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Drug Interactions Associated with the Use of Antidepressant Medications

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LEARNING OBJECTIVES

1. Identify which antidepressants can lead to clinically significant drug interactions involving the cytochrome P-450 (CYP 450) metabolism.
2. Describe the etiology and symptoms of serotonin syndrome.
3. Determine which medication combinations increase a patient's risk for serotonin syndrome.
4. Recognize which medications may augment the norepinephrine and dopamine effects of antidepressants.
5. Identify which antidepressants are highly protein bound and can possibly interact with other protein-bound medications.

ABSTRACT: Serotonin syndrome is a toxic effect attributable to overstimulation of the 5HT-1_A receptor in the central nervous system (CNS). This serious condition is usually caused by a pharmacodynamic drug interaction between 2 or more medications that increase serotonin in the brain. Common signs and symptoms associated with serotonin syndrome are hyperreflexia, fever, mental status changes, agitation, diaphoresis, and diarrhea. Symptoms can range from mild to severe and usually develop within 24 hours of when the causative agent is initiated. Being able to identify the risks and signs of serotonin syndrome might be beneficial for clinicians especially for those who provide care to mental health patients. This syndrome is oftentimes misdiagnosed and results in a delay in treatment.

With polypharmacy being common among patients with psychiatric diagnoses, drug interactions and serotonin syndrome are possible complications that occur with treatment. It is important for clinicians to understand the various ways drug interactions can manifest. Knowing the mechanism of action and major metabolic pathways for different antidepressants will help one to recognize the most clinically relevant interactions. Therefore, an alternative agent can be chosen, dosing can be adjusted, or monitoring can be increased to prevent an adverse effect from happening.

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Drug Interactions Associated with the Use of Antidepressant Medications

Introduction

In relation to drug interactions, 2 types exist: pharmacokinetic and pharmacodynamic. Pharmacokinetic interactions occur when 1 medication (the precipitant drug) changes the absorption, distribution (including protein binding), metabolism, or excretion of another medication (the object drug), resulting in altered concentrations of the object drug. Pharmacodynamic interactions

occur when a medication affects the mechanism of action of the object drug by either augmenting the effects or acting as an antagonist of the object drug. Antidepressant medications are known to be involved in both pharmacokinetic and pharmacodynamic interactions.[1,2]

Pharmacokinetic Drug Interactions

Most antidepressants are metabolized by the cytochrome P-450 (CYP 450) in the liver. Interactions involving the metabolism of these medications are a concerning issue for clinicians, especially when treating patients who are taking multiple medications. Inhibition of antidepressant metabolism may lead to mild adverse effects such as anticholinergic or gastrointestinal symptoms. Serious effects, however, such as prolonged QT interval, ventricular arrhythmias, and seizures have also been noted with elevated antidepressant serum levels.[3-7] Understanding how medications are metabolized through the CYP 450 and being able to identify the clinically significant interactions involving antidepressants will aid clinicians to choose the most appropriate regimen, dosing, and monitoring. Therefore, adverse effects owing to drug-drug interactions can be avoided.

Antidepressants and CYP 450

Liver metabolism of medications is composed of 2 different phases. Phase I metabolism usually involves oxidation, hydrolysis, and reduction of medications to transform the drugs into a more reactive form. During Phase II metabolism (conjugation), a sulfate, glycine, or glucuronic acid is added to a drug inactivating it and making it more polar to where it can be excreted by the kidneys.[1]

CYP 450 are heme containing enzymes mostly found in the mitochondria and endoplasmic reticulum of hepatocytes, which are responsible for Phase I metabolism of endogenous (steroids, fatty acids, prostaglandins) and exogenous substances (medications). Most medications that require metabolism by the liver do undergo both Phase I and Phase II transformation. However, a small number of medications are only metabolized by Phase II. Therefore, these medications are not significantly involved in CYP 450 metabolism.[1-2, 8]

