

DRUG BULLETIN

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Psychotropic Drug Interactions

Graylands Hospital Drug Bulletin 2006 Vol. 14 No. 2 July ISSN 1323-1251

Drug Interactions Overview

A drug interaction occurs when the toxicity or effectiveness of a drug is altered by the concurrent administration of another drug. Drug interactions can be classified as pharmacokinetic or pharmacodynamic in nature. A pharmacokinetic drug interaction occurs when a drug alters the absorption, distribution, metabolism or excretion of another drug. Pharmacodynamic interactions occur when two drugs act on interrelated receptor sites resulting in either additive or antagonistic effects.

A drug interaction can be beneficial, harmful, or have no significant effect. There are numerous known interactions involving psychotropic drugs. Many interactions have minor clinical significance; however, there are many potentially hazardous interactions that should always be considered. The significance of a drug interaction can also vary between individuals depending on factors such as comorbidities, gender or age. It is important to consider drug interactions when initiating drug therapy, changing a dose, changing the route of administration or ceasing therapy¹.

Table 1: Pharmacokinetic Interactions

Mechanism	Interaction	Effect
Absorption	Changes in gastrointestinal pH	Psychotropics with anticholinergic properties can increase the gastric pH. An increase in gastric pH can: <ul style="list-style-type: none"> • Reduce the absorption of drugs such as ketoconazole through reduced dissolution; • Damage enteric coatings on tablets
	Complexing mechanisms	Phenothiazines and phenytoin adsorb with antacids containing magnesium or aluminium salts when given within 2 hours, resulting in reduced absorption.
	Changes in gastrointestinal motility	Psychotropics with anticholinergic properties delay gastric emptying time, this can: <ul style="list-style-type: none"> • Reduce the rate of absorption of other drugs; • Cause degradation of acid-labile drugs.
Distribution	Protein binding	Competition for binding sites may result in an increase in unbound plasma levels of drugs that are highly protein-bound (>90%). Protein-binding interactions may only be significant for drugs with a small volume of distribution or where a temporary increase in plasma levels may result in unacceptable adverse effects and include drugs such as digoxin, warfarin, sulfonyleureas or phenytoin. Most psychotropics are protein-bound to a certain extent with the exception of lithium and gabapentin.
Metabolism	Enzyme induction	Induction increases the metabolism of the substrate drug, causing reduced plasma levels. This is significant for drugs where a reduced plasma level may result in treatment failure and includes drugs such as: the oral contraceptive pill, anticoagulants, anticonvulsants, corticosteroids, digoxin, protease inhibitors, immunosuppressants and theophylline. Enzyme induction of psychotropic drugs may result in reduced efficacy.
	Enzyme inhibition	Inhibition decreases the metabolism of the substrate drug, leading to increased plasma levels. This is significant for drugs with a low therapeutic index, where there is a low ratio between a therapeutic and toxic dose. Notable drugs involved in this reaction include: warfarin, phenytoin and theophylline. The effect of enzyme inhibition on psychotropic drugs is an increase in dose-dependent adverse effects.
	Changes in blood flow through liver	Certain drugs such as cimetidine reduce hepatic blood flow. This may result in an increased availability of drugs that have a high rate of hepatic first-pass metabolism such as buspirone, midazolam, pimoziide and triazolam.
Excretion	Changes in urinary pH	<ul style="list-style-type: none"> • Increase in urinary pH decreases clearance of amphetamines and increases clearance of lithium • Decrease in urinary pH increases clearance of amphetamines
	Changes in kidney blood flow	NSAIDs including COX-2 inhibitors inhibit synthesis of prostaglandins, reducing renal excretion of lithium.
	Changes in active kidney tubule excretion	Drugs that alter the ability of the proximal renal tubule to reabsorb sodium or that cause volume depletion can affect the elimination of lithium. <ul style="list-style-type: none"> • Drugs that reduce lithium excretion and increase levels include: ACE inhibitors, Angiotensin II receptor antagonists, NSAIDs, COX-2 inhibitors, thiazide diuretics and low-sodium diets. • Drugs known to increase the elimination of lithium and decrease levels include: bicarbonate and sodium salts
	Biliary excretion	There are few clinically significant interactions involving psychotropic drugs by this mechanism.

