

## Review Article

# Psychotropic Medications Metabolized by Cytochromes P450 (CYP) 1A2 Enzyme and Relevant Drug Interactions: Review of Articles

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Psychotropic medications metabolized by cytochromes P450 (CYP) 1A2 is reviewed, and the possible relevance of this metabolism to drug-drug interactions is discussed. CYP1A2 is a member of the cytochrome P450 super family, is one of the best characterized. It is responsible for the metabolism of commonly drugs belonging to classes such as antidepressants, antipsychotics, mood stabilizers, beta blockers and Sedative/hypnotics. Fluvoxamine, amitriptyline, clomipramine, trimipramine, imipramine and doxepin are common antidepressants primarily metabolized by CYP1A2 enzymes. First generation antipsychotics such as chlorpromazine, thioridazine, haloperidol, pimozide, stelazine and piperazine are primarily metabolized by CYP1A2 enzyme. Clozapine and Olanzapine are groups of second generation antipsychotics primarily metabolized by CYP1A2. Propranolol, warfarin and theophylline are among the common beta blockers which are primarily metabolized by CYP1A2.

Drugs that inhibit CYP1A2 will predictably increase the plasma concentrations of the medications or decrease in clearance of substrates. Drugs such as ciprofloxacin, fluvoxamine, verapamil, cimetidine, caffeine and isoniazid are inhibitors of CYP1A2 enzyme. Vegetables such as grape fruit juice, cumic and tumeric are inhibitors of the CYP1A2 enzyme which may lead to increase plasma concentration of psychotropics.

Inducers of CYP1A2 enzyme such as Rifampin, Omeprazole, Insulin, Barbiturates, omeprazole and carbamazepine shorten action of drugs or increase effects of those biotransformed to active agents

**Keywords:** Cytochromes P450 (CYP) 1A2, Antipsychotics, Tricyclic antidepressants, Selective serotonin reuptake inhibitors, Beta blockers, Nicotine

**Introduction**

Cytochromes P450 (CYPs) is a microsomal monooxygenase family of enzymes, which oxidize drugs in the liver [1]. These enzymes are haem-containing membrane proteins that are bound to the smooth endoplasmic reticulum of the hepatocytes. Metabolize the widest range of drugs [2,3].

There are more than 50 CYP450 enzymes. CYP1A2 is a member of the cytochrome P450 super family, is one of the best characterized. It is responsible for the metabolism of commonly drugs belonging to classes such as antidepressants, antipsychotics, mood stabilizers, beta blockers and Sedative/hypnotics [2,4].

**Psychotropic Medications Metabolized by CYP1A2****Antipsychotic medications metabolized by CYP1A2**

CYP1A2 is involved in the metabolism of both first and second generation antipsychotics. First generation antipsychotics such as chlorpromazine, thioridazine, haloperidol, pimozide, stelazine and piperazine are primarily metabolized by CYP1A2 enzyme. Clozapine and Olanzapine are groups of second generation

antipsychotics primarily metabolized by CYP1A2 [4-13].

**Antidepressant medications metabolized by CYP1A2**

Fluvoxamine is Selective serotonin Reuptake Inhibitor (SSRI) which is primarily metabolized by CYP1A2 enzymes and is a potent inhibitor of CYP1A2 [14,15].

Tricyclic Antidepressant (TCAs), including amitriptyline, clomipramine, trimipramine, imipramine and doxepin are mainly metabolized by CYP1A2 enzymes [16-22].

Other Antidepressants such as Duloxetine and Mirtazapine are metabolized by CYP1A2. Duloxetine is moderate to potent inhibitor of CYP1A2 but Mirtazapine has no significant inhibitory or inductive capabilities [16].

**Mood stabilizer medications metabolized by CYP1A2**

Majority of mood stabilizers including valproate, lamotrigine and topiramate are not metabolized by CYP1A2 [4,6, 7,8]. Regarding carbamazepine, it is primarily metabolized by P450 3A4, although CYP1A2 metabolism serves as minor pathways and it induces CYP1A2 enzyme actions [23-25].

Lithium is mood stabilizers which is purely renally excreted, with

**Table 1:** Main Psychotropic medications metabolized by CYP1A2.

Group of drugs	Drug name
Antidepressants (tricyclics)	Amitriptyline, Clomipramine, Trimipramine, Imipramine, Doxepine
Antidepressants (SSRIs)	Fluvoxamine
Antidepressants (others)	Duloxetine, Mirtazapine
Antipsychotics (first generations)	Chlorpromazine, Thioridazine, Haloperidol, Pefperazine, Pimozide, Stelazine
Antipsychotics (second generations)	Clozapine, Olanzapine
Beta-blockers	Propranolol, Warfarin, Theophylline