The CYP 450 is composed of more than 30 isoenzymes. Isoenzymes are identified by family (Arabic numeral), subfamily (capital letter), and gene (Arabic numeral). The 5 major pathways of metabolism are 1A2, 2C9, 2C19, 2D6, and 3A4. A medication metabolized by a particular isoenzyme is considered to be a substrate of that isoenzyme. However, some medications also act as inhibitors or inducers of isoenzymes (Table 1). Inducers are medications that result in increased blood flow to the liver or initiate synthesis of additional P-450 enzymes. These actions result in increased metabolic activity of the isoenzymes. Medications that are considered P-450 inhibitors do so by either competing with other substrates for binding at the enzyme or inactivating the enzyme.[2]

Not only do medications influence metabolic activity, but genetic disposition can also affect the activity of certain P-450 enzymes. CYP 1A2 metabolism is decreased in 13% of Caucasians, African Americans, and Asians. Approximately 10% of Caucasians are considered to be poor 2D6 metabolizers, while only 2% of African Americans and Asians have this genetic feature. Five percent of Caucasians and African Americans demonstrate poor metabolism through the 2C19 pathway, but as many as 23% of Asians are poor metabolizers of this enzyme.[1,9]

Multiple P-450 pathways metabolize many antidepressants, and 2D6 and 3A4 are the most common of the pathways. A number of antidepressants will inhibit these pathways as well (Table 2). When reviewing this information for the first time, clinicians may wonder how to determine which potential drug interactions are more

likely to occur and which are less clinically significant. The following factors are important to keep in mind when determining the clinical significance of a potential interaction:[2,8]

1) The type of activity performed at the enzyme site by the antidepressant (e.g., substrate, inhibitor, or inducer)
2) The potency of the inhibitor/inducer
3) The concentration of the inhibitor/inducer at the enzyme site
4) The saturability of the enzyme
5) The extent of the substrate metabolism through a particular enzyme
6) The presence of active metabolites after the substrate is metabolized
7) The therapeutic window of the s ubstrate
8) The enzyme activity of the patient (e.g., poor metabolizer, fast metabolizer)
9) The risk for the patient to experience adverse effects (e.g., elderly)
10) The probability of concurrent use

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) undergo hydroxylation and demethylation through the P-450 system. The 2D6 isoenzymes are exclusively responsible for hydroxylation of these agents. Demethylation usually involves multiple pathways, including CYP 1A2, CYP 2C19, and CYP 3A4. Because 2D6 is a major pathway for TCAs, inhibitors or inducers of these isoenzymes can alter antidepressant levels. TCAs have a narrow therapeutic window; therefore, concurrent use with a potent CYP 2D6 inhibitor can significantly elevate serum levels increasing a patient's risk for anticholinergic adverse effects, orthostasis, arrhythmias, or seizures.[10-13]

Many depressed patients are prescribed more than one medication to treat the disease. Therefore, it may not be unusual for a patient to be taking a TCA and a selective serotonin reuptake inhibitor (SSRI). Fluoxetine and paroxetine are both SSRIs that inhibit CYP 2D6 isoenzymes. Case reports have shown TCA serum levels to double after the addition of either of these 2 agents.[11,14-15] For patients taking a TCA who require an additional antidepressant, fluoxetine and paroxetine should not be considered as first-line therapy.

Phenothiazine antipsychotics have also been shown to inhibit the metabolism of TCA.[16-17] Concurrent use of TCA and phenothiazines should be avoided if possible. Both classes of medications are known to widen the QT interval and induce ventricular arrhythmias. The risk increases if the 2 drug classes are combined. [18]

In addition to hydroxylation, a number of TCAs also undergoes demethylation via CYP 1A2, CYP 2C19, or CYP 3A4. Agents such as clomipramine, doxepin, imipramine, and trimipramine are metabolized by these pathways and should be used cautiously with inhibitors of these isoenzymes.[8]

Even though the liver metabolizes TCAs extensively, TCAs are not considered to be potent inducers or inhibitors of the CYP 450. Therefore, these agents are rarely responsible for affecting the metabolism of other medications.[8]

