An overview of clinically significant drug interactions between medications used to treat psychiatric and medical conditions

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ABSTRACT

Prescription rates and polypharmacy are increasing, resulting in a greater potential for drug interactions. Psychiatric patients frequently have co-morbid medical conditions, which further increases the risk of polypharmacy and drug interactions. Drug interactions that affect drugs with narrow therapeutic windowsare of particular concern. This review presents some of these drug interactions and provides strategies for identifying and resolving them.

KEYWORDS

Drug interactions, polypharmacy, psychotropics

INTRODUCTION

Co-morbid medical illnesses are common in psychiatric patients. Health conditions such as diabetes, dyslipidemia, obesity and high blood pressure all contribute to increased prescription medication rates in the United States. These are common medical conditions in the psychiatric patient. Over four billion prescriptions were written in the United States in 2011, which yields on average 13 prescriptions per person.[1] Drugs that affect the central nervous system top the list of prescribed medications, with certain antipsychotics and antidepressants among the top 10 drugs (in sales) in the United States in 2011.[1] According to the Centers for Disease Control and Prevention, in 2010, 48.5% of Americans took at least one prescription medication, 21.7% took three or more prescription medications and 10.6% took five or more prescription medications.[2] The risk of drug interactions increases as the number of prescriptions and the rate of polypharmacy increase.

Drug interactions are confusing to say the least, with an abundance of conflicting drug interaction data. Drug interaction software often flag not only contraindicated co-prescribed medications, but also theoretical interactions that have no specific case report or study data supporting them. The various drug interaction programs provide variable and even conflicting interaction information. Prescribers and pharmacists may become fatigued by the volume of drug interaction messages and may overlook important warnings while ordering or verifying medications in computerized order systems.

It is not possible to test every new medication that enters the market for interactions with every other drug. The pharmacokinetic data required by the FDA approval process provides the basis for most reported interactions, based upon the known pharmacokinetic and pharmacodynamic characteristics of the new medication and that of other medications on the market. Drug interaction case reports filter into the drug interaction software over time, providing more substantive drug interaction warnings.

Of particular concern are interactions with medications that have a narrow therapeutic window and those with significant consequences if levels or therapeutic effects are altered. While this article reviews some of the more important drug interactions between psychiatric medications and medications used to treat general medication conditions, it is not intended to be a complete list of all possible drug interactions. The following information will provide some tools and a mechanism for evaluating drug interactions.

DRUG INTERACTIONS WITH ANTICOAGULATION MEDICATIONS

Warfarin is a medication that has both a relatively narrow therapeutic window (as measured by International Normalized Ratio or INR) and has significant consequences if an interaction occurs. The S-warfarin enantiomer, roughly five times more active than the R-warfarin enantiomer, is metabolized by cytochrome P450 (CYP450) 2C9 predominantly and to a lesser extent 3A4.[3] R-warfarin is metabolized by CYP450 1A2 predominantly and to a lesser extent 2C19 and 3A4.[3] Medications that induce or inhibit 2C9 or 3A4 can interfere with warfarin

metabolism and affect the patient's INR. Carbamazepine and phenobarbital are potent inducers of 2C9 and 3A4[3] and are known to decrease the INR.[4] Valproic acid and disulfiram are strong 2C9 inhibitors[3] and are associated with reports of increased INR.[4] Fluvoxamine, fluoxetine and modafinil are weaker 2C9 inhibitors[3] and may affect warfarin metabolism and INR.[3]

Apixaban, and rivaroxaban are metabolized by CYP450 3A4, with metabolism increased by strong 3A4 inducers such as carbamazepine and phenobarbital.[3] Thus, these medications may decrease apixaban and rivaroxaban effectiveness and increase the risk of stroke.[5,6]

Concomitant anticoagulants and antidepressants can result in pharmacodynamic interactions. Selective serotonin reuptake inhibitors and serotonin norephinephrine reuptake inhibitors may block platelet uptake of plasma serotonin.[7,8] Platelets cannot produce serotonin, thus they rely on the uptake mechanism to provide serotonin needed for platelet aggregation.[7,8] These medications can increase the risk of bleeding when used with anticoagulants, without affecting the INR or prothrombin time (PTT).[7] Of note, tricyclic antidepressants, trazodone and nefazodone may not generate an interaction warning of this type, but some have a similar mechanism of action.

Clopidogrel requires metabolism through 2C19 to an active metabolite.[3,9] Medications that inhibit 2C19, such as fluoxetine, fluvoxamine, modafinil and oxcarbazepine, and to a lesser extent topiramate and armodafinil,[3] can decrease the effectiveness of clopidogrel.[7,9] It is best to avoid comcomitant use of clopidogrel and 2C19 inhibiting medications and to select other therapies if possible.

