who experience "side effects with all drugs" may be under treated for their illness due to fears of inducing adverse events. For example, a patient who has had severe adverse drug reactions due to drug interactions may be ineffectively treated with sub-therapeutic doses of multiple agents. Therefore, when a patient on more than one drug experiences an extreme or unexpected effect or derives no benefit from adequate doses, drug interactions should be considered.

3.4.1 Risk Factors

The major risk factors for drug interactions are related to patient, drug and other factors (Table 3.8) [60–67]. Patient factors such as age, number of drugs prescribed and concomitant medical illnesses have all been shown to increase the risk of experiencing clinically significant adverse events secondary to a drug interaction. Age related changes in metabolism, excretion and drug sensitivities lead to increased rates of drug interactions in elderly patients. Studies have documented up to 25% of elderly patients experience clinically significant problems due to drug interactions [64, 65].

Risk also increases as the number of prescribed drugs increases. Up to 38% of patients on four drugs and 82% of patients on seven drugs are at risk for a drug interaction [66]. Specific drug characteristics increase the likelihood of clinically significant interactions. For example, narrow therapeutic window drugs such as

lithium and carbamazepine, are more frequently associated with serious events secondary to drug interactions [67]. Drugs that rely primarily on one CYP450 enzyme family for metabolism, such as some antipsychotics, and less selective drugs with activity at multiple receptors and transporters increase the likelihood of experiencing clinically significant interactions [15].

Inhibition and induction of CYP450 enzymes are the most commonly documented cause of significant drug interactions [68]. Specifically CYP450 1, 2, and 3 subfamilies are responsible for the majority of drug metabolism and therefore many drug interactions [49, 53]. Drugs that are strong inducers or inhibitors are more likely to be involved in clinically significant drug interactions. Drugs that are partially metabolized by a specific CYP450 or moderate inhibitors/inducers may be involved interactions but they are less likely to cause serious adverse outcomes [53].

3.5 Drug Interaction Software

While the use of drug interaction software increases the awareness of drug interactions, little is known about their effectiveness in preventing drug related adverse events [69]. Given 80% of computerized drug interaction alerts are over ridden by clinicians, drug interaction software will most likely have limited benefits [70–73]. Patient-specific characteristics, as well as issues with sensitivity and specificity of drug interaction programs, are largely what make our current drug interaction software programs inadequate and justify a strong comprehension of drug interactions by clinicians [47, 73]. As an example, clinicians need to review more than 2,700 alerts to prevent a single serious adverse drug reaction, and at least 4,200 alerts to prevent serious disability or death with most drug interaction software programs. Therefore it is important to develop a system to assess the clinical relevance of drug interactions [73].

3.6 Prevention and Management of Drug Interactions

Initial first steps to decreasing the likelihood of drug interactions are to minimize the number and dose of drugs and, when possible, the duration of drug treatment. Regular review of drugs and discontinuation of drugs with limited or questionable benefit are also important. Prescribers should keep complete medication lists for all patients and update the list regularly. The list should include prescription, over the counter, illicit and herbal drugs and supplements.

A patient's medication taking behavior should be one of the first components assessed. Medication listed in a patient's record does not guarantee the patient is actually ingesting the drug or taking it as prescribed. Also concomitant disease states should also be considered since the risk of potential drug interactions is not

consistent across the population. For instance, the potential for QTc prolongation with citalopram is less worrisome in a young, healthy male than it would be in an older female taking a high dose diuretic.

The individual biology of the patients should also be considered and is often accounted for in clinical practice. For example, if a patient is particularly sensitive to drugs, clinicians may start with lower doses and titrate more slowly. In this way, clinicians can indirectly account for patients who are poor metabolizers of drugs and particularly vulnerable to drug interactions involving inhibition of CYP450 enzymes.

Clinicians should be aware of the psychotropic medications most likely to result in death and permanent disability. In psychiatry these medications include lithium, TCAs, MAOIs and anticonvulsants. Prescribing any of these in combination with other drugs should alert the clinician to pause and assess if the co-prescribed medications could result in a drug interaction.

Certain medications are significantly metabolized by CYP450 enzymes and should trigger a clinician to look for potential drug interactions. Medications which rely on a single CYP450 enzyme for most of its metabolism are more likely to be involved in drug interactions. These medications include antidepressants, antipsychotics and anticonvulsants. Antidepressants and anticonvulsants are also common inducers or inhibitors of CYP450 enzymes. Therefore, prescription of any of the drugs should prompt assessment for drug interactions.

The pharmacologic properties of the suspected drugs should be considered. The time of drug administration, time to onset and elimination half-life should be taken into account. If a drug has metabolites the elimination half-life of the metabolites should be considered as well.

Drugs that have been recently discontinued should be assessed. Fluoxetine's active metabolite norfluoxetine has a longer serum half-life than its parent compound, which has resulted in drug interactions up to 5 weeks after fluoxetine discontinuation [14]. Also, the duration of clinical effects of drugs is important. For example, MAOIs irreversibly inhibit MAO and thus their potential to cause drug interactions is due to the time it takes the body to regenerate MAO, long after the drug has left body [8, 9].

The suspected type of interaction should be considered, as different drug interactions occur at different points in treatment. As an example, induction takes weeks to occur and reverse; leading to the potential for drug interactions well after a medication has been initiated or discontinued.