Selective Serotonin Reuptake Inhibitors

Selective Serotonin Reuptake Inhibitors (SSRIs) are extensively oxidized by the P-450 system, but unlike TCAs, SSRIs have a wide therapeutic index, so inhibition or induction of their metabolism is usually not a significant concern.[8] However, a few documented cases of serotonin syndrome as a result of SSRI metabolism inhibition have been published.[19-20] Fluoxetine and paroxetine are potent 2D6 inhibitors and will increase the serum concentrations of other medications metabolized by this isoenzyme. As mentioned before, TCAs are metabolized by CYP 2D6 and may have to be reduced in dosage if fluoxetine or paroxetine is added to the regimen.[11,14-15] In addition to TCAs,

many antipsychotics are 2D6 substrates and are significantly influenced by the inhibition of this enzyme. A number of case reports have shown an increased incidence of extrapyramidal adverse effects and a prolonged QT interval when fluoxetine or paroxetine are used concurrently with typical antipsychotics.[11, 21-22] Other significant substrates of CYP 2D6, whose metabolism is likely to be affected by fluoxetine or paroxetine, include warfarin, antiarrhythmics, β-blockers, and codeine.[13] In most cases, the inhibition of 2D6 isoenzymes places a patient at risk for drug accumulation and toxicity; therefore, substrate medications usually have to be prescribed at a lower dose. However, the situation is different for codeine metabolism. Codeine must be metabolized to morphine by 2D6 isoenzymes for the drug to provide pain relief. Fluoxetine and paroxetine inhibit the conversion of codeine to morphine, decreasing its analgesic effect. Patients may actually need to take higher doses of codeine to obtain adequate pain relief if they are also taking fluoxetine or paroxetine.[1]

Fluvoxamine is noted to be a potent inhibitor of CYP 1A2, 2C19, and 3A4. Examples of 1A2 substrates include theophylline, clomipramine, imipramine, and clozapine. All 4 of these medications have been documented in case reports to increase in concentration when used concurrently with fluvoxamine.[23-27] Cytochrome P-450 3A4 isoenzymes are responsible for the metabolism of almost half of the medications that enter into the CYP 450 system. Fluvoxamine has been shown to inhibit the 3A4 pathway significantly and has the potential to interact with many of the 3A4 substrates (Table 1). HMG CoA reductase inhibitors, benzodiazepines, haloperidol, phenytoin, carbamazepine, calcium channel blockers, antiarrhythmics, and cyclosporine are 3A4 substrates and, if any are combined with fluvoxamine, they can lead to serious adverse effects if patients are not monitored closely.[8]

Among the SSRI antidepressants, fluoxetine, paroxetine, and fluvoxamine are the most concerning for causing drug interactions by inhibiting CYP pathways. Sertraline, citalopram, and escitalopram are major substrates of the 3A4 and 2C19 isoenzymes, but these SSRIs have not been shown to be significant inhibitors of the P-450 system at normal therapeutic doses.[28-31] Therefore, these 3 agents may be better choices as first-line antidepressants for patients taking multiple medications.

Other Antidepressants

Trazodone is significantly metabolized by 3A4 isoenzymes. Studies have shown trazodone serum levels to increase when used concurrently with potent inhibitors such as ketoconazole and protease inhibitors and result in symptomatic orthostatic hypotension and severe nausea.[32-33] Because of the results of these studies, trazodone package inserts were recently changed to warn of these interactions.[32] Inducers of CYP 3A4 such as carbamazepine have been shown to significantly reduce trazodone levels.[32, 34]

Just like trazodone, nefazodone is a substrate of the 3A4 pathway, but nefazodone is also a potent inhibitor of this enzyme as well. Therefore, nefazodone can increase serum levels of other 3A4 substrates such as benzodiazepines, haloperidol, HMG CoA reductase inhibitors, and calcium channel blockers.[1,8] Nefazodone has been noted to increase benzodiazepine levels by 2 to 3 times normal range and to cause oversedation.[35-36]