Also of concern are medications with the potential to cause thrombocytopenia, which would increase the risk of bleeding in an anticoagulated patient. Antipsychotic medications,[8] carbamazepine and valproic acid have all been associated with thrombocytopenia.[10]

DRUG INTERACTIONS WITH IMMUNOSUPPRESSANTS

Tacrolimus, cyclosporine, sirolimus and prednisone are metabolized exclusively through CYP450 3A4.[3] Carbamazepine and phenobarbital are potent inducers of 3A4,[3] which warrants following immunosuppressant levels closely when these medications are introduced or discontinued. Other barbiturates, modafinil, oxcarbazepine and topiramate are less potent inducers[3] but also warrant close immunosuppressant monitoring during introduction or discontinuation.

Potent 3A4 inhibitors such as nefazodone, fluvoxamine and, to a lesser extent fluoxetine may increase immunosuppressant levels, again making it necessary to monitor immunosuppressant drug levels when introducing or discontinuing one of these medications.[3,11,12]

Concomitant use of clozapine and mycophenoloic acid medications may increase the risk of agranulocytosis.[12]

DRUG INTERACTIONS WITH CANCER MEDICATIONS

Tamoxifen is a prodrug that requires CYP450 2D6 metabolism to become an active metabolite.[3,13] Although tamoxifen is metabolized through other CYP450 enzymes as well as 2D6,[3] these metabolic routes fail to produce the necessary active metabolite.[14] Bupropion, fluoxetine, and paroxetine are potent 2D6 inhibitors and citalopram, desvenlafaxine, duloxetine, escitalopram, fluvoxamine, risperidone, sertraline, clomipramine, diphenhydramine, doxepin, chlorpromazine, methadone, perphenazine and haloperidol are less potent 2D6 inhibitors.[15] A retrospective analysis of breast cancer patients found a 1.9 fold increase in breast cancer recurrence rate in patients taking concomitant tamoxifen and potent 2D6 inhibiting medication.[16] Thus, it is best to avoid using 2D6 inhibiting medications with tamoxifen.[15,17]

DRUG INTERACTIONS WITH HIV MEDICATIONS

Protease inhibitors (atazanavir, darunavir, fosamprenavir, ritonovir etc) are strong 3A4 inhibitors.[3] Some are contraindicated with midazolam, triazolam and pimozide.[10,18] Concomitant use will likely increase the effects of alprazolam, clonazepam, clorazepate, diazepam, lorazepam and flurazepam.[18] Protease inhibitors may also increase olanzapine, quetiapine, risperidone, chlorpromazine, haloperidol, trifluoperazine, fluphenazine, clozapine, ziprasidone and aripiprazole effects.[18]

Efavirenz inhibits 2C9, 2C19 and 3A4 and will likely increase midazolam exposure (contraindicated).[10,18] Zolpidem and eszopiclone can increase protease inhibitor and decrease nonnucleoside reverse transcriptase inhibitor levels.[18]

Etravirine and maraviroc may increase methadone levels, while efavirenz, nevirapine, darunavir, fosamprenavir, lopinavir, saquinavir and ritonavir may lower methadone levels.[18] Methadone can increase zidovudine levels.[18]

Ritonavir and atazanivir may increase buprenorphine levels while efavirenz and nevirapine may decrease buprenorphine effectiveness.[18]

DRUG INTERACTIONS WITH BETA BLOCKING MEDICATIONS

Fluoxetine, paroxetine, duloxetine and bupropion are CYP450 2D6 inhibitors[3] that can increase exposure of some beta blocking medications.[10] Carvedilol, metoprolol, nebivolol, propranolol and timolol are metabolized through 2D6,[3] thus their effects may be increased when used with 2D6 inhibiting antidepressants. When adding or discontinuing a 2D6 inhibiting antidepressant, monitor blood pressure and heart rate.

DRUG INTERACTIONS WITH ANTIFUNGALS

Many antifungals such as fluconazole, itraconazole, ketoconazole, posaconazole and voriconazole are strong 3A4 inhibitors.[3] These are contraindicated with many medications including pimozide, midazolam and triazolam.[10] Voriconazole is contraindicated with carbamazepine, and concomitant carbamazepine use with itractonazole or ketoconazole is not recommended. [10] Itraconazole use is contraindicated with methadone. [10]

DRUG INTERACTIONS WITH DIABETIC MEDICATIONS

Carbamazepine and phenobarbital may decrease linagliptin exposure through CYP450 3A4 induction.[3,10] Carbamazepine induction of 3A4[3] may also decrease repaglinide exposure.[10] Phenobarbital may decrease canagliflozin exposure through uridine 5'-diphosphate glucoronosyltransferases (UGT) induction.[10] Topiramate may decrease pioglitazone exposure.[10] Monoamine oxidase inhibitors (MAOIs) may stimulate insulin secretion lowering blood glucose when added to insulins, acarbose, miglitol, metformin, nateglinide, repaglinide, canagliflozin, chlorpropamide, glimepiride, glipizide and tolbutamide.[9] Fluoxetine may increase blood glucose lowering effects of some medications (insulins, glimepiride, and glyburide) through an unknown mechanism.[10] Propranolol (and other beta-blockers) may alter glucose metabolism and mask symptoms of hypoglycemia.[10] Use with caution in diabetic patients.[10] It is best to monitor blood glucose more closely when adding or discontinuing these medications that can alter blood glucose.