3.7 Resources for Assessing Drug Interactions

While imperfect, computer software programs can help prevent some potential drug interactions. Consulting with pharmacists, who have extensive training in pharmacodynamics and pharmacokinetics, should be considered. Another important source of useful drug information is the prescribing information or package insert (PI). The PI provides useful information on drug metabolism, elimination and interactions but is often overlooked as a useful clinical tool. Table 3.9 offers guidance in assessing the likelihood of an adverse event is due to a drug interaction [60–67].

Table 3.9 When to suspect a drug interaction [60–67]

	Yes	No
Patient factors		
Is the patient >64 years old		
Are there multiple comorbidities		
Does the patient take over the counter medications or supplements		
Drug factors		
Has a drug recently started, stopped or reached steady state		
Are any of the drugs strong inhibitors or inducers or CYP450 enzymes		
Are any of the drugs strong P-gp inhibitors		
Were there high concentration of the drug		
Did the reaction worsen with increased dose		
Other factors		
Are medications prescribed by >1 clinician		

If the answer is yes to any of the following for a patient on polypharmacy, investigate for potential drug interaction

3.8 Conclusions

Whenever a patient experiences an unexpected adverse drug event or therapeutic failure, drug interactions should be included in the differential diagnosis. Most psychotropic drug interactions are pharmacokinetic involving CYP450 enzymes. Familiarity of high risk medications (e.g. lithium, MAOIs) and drugs involved with significant CYP450 interactions (e.g. antidepressants, antipsychotics, anticonvulsants) can serve as a prompt to investigate potential drug interactions. Minimization of drugs and discontinuation of unnecessary drugs, including over the counter medications and supplements, can also further decrease the risk of drug interactions. Drug interaction software, consults with pharmacists, medical literature review and prescribing information can all help clinicians assess the likelihood of and clinical significance of potential drug interactions.

Appendix. Commonly Encountered Psychotropic Interactions [9, 47, 59, 74]

Drug	Comment
Second generation antipsychotics	
Aripiprazole	Adjust dose with 2D6/3A4 inducers and inhibitors
	Long half life, maximum effects not seen for 3 weeks
Asenapine	Additive QTc prolongation potential
	Adjust dose with 1A2 inducers and inhibitors
Clozapine	Decreased levels in cigarette smokers
	Adjust dose with 1A2 inducers and inhibitors
Iloperidone	Adjust dose with 2D6 inducers and inhibitors
Lurasidone	Adjust dose with 3A4 inducers and inhibitors

(continued)

(continued)

Drug	Comment
Olanzapine	Decreased levels in cigarette smokers
	Adjust dose with 1A2 inducers and inhibitors
	Additive cardiopulmonary depression (IM highest risk)
Paliperidone	Adjust dose in renal impairment
Risperidone	Adjust dose in renal impairment
	Additive QTc prolongation potential
	Adjust dose with 2D6 inducers and inhibitors
Quetiapine	Adjust dose with 3A4 inducers and inhibitors
	Additive QTc prolongation potential
Ziprasidone	Must be taken with food for absorption
	Additive QTc prolongation potential
	Increased risk of QTc prolongation with inhibitors
First generation antipsychotics	
Chlorpromazine	Adjust dose with 2D6 inducers and inhibitors
Fluphenazine	Adjust dose with 2D6 inducers and inhibitors
Haloperidol	Adjust dose with 2D6 and 3A4 inducers and inhibitors
	Additive QTc prolongation potential (IV highest risk)
Perphenazine	Adjust dose with 2D6 inducers and inhibitors
Thioridazine	Additive QTc prolongation potential
	Increases levels of 2D6 substrates
Trifluoperazine	Adjust dose with 1A2 inducers and inhibitors
Anticonvulsants	
Carbamazepine	Decreases levels of 1A2, 2B6, 2C19, 2C9, 2D6, 3A4 substrates
	Decreased oral birth control efficacy
Lamotrigine	Levels significantly increased with valproate
Oxcarbazepine	Decreases levels of 3A4 substrates
Valproate	Significantly increases lamotrigine levels
	Increases TCA levels
Antidepressants	
Bupropion	Inhibits metabolism of 2D6 substrates
Citalopram	Adjust dose with 2C19 and 3A4 inhibitors
	Additive QTc prolongation potential
Duloxetine	Adjust dose with 2D6 inducers and inhibitors
Mirtazapine	Adjust dose with 1A2, 2D6, 3A4 inducers and inhibitors
	May decrease alpha antagonist effect
Nefazodone	Adjust dose with 3A4 and 2D6 inducers and inhibitors
	Increases concentration of 3A4 substrate
MAOIs	Hypertensive crisis
	Serotonin syndrome
SSRIs/SNRIs	Substrates, inducers and inhibitors of CYP450 enzymes (see Table 3.6)
	Increased bleeding with anticoagulants and NSAIDs
TCAs	Substrates, inducers and inhibitors of CYP450 enzymes (see Table 3.6)

(continued)

(continued)

Drug	Comment
Benzodiazepines	
Alprazolam	Adjust dose with 3A4 inducers and inhibitors
Chlordiazepoxide	Adjust dose with 3A4 inducers and inhibitors
Clonazepam	Adjust dose with 3A4 inducers and inhibitors
Diazepam	Adjust dose with 2C19, 3A4 inducers and inhibitors
Traizolam	Adjust dose with 3A4 inducers and inhibitors
Opiates	
Buprenorphine	Adjust dose with 3A4 inducers and inhibitors
Methadone	Significant QTc prolongation Adjust dose with 2B6 and 3A4 inducers/inhibitors

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