Bupropion is metabolized by 4 of the major enzymes (1A2, 2C9, 2D6, 3A4), but the drug is considered to be a weak substrate of all these pathways. Therefore, inhibition or induction of these 4 enzymes is usually not a worry in respect to bupropion levels. However, some clinicians note a concern with bupropion and P-450 inhibitors. Since supratherapeutic bupropion levels can increase the risk of seizures, inhibitors of

1A2, 2C9, 2D6, and 3A4 should be used cautiously with this antidepressant.[8]

Venlafaxine and the newly approved antidepressant duloxetine both treat depression by inhibiting the reuptake of norepinephrine and serotonin. The 2D6 enzyme significantly metabolizes venlafaxine and duloxetine. Therefore, inducers and inhibitors of these isoenzymes can potentially alter drug levels. However, similar to SSRI, venlafaxine and duloxetine have a large therapeutic window, and alterations in levels may not necessarily result in clinical effects.[8,37] Duloxetine has been found to be a potent inhibitor of CYP 2D6 and has been noted to significantly increase TCA levels.[38] Other 2D6 substrates such as antiarrhythmics, β-blockers, and antipsychotics may also need to be lowered in dose if used concurrently with duloxetine.

Mirtazapine is a weak inhibitor of P-450 enzymes and has little potential to be the cause of drug interactions. However, the antidepressant is a substrate of 1A2, 2D6, and 3A4. Theoretically, inhibitors and inducers of these enzymes can alter mirtazapine levels.[8]

Highly Protein-Bound Antidepressants

Oftentimes, when pharmacokinetic drug interactions are discussed, the focus is mainly on the CYP 450 system and how medications affect it. But, clinicians must remember that highly protein-bound medications can interact with each other by competing for binding sites and result in an increased active drug. Antidepressants that are considered highly protein bound include nortriptyline, trimipramine, fluoxetine, paroxetine, sertraline, duloxetine, and trazodone.[39,40] These antidepressants can influence active drug levels of warfarin, phenytoin, and valproic acid, which are also highly protein-bound medications.[2,39,40]

Pharmacodynamic Drug Interactions

To predict the risk of pharmacodynamic drug interactions with antidepressants, clinicians should be familiar with the neurotransmitters and receptors affected by each agent. With the exception of bupropion, all antidepressants augment the effects of serotonin in the central nervous system (CNS), even though the mechanism of action may vary among the different drug classes. With the use of antidepressants, a condition known as serotonin syndrome is a possible risk especially for patients who take multiple serotonergic medications concurrently. The cause, clinical presentation, and treatment of serotonin syndrome are discussed in detail throughout this article. A review of the mechanism of actions of each antidepressant class and other possible pharmacodynamic interactions are also covered.

Serotonin Syndrome

Serotonin syndrome is a toxic effect resulting from overstimulation of the 5-HT_{1A} and possibly the 5-HT_2 receptors in the CNS.[41] This serious condition is usually caused by a pharmacodynamic drug interaction between 2 or more medications that increase serotonin in the brain. Theoretically, any medication that increases serotonin in the CNS can increase the risk of serotonin syndrome (Table 3). Medications that augment the effects of serotonin in the CNS (serotonergic medications) usually do so by 1 or more of the following mechanisms:[42]

1.) Inhibiting serotonin metabolism by monoamine oxidase inhibition
2.) Increasing the release of serotonin
3.) Acting as a serotonin receptor agonist
4.) Inhibiting serotonin uptake

Many documented cases of severe serotonin syndrome have involved the use of a SSRI and/or a monoamine oxidase inhibitor (MAOI).[41,43-45] MAOI increase CNS serotonin levels by irreversibly inhibiting the breakdown of the neurotransmitter. Because the effects of MAOI are irreversible, serotonin syndrome is still a risk even if the medication has been stopped.