DRUG INTERACTIONS WITH CONTRACEPTIVES

Carbamazepine, oxcarbazepine, topiramate, and phenobarbital decrease the effectiveness of oral contraceptives by inducing metabolism of estrogen or progesterone.[19] Alternative methods of birth control are necessary with concurrent use of these medications. Conversely, oral contraceptive UGT induction decreases the effectiveness of lamotrigine.[19,20]

DRUG INTERACTIONS WITH LITHIUM

A 2010 retrospective analysis of adverse drug reactions in hospitalized psychiatric patients found lithium to be the most common psychiatric medication involved in ADRs.[21] Lithium is not metabolized; interactions are through other mechanisms. Diuretics are contraindicated and angiotensin-converting enzyme inhibitors can be used cautiously with lithium as they can increase the lithium level leading to toxicity.[9,10] Drugs that reduce renal elimination of lithium such as nonsteroidal anti-inflammatory medications, cycloxygenase inhibitors type 2 and metronidazole can increase lithium levels as well.[10,22] Lithium toxicity has been reported when calcium channel blockers, methyldopa and carbamazepine are used concomitantly with lithium.[10,22] Decreased lithium levels have been associated with acetazolamide, alkalizing agents, and xanthines (aminophylline, dyphylline, and theophylline).[10] Lithium can be used cautiously with nephrotoxic medications such as cyclosporine.[12] Finally, lithium may prolong the effects of neuromuscular blocking agents used in surgeries and ECT.[9]

DRUG INTERACTIONS WITH MONOAMINE OXIDASE INHIBITORS

Monoamine oxidase inhibitors (MAOIs) interact with many medications including some internal medicine, psychiatric and over the counter medications and supplements/herbals. MAOIs (isocarboxazid, phenelzine, selegiline transdermal, tranylcypromine) interact with medications with serotonin activity, resulting in the risk of serotonin syndrome. Cyclobenzaprine, dextromethorphan, fentanyl, meperidine, milnacipran, tapentadol, tetrabenazine, and tramadol may have serotonergic activity.[10] Meperidine is contraindicated with MAOIs.[9,10]

Medications with sympathomimetic activity also interact with MAOIs through norepinephrine or dopaminergic effects, including cocaine, dopamine, ephedrine, epinephrine, norepinephrine, phenylephrine, isometheptene, phenmetrazine, phentermine, pseudoephedrine, and tapentadol.[9] When used with a MAOI, the result can be severe hypertension, hyperpyrexia, arrhythmia and even death.[9,10] Some sympathomimetics are contraindicated with MAOIs. [10] Anesthetics with sympathomimetic vasoconstriction effects can have increased hypotensive effects when coadministered with MAOIs.[9]

Beta-blockers with MAOIs can have exaggerated hypotensive and bradycardic effects, requiring careful

coadministration.[9,10] The hypoglycemic effects of insulins and sulfonylurea may be potentiated by MAOI, requiring close blood glucose monitoring when used concomitantly.[10] Apraclonidine is contraindicated with MAOIs, as it potentiates MAOI effects.[10]

Linezolid is a weak MAOI that interacts with monoamine oxidase inhibiting and other antidepressants. The FDA Adverse Event Reporting System includes reports of serotonin syndrome with linezolid when used in combination with citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, desvenlafaxine, duloxetine and venlafaxine.[23] Other medications with serotonergic action such as TCAs, trazodone, nefazodone, bupropion, buspirone, maprotiline, mirtazapine will generate warnings with linezolid as well, though interactions have not been reported to the FDA.[23] Carbamazepine is also contraindicated with linezolid,[9,10] though there are literature reports of safe concurrent use.[9] Methylene blue, rasagiline and selegiline are MAOIs as well and should not be combined with nonselective psychiatric MAOIs and are subject to many of the interactions listed previously.[10]

MEDICATIONS THAT PROLONG THE QTC INTERVAL

Many medications can prolong the QTc interval and when used in combination, prolong in an additive fashion. QTc prolongation effects of some medications are dose related. Thus, when adding a medication that inhibits the metabolism of the QTc prolonging medication, the risk of QTc prolongation and potentially torsades de pointes, increases.