Pharmacokinetic interactions

Table 1 outlines the mechanisms of pharmacokinetic interactions involving psychotropic drugs^{2,3}. Of the pharmacokinetic drug interactions, the most clinically significant interactions include metabolism interactions, and elimination interactions involving lithium. Metabolism interactions are also the most frequently encountered pharmacokinetic interactions, and these are discussed further below.

Metabolism

Very few drugs are excreted from the body unchanged in the urine; most are metabolised within the body to less lipid-soluble compounds that are excreted by the kidneys.

The most clinically significant and well-studied metabolism interactions involve phase I metabolism, which mainly involve hepatic microsomal enzymes. These enzymes belong to the cytochrome P450 (CYP450) family of isoenzymes, of which there are about thirty. However, only a few subfamilies are responsible for the metabolism of the majority of drugs². Table 2 lists psychotropic drugs that inhibit, induce or are substrates for metabolism according to isoenzyme^{3,4}. A more comprehensive list of CYP450 interactions can be found at <http://medicine.iupui.edu/flockhart/>.

Phase II drug interactions are not as well studied as the CYP450 interactions, although many psychotropics are substrates for, or inducers or inhibitors of this pathway, in particular glucuronidation⁵. An example of a glucuronidation interaction occurs between sodium valproate and lamotrigine. These drugs compete for metabolism by glucuronidation, with a resultant increase in

lamotrigine levels⁶. Other psychotropic substrates of phase II glucuronidation include sodium valproate, lorazepam, oxazepam and olanzapine⁷.

Metabolic Drug Interaction Considerations

Enzyme inhibition has the effect of increasing the levels of the substrate that is metabolised by the inhibited enzyme. Enzyme inhibition begins to occur with the first dose of the inhibitor and is maximal when the inhibitor reaches steady state, which is usually after four to seven half-lives². Enzyme induction occurs when a drug stimulates the synthesis of more enzymes. The effect of enzyme induction is an increase in the rate of metabolism of the substrate, resulting in potentially reduced efficacy. The effects of an enzyme-inducing drug are less predictable than for enzyme inhibitors. The time course of enzyme induction onset and offset is related to the plasma concentration of the inducer as well as the half-life of enzyme production and degradation.

With metabolic interactions, it is important to note that many drugs are substrates for more than one enzyme, so often there is an alternative route of CYP450 metabolism, and many drugs are also metabolised by phase II conjugation reactions. An example of this is sodium valproate, which is metabolised 40-60% by glucuronidation and hence inhibition of CYP450 metabolism does not have a significant effect on clearance of valproate, as it is considered to be a minor secondary pathway of metabolism².

Drugs can also have different affinities for the isoenzymes and therefore differ in their potential for significant interactions. For example, paroxetine, fluvoxamine and fluoxetine are considered potent CYP450 inhibitors whereas sertraline, citalopram, venlafaxine, mirtazapine and reboxetine are weak inhibitors; hence, there is a lower likelihood of

Table 2: Psychotropic drugs that are substrates, inhibitors and inducers of cytochrome P450 isoenzymes