After a MAOI is discontinued, the CNS needs approximately 2 weeks before monoamine oxidase levels return to a normal level to begin metabolizing serotonin again. The concurrent use of serotonergic medications such as meperidine in addition to MAOI is contraindicated. If a MAOI is discontinued and another serotonergic drug is needed, clinicians should advise patients to wait 2 weeks after discontinuation of the MAOI before starting the new medication.[8,42]

SSRIs block the reuptake of serotonin in the CNS resulting in higher concentrations of the neurotransmitter in the synaptic cleft. Concurrent use of a SSRI with other serotonergic medications should be avoided if possible. However, if the combination is needed, clinicians are asked to monitor the patient closely for adverse effects. If concurrent use is not desired, it is probably best if one waits 2 weeks after discontinuing a SSRI before starting a new serotonergic agent.[8] This rule applies for all SSRIs except fluoxetine. Since fluoxetine and its metabolite norfluoxetine have such a long half-life, a 5-week, drug-free period should be incorporated between the discontinuation of fluoxetine and the initiation of the new serotonergic medication.[8,46]

A patient is diagnosed with serotonin syndrome when an immediate history of serotonergic medication use is confirmed and if he or she exhibits any of the following set of symptoms:[47]

1.) Spontaneous clonus
2.) Inducible clonus in addition to agitation or diaphoresis
3.) Ocular clonus, in addition to agitation or diaphoreses
4.) Tremor with hyperreflexia
5.) Hypertonicity with hyperthermia and clonus

Other clinical features of serotonin syndrome include vomiting, diarrhea, mydriasis, vital fluctuations, mental status changes, and seizure activity.[41,46,48] The symptoms of serotonin syndrome can be classified as mild, moderate, or toxic. Mild cases usually present with tachycardia, intermittent tremor, myoclonus involving the lower extremities, diaphoresis, and restlessness. Moderate symptoms often involve mental status changes, tachycardia, hypertension, hyperactive bowel, body temperature as high as 40ºC, clonus, and hyperthermia. Toxic symptoms include severe tachycardia and hypertension, agitated delirium, hypertonicity, coma, tonic-clonic seizures, and fever > 41.1 ºC. The onset of symptoms usually occurs within 24 hours of when the precipitating medication is started.[41,46]

The first step in treating serotonin syndrome is to discontinue the serotonergic agents. For mild cases, this is usually the only action needed. Symptoms will begin to disappear after 24 hours of stopping the medications. Moderate to severe cases of serotonin syndrome may require intravenous hydration, sedation, neuromuscular paralysis, and intubation.[41,46] Serotonin antagonists such as cyproheptadine have been documented to help in some situations.[46,49] Benzodiazepines are often used to help treat agitation and myoclonus.[42,46] If serotonin syndrome is left untreated, then more serious complications can occur such as renal failure, disseminated intravascular coagulopathy, seizures, hyperthermia, metabolic acidosis, rhabdomyolysis, coma, or death.[50] The reported death rate attributable to serotonin syndrome is between 2% to 12%[41]

At this time, there are no definitive lab tests available to aid in the diagnosing of serotonin syndrome. Sometimes an elevated creatinine phosphokinase, elevated white blood cell count, or a low bicarbonate level is observed in severe cases.[41,46] Obtaining serotonin blood levels is not useful for diagnosis. The synaptic concentrations are responsible for the adverse effects, and blood serotonin levels have not been shown

to correlate with these CNS concentrations.[41]

Serotonin syndrome is often confused with neuroleptic malignant syndrome (NMS) because the clinical presentation is similar; the causes, however, of the 2 syndromes are different. NMS is precipitated by a sudden deficiency in CNS dopamine. This syndrome is usually a result of antipsychotic use (especially the high potency typical antipsychotics) or the sudden withdrawal of anti-Parkinson medications. When serotonin syndrome or NMS is suspected, clinicians should first inquire about the patient's medications. Knowing which medications the patient has been taking—serotonergic drugs versus antipsychotics—will provide a big indication to which of the 2 syndromes the patient is most likely experiencing.[42,50]

Owing to the seriousness of serotonin syndrome, it is best if it can be prevented. One important approach to preventing the syndrome is to decrease a patient's number of CNS medications.[46] If combined serotonergic therapy is required, the smallest efficacious dose of each drug should be used and the patient should be counseled on the symptoms of serotonin syndrome.