CredibleMeds (formerly AZCERT - Arizona Center for Education and Research) has three very helpful tables that list medications with known torsades de pointes (TdP) risk, with possible TdP risk and with conditional TdP risk. These tables can be found at www.crediblemeds.org. Some antipsychotic medications, antidepressant medications, antihistamines, lithium and methadone appear on these lists.

MEDICATIONS THAT LOWER THE SEIZURE THRESHOLD

Medications can additively lower the seizure threshold. TCAs (especially clomipramine,) atypical antipsychotics (especially clozapine,) antidepressants (especially bupropion,) psychostimulants, narcotics, some immunosuppressants (e.g. cyclosporine, chlorambucil, prednisone), some antibiotics (e.g. isoniazid, lindane, metronidazole, nalidixic acid, penicillins), oral hypoglycemic agents, anticholinergics (e.g. dimenhydrinate, diphenhydramine, cyclizine, meclizine, scopolamine, trimethobenzamide), anticholinesterases and lithium may lower the seizure threshold.[24,25]

MEDICATIONS WITH ANTICHOLINERGIC EFFECTS

Anticholinergic medications can additively lead to toxicity with symptoms that include confusion, hypertension, tachycardia, flushing, pyrexia, etc.[26] Antihistamines (e.g. chlorpheniramine, cyproheptadine, diphenhydramine, hydroxyzine), some antidepressants (especially the TCAsand paroxetine), some antipsychotics (e.g. clozapine, olanzapine, chlorpromazine, thioridazine), antidiarrheals (e.g. diphenoxylate, atropine), antiemetics (e.g prochlorperazine, promethazine), antivertigo agents (e.g cyclizine, dimenhydrinate, meclizine, scopolamine, trimethobenzamide) and some H2 blockers (e.g cimetidine, ranitidine) are anticholinergic.[26,27] Some cardiac medications (e.g. digoxin, disopyramide, furosemide, nifedipine, atropine), some GI medications (e.g dicyclomine, glycopyrrolate, hyoscyamine, mepenzolate, methscopolamine propantheline), some Parkinson's medications (e.g. amantadine, benztropine, trihexyphenidyl), some muscle relaxants (e.g. cyclobenzaprine, dantrolene, orphenadrine) some urinary antispasmotics (e.g fesoterodine, flavoxate, oxybutynin, solifenacin, tolterodine, trospium) also have anticholinergic properties.[26,27] Monitor for signs and symptoms of anticholinergic toxicity when using multiple anticholinergic medications, especially in older adults and those with intellectual disabilities who may be more susceptible.[27]

MEDICATIONS WITH SEROTONERGIC EFFECTS

Using multiple medications with serotonergic effects can lead to serotonin syndrome, the risk of which increases with the number of medications that increase serotonin. Triptans, SSRIs, SNRIs, TCAs, MAOIs, nefazodone, tramadol, fentanyl, meperidine, tapentadol, cyclobenzaprine, carbamazepine, lithium, ondansetron, granisetron, lorcaserin, dextromethorphan, procarbazine all have serotonergic effects which could contribute to serotonin toxicity.[9,10]

RECOGNIZING INTERACTIONS

When adding or removing a medication from a patient's regimen, it is important to examine the impact of that change in the terms of drug interactions. Knowing the mechanisms of metabolism of the added or removed medication will help to determine the impact to the other medications in the patient's regimen. Adding a CYP450 enzyme inducer will decrease the level of other medications metabolized by the same enzyme. In addition, an enzyme inducer will increase the metabolites

of those medications.[20] Conversely, discontinuing a CYP450 enzyme inducer will increase the level of other medications metabolized by the same enzyme. Adding a CYP450 enzyme inhibitor will increase the level of other medications metabolized by the inhibited enzyme. In addition, an enzyme inhibitor will decrease the metabolites of those medications.[20] Conversely, discontinuing a CYP450 enzyme inhibitor will decrease the level of the other medications metabolized by the inhibited enzyme. Enzyme induction involves increased production of the enzyme and takes some time to occur and resolve.[20] Thus, the onset of an induction drug interaction is slow, and upon discontinuation of the inducing medication, will resolve slowly, as well. Enzyme inhibition can occur and resolve rather quickly and is more dependent on the dose and half-life of the enzyme inhibiting medication.[20]

There is inter-patient variability in CYP450 metabolic capacity, called polymorphism.[20] Poor metabolizers have reduced metabolic capacity resulting in higher drug levels that may result in increased side effects and toxicity.[20] This situation resembles enzyme inhibition, as described above. Ultraextensive metabolizers have excess metabolic capacity and may have treatment failures or need higher doses of medications to achieve the desired effect.[20] Patients with average metabolic capacity are called extensive metabolizers.[20] Polymorphism has been identified in CYP450 1A2, 2A6, 2C8, 2C9, 2C19 and 2D6.[20] Genetic testing is available to determine enzyme capacity, but this does not correlate with known medication dose adjustments.