**Table 2:** Summary cytochrome CYP1A2 substrates, inhibitors and inducers.

	Substrate		Inhibitors	Inducers
Olanzapine	Clozapine	Caffeine	Citalopram	Carbamazepine
Pimozide	Cyclobenzaprine	Cimetidine	Clarithromycin	Primidone
Propranolol	Doxepin	Warfarin	Diltiazem	Rifampin
Ramelteon	Duloxetine	Verapamil	Erythromycin	Tobacco
Rasagiline	Theophylline	Diltiazem	Ethinyl Estradiole	Omeperazole
Riluzole	Trifluoperazine	Methoxsalen	Isoniazid	Insulin
Ropinirole	Alosetron	Mexiletine	Ketoconazole	Barbiturates
Acetaminophen	Aminophylline	Nalidixic acid	Oral-Contraceptives	Cruciferous Vegetables
Amitriptyline	Clomipramine	Norethindrone	Paroxetine	Grilled meat
Caffeine	(Estrogens: conjugated and estropipate estrone)	Norfloracin	Tacrine	
Chlordiazepoxide		Ciprofloxacin	Ticlopidine	
Clopidogrel	Mexiletine	Caffeine	Troleandomycin	
Fluvoxamine	Naproxen	Theophylline	Fluvoxamine	
Guanabenz	Nortriptyline	Antipyrene	Melatonin	
Mirtazapine	Ondansetron	Tacrolimus	Fluoxetine	
Desipramine	Propafenone	Grapefruit juice	Desipramine	
Diazepam	Riluzole		Miodarone	
Estradiol	Ropinirole			
Flutamide	Ropivacaine			
Haloperidol	Tacrine			
Imipramine	Verapamil			
levobupivacaine				
Warfarin				
Chlorpromazine				

no hepatic metabolic component. It lacks any inhibitory or inductive capabilities.

### Beta blockers metabolized by CYP1A2

CYP1A2 is also involved in metabolism of beta blockers. Propranolol, warfarin and theophylline are among the common beta blockers which are primarily metabolized by CYP1A2.

## Drug Interactions Involving CYP1A2 Enzyme

### SSRI and antipsychotic interactions

Coadministration of fluvoxamine with second generation antipsychotics will increase their blood concentrations. Administration of Fluvoxamine, a Selective Serotonin Reuptake Inhibitor (SSRI), a potent inhibitor of CYP 1A2, will elevate clozapine concentrations with potential for seizures and hypotension. Fluvoxamine also can cause increases in olanzapine levels. Concurrent use of clozapine with fluvoxamine could reduce the clearance of clozapine by up to 50%, an effect which would be comparable with a doubling of the dose. This could lead to a three fold increase in the risk of the patient suffering a seizure [26-39].

### Beta blockers and psychotropic's

Propranolol, warfarin and theophylline are among the common beta blockers which are primarily metabolized by CYP1A2, so that coadministration of drugs and other substances metabolized by cytochrome CYP1A2 affects the concentration of these drugs. Beta

blockers such as Warfarin and theophylline are potent inhibitors of the hepatic enzyme CYP1A2, can produce toxicity in combination with psychotropic medication metabolized by CYP1A2, results in elevated plasma levels of other CYP1A2 substrates including antidepressants and antipsychotics [4,40,41].

### Cigarette smoking and psychotropic's

Cytochrome P450 (CYP) 1A2 enzymes metabolise several clinically important drugs such as antidepressants and antipsychotics and a number of procarcinogens (such as those in cigarettes). Cigarette smoking induces the activity of cytochrome P450 (CYP) 1A2 (via chemicals in cigarette smoke such as polycyclic aromatic hydrocarbons). cytochrome CYP1A2 is the only isoenzyme affected by tobacco. Cigarette smoking may lead to a three fold increase in 1A2 activity, which explains why smokers require higher doses of beta blockers than non-smokers. Cigarette smoking induces drugs metabolized by CYP1A2 such as antidepressants (amitriptyline, duloxetine, fluvoxamine, imipramine), antipsychotics (clozapine, haloperidol, olanzapine) and beta blockers (propranolol, theophylline and warfarin) [42-49]. Smoking as a potent inducer of CYP1A2, results in smokers having significantly reduced plasma concentrations of clozapine (up to 50%) and olanzapine compared to non-smokers. Some constituents of tobacco smoke are potent inducers of CYP1A2, but nicotine replacement therapy products do not produce the same effects due to the effect of smoking on hepatic enzymes is not related to the nicotine component of tobacco. When patients taking clozapine

have ceased smoking, clozapine levels in clinical trials have risen 13-260% which increase risks of side effects especially seizure [42,43]. Serum concentrations antidepressants, such as fluvoxamine may increase to toxic levels and result in adverse effects when a person quits smoking cigarette [48,49].

## Common Medications, Nutrients and Substances Metabolized by Cytochrome CYP1A2, Inhibitors and Inducers of CYP1A2

Drugs metabolized by CYP1A2 are called CYP1A2 substrates. A number of other drugs which are metabolized by CYP1A2 may inhibit or induce the action of the enzyme. Drugs that inhibit CYP1A2 will predictably increase the plasma concentrations of the medications or decrease in clearance of substrates. Drugs such as ciprofloxacin, fluvoxamine, verapamil, cimetidine, caffeine and isoniazid are inhibitors of CYP1A2 enzyme [40,41]. Vegetables such as grape fruit juice, cumic and tumeric are inhibitors of the CYP1A2 enzyme which may lead to increase plasma concentration of psychotropics [40].

Inducers of CYP1A2 enzyme such as Rifampin, Omeperazole, Insulin, Barbiturates, omeperazole and carbamazepine shorten action of drugs or increase effects of those biotransformed to active agents. From psychoactive substance tobacco and vegetable char-grilled meat, cauliflower, broccoli and brussels sprouts increase the activity of the cytochrome P450 1A2 isozyme [40,41].

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