Antidepressant Mechanisms of Action and Possible Pharmacodynamic Interactions

Monoamine Oxidase Inhibitors

MAOIs such as phenelzine and tranylcypromine inhibit the breakdown of norepinephrine, dopamine, and serotonin resulting in increased neurotransmitter levels in the CNS. Phenelzine and tranylcypromine are classified as nonselective MAOIs, meaning they inhibit both monoamine oxidase-A and monoamine oxidase-B. Tyramine, which is an indirect-acting sympathomimetic amine found in many types of foods, is normally metabolized in the body by peripheral monoamine oxidase-A. If, however, a patient is taking a MAOI, then tyramine metabolism is decreased and more tyramine is available to be taken up into synaptic nerve terminals, thus resulting in an overrelease of norepinephrine. This overrelease of norepinephrine can cause elevated blood pressure and even hypertensive crisis. Tyramine-containing foods such as aged cheese, wine, dry sausage, and yogurt should be avoided in patients taking MAOIs.[8]

As stated in the previous section, MAOIs should not be taken with medications that increase CNS serotonin because of the risk of serotonin syndrome. Other medications that increase the effect of norepinephrine such as sympathomimetics and stimulants should also be avoided in patients taking MAOIs because of the risk of hypertensive crisis and tachycardia. Anti-Parkinson's medications such as levodopa and dopamine agonists can increase the risk of dopamine adverse effects such as nausea, vomiting, hypertension, agitation, and psychosis when used concurrently with a MAOI.[8, 39]

Tricyclic Antidepressants

Tricyclic Antidepressants (TCAs) affect many receptor sites and, therefore, increase the risk of pharmacodynamic drug interactions more than any other antidepressant class. TCAs treat depressive symptoms by inhibiting the reuptake of serotonin and norepinephrine. However, TCAs also block histamine, α, and muscarinic receptors, which result in adverse effects for many patients.[8,39,40] Because TCAs augment serotonin levels in the CNS, using another serotonergic drug concurrently can increase a patient's risk of serotonin syndrome. Tachycardia and hypertension can occur with TCA use as a result of its ability to increase norepinephrine levels. Therefore, other agents that increase norepinephrine stimulation such as sympathomimetic and stimulant medications (e.g., pseudoephedrine, methylphenidate) should be used cautiously with TCAs owing to increased risk of tachycardia and hypertensive crisis.[8,39,40] Clinicians should also be aware that TCAs can decrease the effectiveness of antihypertensives,

specifically adrenergic neuron blockers (e.g., guanethidine) or central acting agents such as clonidine.[51-54]

Because TCAs antagonize muscarinic-1 receptors, these medications often cause anticholinergic adverse effects such as dry mouth, blurred vision, urinary retention, and constipation. When combined with another agent that blocks muscarinic receptors (e.g., oxybutynin, hyoscyamine), the risk and severity of anticholinergic adverse effects increases. The α-1 and histamine-1 receptors are also antagonized by TCAs, and side effects such as orthostatic hypotension, dizziness, and sedation are common complaints with the use of these agents. Therefore, other medications that cause these same effects such as opioids and benzodiazepines should be used carefully with TCAs.[39]

Other Antidepressants

Trazodone and nefazodone are considered serotonin modulators. Both medications weakly inhibit the reuptake of serotonin but they also act as an antagonist to 5-HT2 postsynaptic receptors. Patients taking one of these medications in addition to another serotonergic medication may have an increased risk for serotonin syndrome.[8,39] Trazodone and nefazodone both block α-1 receptors causing orthostatic hypotension in some patients. The blood pressure lowering effect of α-1 antagonists such as prazosin and terazosin can be augmented with the concurrent use of trazodone or nefazodone.[8] Other medications associated with orthostatic hypotension (e.g., typical antipsychotics) should be avoided with the use of trazodone or nefazodone.[55]