There are many resources available to help identify drug interactions. There are a number of computer software tools designed to check for drug interactions. After entering the patient's medication list, the software will flag interactions, providing levels of severity for each. These tools tend to vary some in the interactions they flag. Some of these software tools are built into computerized medication ordering systems to allow for real-time interaction identification.

There are also a number of tables on the internet and in drug interaction books that provide metabolism information on the medications known to induce, inhibit or that are substrates of the various CYP450 enzymes. These can be very helpful as one can use them to assess the metabolism of specific medications and identify potential drug interactions.

The course of action as the result of a drug interaction depends upon the severity of the result of that interaction. Some interactions can be managed with additional side effect monitoring, dose adjustments or with additional drug levels. Others, with the potential for more serious effects, are best avoided by choosing alternative therapies that do not interact.

SUMMARY

With the increased number of prescriptions written on an annual basis and the prevalence of polypharmacy, drug interactions are becoming more common. Drug interactions may present in a patient as treatment failure or as troublesome side effects. Not all drug interactions are life- threatening. Fortunately, we are learning more and more about drug metabolism and can be proactive in preventing these treatment failures and adverse effects. There are several software programs available that allow one to enter a list of medications and obtain a list of drug interactions, including the severity of each. The resolution of a drug interaction depends upon the severity of the possible outcome, and may include monitoring for side effects, adjusting doses, following drug levels or choosing alternate therapies.

The following tables were constructed using data from a number of sources. Prodrugs were identified through reference 14. Inducers, inhibitors and substrates were identified through references 3, 13, 14, 28 and 29. Preferred routes of metabolism were identified through reference 3. Metabolism of vortioxetine was identified through references 30, 31 and 32. Metabolism of levomilnacipran was identified through reference 33.

Table 1. CYTOCHROME P450 1A2

Psychiatric Medications				
Inducers	**Strong Inducers**	**Inhibitors**	**Strong Inhibitors**	**Substrates**
Deferasirox	Barbiturates		Fluvoxamine	Amitriptyline
	Carbamazepine			**Asenapine**
	Phenobarbital			Chlorpromazine
	Cigarette smoking			Clomipramine
	Char-grilled meats			***Clozapine***
	Cruciferous vegetables			Diphenhydramine
				Duloxetine
				Fluvoxamine
				Impipramine
				Melatonin
				Mirtazapine
				Olanzapine
				Pimozide
				Propranolol
				Ramelteon
				Thioridazine
				Zolpidem
Other Medications				
Inducers	**Strong Inducers**	**Inhibitors**	**Strong Inhibitors**	**Substrates***
	Phenytoin	Caffeine	Artemisinin	**Anagrelide**
	Primidone	Ethinyl Estradiol	Atazanavir	**Bendamustine**
	Rifampin	Norfloxacin	Cimetidine	**Caffeine**
	Cigarette smoking		Ciprofloxacin	**Flutamide**
	Char-grilled meats		Enoxacin	**Frovatriptan**
	Cruciferous vegetables		Mexiletine	***Lidocaine***
			Tacrine	**Ondansetron**
			Thiabendazole	**Rasagiline**
			Ticlopidine	**Riluzole**
			Vemurafenib	**Ropinirole**
			Zileuton	***Ropivacaine***
				Tacrine
				Theophylline
				Thiabendazole
				Tizanidine
				Triamterene
				R-Warfarin
				Zileuton
				Zolmitriptan

Italics indicate medications whose preferred route of metabolism is through 1A2
Bold indicates medications whose solitary route of metabolism is through 1A2
*There are many additional substrates for 1A2

Table 2. CYTOCHROME P450 2B6

Psychiatric Medications				
Inducers	**Strong Inducers**	**Inhibitors**	**Strong Inhibitors**	**Substrates**
				Bupropion
				Clobazam
				Ketamine
Other Medications				
Inducers	**Strong Inducers**	**Inhibitors**	**Strong Inhibitors**	**Substrates**
Rifampin	Efavirenz	Thiotepa	Clopidogrel	Artemisinin
	Ritonavir		Cyclophosphamide	Cyclophosphamide(p)
			Ticlopidine	***Efavirenz***
				Ifosfamide(p)
				Ketamine
				Methadone
				Nevirapine
				Prasugrel
				Propofol
				Selegiline

Italics indicate medications whose preferred route of metabolism is through 2B6
Bold indicates medications whose solitary route of metabolism is through 2B6
(p) indicates a prodrug