	CYP1A2	CYP2B6	CYP2C19	CYP2C9	CYP2D6	CYP3A4,5,7
Substrates	amitriptyline, chlorpromazine, clomipramine, clozapine, fluvoxamine, haloperidol, imipramine, methadone, olanzapine, pimozide, thioridazine	bupropion, methadone	amitriptyline, citalopram, clomipramine, diazepam, imipramine, moclobemide, phenobarbitone	amitriptyline, fluoxetine, phenytoin	amitriptyline, amphetamine, aripiprazole, atomoxetine, chlorpromazine, clomipramine, desipramine, donepezil, fluoxetine, fluvoxamine, galantamine, haloperidol, imipramine, nortriptyline, olanzapine, paroxetine, risperidone, sertraline, thioridazine, venlafaxine, zuclopenthixol	alprazolam, amitriptyline, aripiprazole, buprenorphine, buspirone, carbamazepine, clomipramine, clonazepam, clozapine, diazepam, donepezil, galantamine, haloperidol, imipramine, methadone, midazolam, mirtazapine, pimozide, quetiapine, reboxetine, sertraline, triazolam, zolpidem, zopiclone
Inhibitors	fluvoxamine		fluoxetine, fluvoxamine, modafinil, paroxetine, topiramate, valproate	fluoxetine, fluvoxamine, paroxetine, sertraline	bupropion, chlorpromazine, citalopram, clomipramine, doxepin, duloxetine, escitalopram, fluoxetine, haloperidol, methadone, moclobemide, paroxetine, reboxetine, sertraline, thioridazine, valproate	fluoxetine, fluvoxamine, valproate
Inducers	barbiturates, cigarette smoke, modafinil	phenobarbitone	carbamazepine	barbiturates		barbiturates, carbamazepine, modafinil, phenytoin, St John's Wort

significant metabolic drug interactions with these drugs³.

It is also important to consider the effect of stopping an enzyme-inducing or enzyme-inhibiting agent after long-term therapy, as this can affect the levels of the substrate. An example of this is the average of 72% increase in clozapine levels that is observed when cigarette smoking is stopped due to reversal of CYP1A2 induction⁸.

There is also large inter-individual variation in the amount of isoenzymes that individuals possess; different individuals can be poor metabolisers or ultra-fast metabolisers with respect to particular CYP450 enzymes.

Pharmacodynamic interactions

The most commonly encountered interactions in practice are pharmacodynamic interactions. Clinically significant pharmacodynamic drug interactions with psychotropic drugs are discussed below.

Antagonistic interactions

Antipsychotics that are potent dopamine D₂ antagonists oppose the effect of dopamine agonists used in Parkinson's disease. When used together, the therapeutic effect of both drugs will be diminished.

Psychotropics with anticholinergic properties can pharmacodynamically oppose the effects of anticholinesterase drugs used in Alzheimer's disease as well as prokinetic agents such as metoclopramide used for motility disorders.

Cyproheptadine antagonizes postsynaptic serotonin receptors. Concomitant use of cyproheptadine with drugs that possess serotonin-enhancing properties might be expected to result in a pharmacodynamic interaction. Lack of antidepressant efficacy has been reported when cyproheptadine was given concurrently with fluoxetine and paroxetine⁹.

Additive Pharmacodynamic Interactions

Oversedation

Oversedation due to the additive effects of drugs with sedative properties is often encountered when combining psychotropic drugs. Oversedation may also occur as the result of inhibition of metabolism of the sedating drug through CYP450 metabolism. Severe oversedation can lead to falls, injury, venous thromboembolism or hypostatic pneumonia¹⁰.

Neurotoxicity

Concurrent use of lithium and antipsychotics or carbamazepine may result in neurotoxicity characterized by weakness, dyskinesias, increased extrapyramidal symptoms, encephalopathy, and brain damage. This interaction is rare and is more likely to occur with higher plasma levels of lithium⁸.

Seizures

Seizures may result from the additive effects of two or more drugs that lower the seizure threshold. Most antipsychotics and antidepressants can reduce the seizure threshold. Of the antipsychotics, clozapine and chlorpromazine have the greatest epileptogenic potential and for antidepressants, the tricyclic antidepressants (TCAs) pose the greatest risk¹¹. Patients that require a combination of drugs that reduce the seizure threshold should be maintained on the lowest effective dose, using a slow rate of introduction and withdrawal⁸. High-risk drugs and combinations in patients with underlying conditions that might predispose them to seizures should be avoided.