Bupropion and its active metabolites inhibit the reuptake of norepinephrine and dopamine. Because bupropion has little effect on CNS serotonin levels, serotonin syndrome is not a concern with this medication. Buproprion, however, in addition to other medications that increase levels of norepinephrine (e.g., sympathomimetics, stimulants, MAOIs) and dopamine (e.g., anti-Parkinson's medications, MAOIs) can potentially result in hypertension, tachycardia, gastrointestinal adverse effects, severe agitation, and psychosis.[8,56] Theoretically, the effectiveness of antihypertensives can be decreased if used in combination with bupropion. High doses of bupropion have been linked to an increase risk of seizures. Therefore, bupropion should not be used with other medications that lower seizure threshold such as TCAs.[57]

Venlafaxine and duloxetine inhibit the reuptake of serotonin and norepinephrine but have very little effect on histamine, muscarinic, and α receptors.[8] Venlafaxine is a weak inhibitor of the reuptake of norepinephrine compared with duloxetine. Low to moderate doses (< 200 mg) of venlafaxine usually result in serotonin reuptake inhibition similar to the SSRIs. Once a larger dose is reached then the reuptake inhibition of norepinephrine occurs.[56] When used concurrently with other serotonergic medications, venlafaxine[3,43] and duloxetine can increase the risk of serotonin syndrome. Theoretically, drugs that increase norepinephrine such as sympathomimetics can increase the risk of hypertension and tachycardia if used in combination with venlafaxine and duloxetine. Furthermore, these 2 medications can possibly decrease the blood pressure lowering effect of antihypertensives.[8, 37, 56]

Mirtazapine works differently than most antidepressants. It does not inhibit the reuptake of neurotransmitters nor does it inhibit the metabolism of the monoamines. Mirtazapine increases norepinephrine and serotonin transmission by antagonizing the central α-2 receptors.[8] The antidepressant also antagonizes histamine-1 receptors which, most likely, is responsible for its common side effects of weight gain and sedation.[39] Like other antidepressants that increase norepinephrine and serotonin, mirtazapine should be used cautiously with other medications that increase these 2

neurotransmitters. Serotonin syndrome and hypertension are possible adverse effects caused by pharmacodynamic interactions with mirtazapine.[40]

Mirtazapine can decrease the effectiveness of antihypertensives, especially clonidine. Clonidine lowers blood pressure by acting as a central α-2 receptor agonist, the opposite mechanism of mirtazapine. One case report has documented the occurrence of hypertensive urgency for a patient controlled with clonidine when mirtazapine was added.[58] Patients taking mirtazapine should try to avoid other sedating medications and those that block histamine-1 receptors to avoid oversedation.[8]

Conclusion

Avoiding polypharmacy is the optimal method in preventing drug-drug interactions. Many patients, however, require multiple medications to treat their psychiatric diagnoses and other comorbities. Knowing the pharmacology and the kinetics of each antidepressant class will help clinicians foresee possible interactions. Therefore, alternative agents can be chosen, dosing can be adjusted, or monitoring can be increased to prevent an adverse effect from happening.

Table 1. Substrates, inhibitors, and inducers of the CYP 450 [2,8,9,40,59]

CYP 450 Isoenzyme	Substrates	Inhibitors	Inducers
1A2	Clozapine Haloperidol Theophylline Caffeine Chlordiazepoxide Diazepam Thiothixene Trifluoperazine Cyclobenzaprine Propranolol	Ciprofloxacin Cimetidine	Cigarette smoking Rifampin Phenytoin Phenobarbital Carbamazepine
2C9	Amiodarone Carvedilol Glipizide Losartan Phenytoin Rifampin Warfarin	Amiodarone Fluconazole Fluvastatin	Carbamazepine Phenobarbital Phenytoin Rifampin
2C19	Carisoprodol Diazepam Phenobarbital Phenytoin Propranolol	Omeprazole Fluconazole Omeprazole	Carbamazepine Phenytoin Rifampin
2D6	Aripiprazole Carvedilol Chlorpromazine Codeine Dextromethorphan Flecainide Fluphenazine Haloperidol Labetalol	Quinidine Propafenone Amiodarone Cimetidine Haloperidol Perphenazine Ritonavir Thioridazine Valproate	