Table 3. CYTOCHROME P450 2C8

Psychiatric Medications				
Inducers	**Strong Inducers**	**Inhibitors**	**Strong Inhibitors**	**Substrates**
				Carbamazepine
				Clonazepam
				Levomilnacipran
				Zopiclone
Other Medications				
Inducers	**Strong Inducers**	**Inhibitors**	**Strong Inhibitors**	**Substrates**
			Amiodarone	Cabazitaxel
			Clopidogrel	Chloroquine
			Co-trimoxazole	Diclofenac
			Deferasirox	Fluvastatin
			Gemfibrozil	**Gemfibrozil**
			Lapatinib	Ibuprofen
			Trimethoprim	Loperamide
				Montelukast
				Paclitaxel
				Phenytoin
				Pioglitazone
				Repaglinide
				Rosiglitazone
				Treprostinil

Italics indicate medications whose preferred route of metabolism is through 2C8
Bold indicates medications whose solitary route of metabolism is through 2C8

Table 4. CYTOCHROME P450 2C9

Psychiatric Medications					
Inducers	**Strong Inducers**	**Inhibitors**	**Strong Inhibitors**	**Substrates**	
	Carbamazepine	Fluoxetine	Disulfiram	Doxepin	Fluoxetine
	Phenobarbital	Fluvoxamine	Valproic Acid	Melatonin	Phenobarbital
	Barbiturates	Modafinil		Ramelteon	Vortioxetine
				Zolpidem	
Other Medications					
Inducers	**Strong Inducers**	**Inhibitors**	**Strong Inhibitors**	**Substrates**	
Aprepitant	Aminoglutethimide	Fluvastatin	Alcohol	Alosetron	Amprenavir
	Barbiturates	Gemfibrozil	Amiodarone	**Azapropazone**	**Azilsartan**
	Griseovfulvin	Toremifene	Azapropazone	Bosentan	**Candesartan**
	Phenytoin		Berberine	Carvedilol	**Celecoxib**
	Primidone		Bosentan	**Chlorpropamide**	Clopidogrel
	Rifampin		Capecitabine	Co-trimoxazole	Diclofenac
	Rifapentine		Co-trimoxazole	**Dronabinol**	Etravirine
	Ritonavir		Delavirdine	**Flurbiprofen**	Fluvastatin
			Doxifluridine	**Glimepiride**	**Glipizide**
			Efavirenz	**Glyburide**	Ibuprofen
			Etravirine	**Indomethacin**	**Irbesartan**
			Fluconazole	Ketamine	***Losartan*#**
			Fluorouracil	***Meloxicam***	Montelukast
			Imatinib	**Naproxen**	***Nateglinide***
			Leflunomide	Prasugrel	***Phenytoin***
			Metronidazole	Pioglitazone	**Piroxicam**
			Miconazole	**Pitavastatin**	Rosiglitazone
			Nafcillin	**Rosuvastatin**	Sildenafil
			Sulfamethizole	***Sulfamethoxazole***	**Tolbutamide**
			Sulfamethoxazole	**Torsemide**	Valdecoxib
			Sulfaphenazole	**Valsartan**	Voriconazole
			Sulfinpyrazone	***S-Warfarin***	***Zafirlukast***
			Tamoxifen		
			Voriconazole		
			Zafirlukast		

Italics indicate medications whose preferred route of metabolism is through 2C9
Bold indicates medications whose solitary route of metabolism is through 2C9
# indicates the metabolite produced is responsible for the majority of drug effect

Table 5. CYTOCHROME P450 2C19

Psychiatric Medications					
Inducers	**Strong Inducers**	**Inhibitors**	**Strong Inhibitors**	**Substrates**	
	Barbiturates	Armodafinil	Fluoxetine	Amitriptyline	***Citalopram***
	Phenobarbital	Topiramate	Fluvoxamine	Clobazam	Clomipramine
	St. John's Wort		Modafinil	Clozapine	Desipramine
			Oxcarbazepine	***Diazepam***	Diphenhydramine
				Doxepin	***Escitalopram***
				Fluoxetine	Imipramine
				Levomilnacipran	Phenobarbital
				Propranolol	***Sertraline***
				Venlafaxine	Vilazodone
				Vortioxetine	
Other Medications					
Inducers	**Strong Inducers**	**Inhibitors**	**Strong Inhibitors**	**Substrates***	
	Artemisinin	Etravirine	Chloramphenicol	**Carisoprodol**	
	Phenytoin		Cimetidine	***Clopidogrel(p)***	
	Primidone		Clopidogrel	***Esomeprazole***	
	Rifampin		Delavirdine	***Etravirine***	
			Efavirenz	**Lacosamide**	
			Esomeprazole	***Omeprazole***	
			Felbamate	***Pantoprazole***	
			Fluconazole	**Pentamidine**	
			Isoniazid	**Proguanil(p)**	
			Moclobemide	**Rabeprazole**	
			Omeprazole	**Thalidomide**	
			Oxcarbazepine		
			Ticlopidine		
			Voriconazole		