Serotonin syndrome

Serotonin syndrome can occur with one or more serotonergic drugs. Serotonin syndrome is a potentially life threatening condition characterized by mental state changes, myoclonus, tremor, hyperreflexia, fever, sweating, shivering and diarrhoea. All of the antidepressants, except reboxetine, can contribute to serotonin syndrome, and there is a greater risk of serotonin syndrome with combinations of selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs) or SSRIs and serotonergic TCAs (clomipramine, amitriptyline, and imipramine)³. Other drugs such as opioids (tramadol, pethidine, and dextromethorphan), stimulants (phentermine, diethylpropion, amphetamines, and sibutramine), 5HT₁ agonists (sumatriptan, naratriptan, and zolmitriptan) and others (illicit drugs, selegiline, tryptophan, buspirone, lithium, linezolid and St John's wort) can also contribute to serotonin syndrome¹². Combined use of serotonergic drugs should be avoided or monitored carefully.

Hypertension

The concomitant use of MAOIs and tyramine containing food, or drugs that increase the level of monoamines (serotonin, noradrenaline, or dopamine) can result in interactions that have the potential to cause hypertensive crisis⁶. Combinations of MAOIs and these drugs are contraindicated. The severity and consequences of such interactions vary among individuals. If substantial and rapid increases in blood pressure (an increase of 30 mm Hg or more in systolic blood pressure within 20 minutes) occur, patients may experience symptoms associated with subarachnoid haemorrhage or cardiac failure⁹.

Anticholinergic effects

Caution should be used when combining drugs with anticholinergic properties due to enhanced anticholinergic effects such as dry mouth, urinary retention and constipation. There is also an increased risk of developing ileus, or central anticholinergic delirium characterised by cognitive changes as well as symptoms including: hot, dry skin; dry mucous membranes; dilated pupils; tachycardia; and absent bowel sounds¹³.

Hypotension

Caution should be used when combining drugs with an antihypertensive effect. Hypotension is a common adverse effect of many psychotropic drugs due to alpha-adrenergic blockade. Hypotension is a dose-related and additive adverse effect. It is a potentially serious adverse reaction due to the risk of falls, cerebral ischaemia or myocardial ischaemia⁸.

QTc prolongation

Many psychotropic drugs including certain antidepressants, antipsychotics and lithium have been associated with lengthening of the cardiac QTc interval, which increases the risk of ventricular arrhythmias such as torsades de pointes. Psychotropics with the greatest effect on QTc interval include chlorpromazine, haloperidol, droperidol, pimozide and thioridazine¹¹. The risk of cardiac arrhythmia and sudden death may be further increased when these drugs are used concomitantly with other QTc prolonging drugs, and in most cases, combinations are contraindicated. A complete list of drugs that affect the QTc interval can be found at www.qtdrugs.org. QTc prolongation is a dose dependent effect; hence inhibition of drug metabolism is also an important interaction to consider.

Indirect pharmacodynamic interactions with psychotropics that prolong the QTc interval should also be considered. These interactions involve drugs that affect the electrolyte balance, or that cause bradycardia, thereby increasing the risk of arrhythmia¹¹.

Haematological effects

Psychotropic drug-induced haematological problems are rare; however consideration should be given to additive drug effects, in particular, effects on white blood cells and platelets¹⁴.

Of greatest clinical significance are interactions between clozapine and drugs known to be myelosuppressive, and due to the risk of agranulocytosis, these combinations are contraindicated. Many other psychotropic drugs have also been associated with agranulocytosis, most notably carbamazepine and the phenothiazines.

Serotonergic drugs and valproate can affect platelet function. SSRIs can inhibit serotonin reuptake into the platelets, reducing platelet aggregability. When SSRIs are used in combination with NSAIDs or anticoagulants the risk of bleeding may increase although this interaction is usually uneventful¹². Valproate can inhibit the second stage of platelet aggregation and increase bleeding time. Caution is required when valproate is used with other drugs that affect coagulation or platelet function.

Conclusions

While there are numerous theoretical and documented drug interactions, many are of little clinical significance. Assessment of the pharmacodynamic and pharmacokinetic profile of psychotropic and other drugs can help determine the clinical significance of any interactions and prevent the serious consequences of drug interactions.

Acknowledgment

This article was prepared by Karolina Golebiewski, Drug Information Pharmacist and was reviewed by members of the Pharmacy Department and Dr Ancy John

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References available on request