	Lidocaine Metoprolol Mexiletine Oxycodone Perphenazine Procainamide Propafenone Propranolol Risperidone Thioridazine Warfarin		
3A4	Alprazolam Amlodipine Aripiprazole Atorvastatin Bisoprolol Buspirone Carbamazepine Chlordiazepoxide Clarithromycin Clonazepam Clorazepate Cyclosporine Diazepam Diltiazem Disopyramide Erythromycin Felodipine Fentanyl Flurazepam Haloperidol Itraconazole Ketoconazole Lidocaine Lovastatin Methadone Nifedipine Phenytoin Quetiapine Quinidine Rifampin Sildenafil Simvastatin Theophylline Triazolam Verapamil Zolpidem	Amiodarone Cimetidine Ciprofloxacin Clarithromycin Diltiazem Erythromycin Fluconazole Grapefruit juice Indinavir Itraconazole Ketoconazole Nelfinavir Omeprazole Ritonavir Saquinavir Verapamil	Carbamazepine Oxcarbazepine Phenobarbital Phenytoin Rifampin

Table 2. CYP 450 involvement of the antidepressants [2, 8, 9, 40, 59]

	1A2	2C9	2C19	2D6	3A4
Tricyclics					
Amitriptyline	S, IH	S, IH	S, IH	**S,** IH	S
Amoxapine	-	-	-	**S**	-
Clomipramine	**S**	S	**S**	**S, IH**	**S**
Desipramine	S	-	-	**S**, IH	S
Doxepin	**S**	-	-	**S**	**S**
Imipramine	S, IH	S	**S**, IH	**S**, IH	S
Nortriptyline	S	-	S	**S**, IH	S
Trimipramine	-	-	**S**	**S**	**S**
SSRIs					
Citalopram	IH	-	**S**, IH	S, IH	**S**
Escitalopram	-	-	**S**, IH	S, IH	**S**
Fluoxetine	S, IH	**S**, IH	S, **IH**	**S, IH**	S, IH
Fluvoxamine	**S, IH**	IH	**IH**	**S**, IH	**IH**
Paroxetine	IH	IH	IH	**S, IH**	IH
Sertraline	IH	**S,** IH	**S,** IH	S, IH	**S,** IH
Other					
Bupropion	S	S	-	S, IH	S
Duloxetine	**S**	-	-	**S, IH**	-
Mirtazapine	**S**, IH	S	-	**S**, IH	**S**, IH
Nefazodone	IH	-	-	**S,** IH	**S, IH**
Phenelzine	-	-	-	-	-
Tranylcypromine	IH	IH	IH	IH	IH
Trazodone	S	-	-	S, IH	**S**
Venlafaxine	-	S	S	**S,** IH	S**,** IH

S = substrate, IH = inhibitor, **bolded = clinically significant**

Table 3. Medications that increase serotonin [8, 21, 41, 43, 46, 50]

Inhibition of Serotonin Metabolism	Increased Release of Serotonin	Serotonin Receptor Agonist	Inhibition of Serotonin Reuptake
Phenelzine Tranylcypromine Selegiline Linezolid St. John's Wort	Mirtazapine Meperidine Dextromethorphan Cocaine LSD Ecstasy	Buspirone Lithium Sumatriptan and related compounds	SSRIs* TCAs** Trazodone Nefazadone Venlafaxine Duloxetine

			Sibutramine Tramadol Dextromethorphan Meperidine

*SSRIs = Selective Serotonin Reuptake Inhibitors, **TCAs = Tricyclic Antidepressants

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