Italics indicate medications whose preferred route of metabolism is through 2C19
Bold indicates medications whose solitary route of metabolism is through 2C19
(p) indicates a prodrug
*There are many additional substrates for 2C19

Table 6. CYTOCHROME P450 2D6

Psychiatric Medications					
Inducers	**Strong Inducers**	**Inhibitors**	**Strong Inhibitors**	**Substrates**	
		Asenapine	Bupropion	***Amitriptyline***	**Amoxepine**
		Citalopram	Chlorpromazine	***Aripiprazole***	**Atomoxetine**
		Desvenlafaxine	Clobazam	Citalopram	***Clomipramine***
		Duloxetine	Diphenhydramine	Clozapine	***Desipramine***
		Escitalopram	Fluoxetine	**Diphenhydramine**	***Doxepin***
		Fluvoxamine	Haloperidol	Duloxetine	***Escitalopram***
		Risperidone	Paroxetine	***Fluoxetine***	***Fluvoxamine***
		Sertraline	Perphenazine	***Haloperidol***	***Iloperidone***
			Thioridazine	***Imipramine***	Levomilnacipran
				Maprotiline	**Mesoridazine**
				Methamphetamine	**Mianserin**
				Mirtazapine	***Nortriptyline***
				Olanzapine	**Paliperidone**
				Paroxetine	**Perphenazine**
				Propranolol	**Protriptyline**
				Risperidone	Sertraline
				Thioridazine	***Trazodone***
				Venlafaxine	Vilazodone
				Vortioxetine	
Other Medications					
Inducers	**Strong Inducers**	**Inhibitors**	**Strong Inhibitors**	**Substrates***	
Rifampin		Cimetidine	Abiraterone	**Alprenolol**	**Clonidine**
		Methadone	Amiodarone	**Codeine(p)**	**Debrisoquin**
		Pazopanib	Berberine	***Dextromethorphan***	**Dihydrocodeine**
		Ranolazine	Celecoxib	***Diphenhydramine***	***Dolasetron(p)***
		Vemurafenib	Chlorquine	**Encainide**	***Flecainide***
			Chlorpheniramine	**Hydrocodone(p)**	**Metoclopramide**
			Cinacalcet	**Metoprolol**	***Mexiletine***
			Cobicistat	**Nebivolol**	***Palonsetron***
			Darifenacin	**Perhexiline**	**Promethazine**
			Diphenhydramine	***Propafenone***	**Propranolol**
			Dronedarone	Tamoxifen(p)	**Tetrabenazine**
			Flecainide	**Timolol**	***Tolterodine***
			Halofantrine	***Tramadol***	
			Hydroxychloroquine	**Treprostinil**	
			Imatinib		
			Lumefantrine		
			Promethazine		
			Propafenone		
			Quinacrine		
			Quinidine		
			Quinine		
			Ritonavir		
			Terbinafine		

Italics indicate medications whose preferred route of metabolism is through 2D6
Bold indicates medications whose solitary route of metabolism is through 2D6
*There are many additional substrates for 2D6
(p) indicates a prodrug

Table 7. CYTOCHROME P450 3A4

Psychiatric Medications					
Inducers	**Strong Inducers**	**Inhibitors**	**Strong Inhibitors**	**Substrates**	
Clobazam	Armodafinil	Fluoxetine	Fluvoxamine	**Alprazolam**	Amitriptyline
Oxcarbazepine	Barbiturates		Nefazodone	**Armodafinil**	**Buspirone**
Topiramate	Carbamazepine			Carbamazepine	Citalopram
	Modafinil			***Clobazam***	**Clomipramine**
	Phenobarbital			Clonazepam	Clozapine
	St. John's Wort			**Desvenlafaxine**	**Diazepam**
				Escitalopram	**Estazolam**
				Eszopiclone	**Guanfacine**
				Haloperidol	Iloperidone
				Imipramine	***Levomilnacipran***
				Lurasidone	Mirtazapine
				Modafinil	**Nefazodone**
				Nortriptyline	Olanzapine
				Pimozide	**Quazepam**
				Quetiapine	Ramelteon
				Risperidone	Thioridazine
				Topiramate	Trazodone
				Triazolam	***Vilazodone***
				Venlafaxine	Vortioxetine
				Zaleplon	***Zolpidem***
				Ziprasidone	
Other Medications					
Inducers	**Strong Inducers**	**Inhibitors**	**Strong Inhibitors**	**Substrates***	
Deferasirox	Aminoglutethimide	Basiliximab	Amiodarone	**Abiraterone**	**Alfentanil**
Oxcarbazepine	Artemether	Cilostazol	Amprenavir	**Alfuzosin**	**Aliskiren**
	Bexarotene	Deferasirox	Aprepitant	**Amlodipine**	***Amprenavir***
	Bonsetan	Interleukin-10	Atazanavir	***Aprepitant***	**Artemether**
	Dexamethasone	Ivacaftor	Berberine	**Astemizole**	**Atazaniver**
	Efavirenz	Linagliptin	Boceprevir	**Atorvastatin**	**Avanafil**
	Etravirine	Nicardipine	Choramphenicol	**Bepridil**	**Bexaroten**
	Griseofulvin	Nilotinib	Ciprofloxacin	**Boceprevir**	***Bortezomib***
	Mitotane	Pazopanib	Clarithromycin	**Brentuximab**	**Bromocriptine**
	Nafcillin	Ranolazine	Cobicistat	**Budesonide**	**Bupivacaine**
	Nevirapine	Ticagrelor	Conivaptan	**Buprenorphine**	***Cabazitaxel***
	Phenytoin		Crizotinib	**Cabozanitinib**	**Cobicistat**
	Primidone		Cyclosporine	**Colchicine**	**Conivaptan**
	Rifabutin		Dalfopristin	**Crizotinib**	**Cyclosporine**
	Rifampin		Danazol	**Dapsone**	**Darunavir**
	Rifapentine		Darunavir	**Dastinib**	**Delavirdine**
	Vemurafenib		Dasatinib	**Dexamethasone**	**Dihydroergotamine**
			Delavirdine	**Diltiazem**	**Disopyramide**
			Diltiazem	**Docetaxel**	***Donepezil***
			Dronedarone	**Doxorubicin**	**Dronedarone**
			Erythromycin	**Droperidol**	**Dutasteride**
			Ethinyl Estradiol	**Ebastine**	**Eletriptan**
			Fluconazole	**Elvitegravir**	**Eplerenone**
			Fosamprenavir	**Ergotamine**	***Erlotinib***
			Grapefruit	**Erythromycin**	**Ethinyl Estradiol**
			Imatinib	**Ethosuximide**	**Etoposide**
			Indinavir	**Everolimus**	**Exemestane**

Table 7. CYTOCHROME P450 3A4 (continued)

Other Medications					
Inducers	**Strong Inducers**	**Inhibitors**	**Strong Inhibitors**	**Substrates***	
			Isoniazid	**Felodipine**	**Fentanyl**
			Itraconazole	*Fesoterodine*	**Finasteride**
			Ketoconazole	**Fosamprenavir**	***Fovatriptan***
			Lapatinib	***Galantamine***	**Granisetron**
			Miconazole	**Guanfacine**	**Halofantrine**
			Mifepristone	**Ifosfamide**	**Imatinib**
			Nelfinavir	**Indacaterol**	**Indinavir**
			Posaconazole	**Irinotecan**	**Isradipine**
			Primidone	**Itraconazole**	**Ivabradine**
			Quinupristin	**Invacaftor**	**Ixabepilone**
			Ritonavir	**Ketaconazole**	**Lapatinib**
			Saquinavir	**Levomethadyl**	**Lopinavir**
			Tamoxifen	***Loratidine***	***Lovastatin***
			Telaprevir	**Lumefantrine**	**Maraviroc**
			Telithromycin	**Mefloquine**	**Methylprednisolone**
			Troleandomycin	**Midazolam**	**Mifepristone**
			Verapamil	**Mometasone**	**Nicardipine**
			Voriconazole	**Nifedipine**	**Nilotinib**
			Zafirlukast	**Nimotidine**	**Nisoldipine**
				Nitrendipine	**Oxybutinin**
				Oxycodone	**Paricalcitol**
				Prednisolone	**Praziquantel**
				Prednisone	**Quinacrine**
				Quinidine	**Quinine**
				Ranolazine	**Regorafenib**
				Rifabutin	**Rilpivirine**
				Ritonavir	**Rivaroxaban**
				Romidepsin	**Ruxolitinib**
				Salmeterol	**Saquinavir**
				Saxagliptin	***Sildenafil***
				Sildosin	***Simvastatin***
				Sirolimus	**Sitagliptin**
				Solifenacin	***Sorafenib***
				Sufentanil	**Sunitinib**
				Tacrolimus	**Tadalafil**
				Tamoxifen	**Telaprevir**
				Temsirolimus	**Teniposide**
				Terfenadine	**Testosterone**
				Tiagabine	**Ticagrelor**
				Tinidazole	**Tipranavir**
				Tolvaptan	**Toremifene**
				Triamcinolone	**Ulipristal**
				Vandetanib	**Vardenafil**
				Vemurafenib	**Verapamil**
				Vesnarinone	**Vinblastine**
				Vincristine	*Vinorelbine*

Italics indicate medications whose preferred route of metabolism is through 3A4
Bold indicates medications whose solitary route of metabolism is through 3A4
*There are many additional substrates for 3A4
(p) indicates a prodrug

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