

Review Article

Psychotropic Medications Metabolized by Cytochromes P450 (CYP) 3A4 Enzyme and Relevant Drug Interactions: Review of Articles

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Psychotropic medications metabolized by cytochromes P450 (CYP) 3A4 are reviewed and the possible relevance of this metabolism to drug-drug interactions is discussed. Cytochrome P4503A4 (CYP3A4) is the most prevalent of all Cytochromes P450 (CYPs) enzymes. It is found in large quantities in the liver and in the intestine, and involved in the metabolism of hundred of drugs including antipsychotics, mood stabilizers, hypnotics, anti anxiety drugs, antidepressants, calcium channel blockers, steroids and opiate analgesics. It is responsible for the metabolism of more than 50% of the commonly prescribed drugs. CYP3A4 metabolizes typical antipsychotic medications.

Haloperidol, perphenazine, aripiprazole, quetiapine, risperidone and ziprasidone from second generation antipsychotics. Amitriptyline, imipramine, clomipramine, citalopram, escitalopram, paroxetine, fluoxetine, venlafaxine, trazodone, buspirone, nefazodone and mirtazapine are antidepressants which are metabolized by CYP3A4. Alprazolam, diazepam, medazolam, temazepam, lorazepam and clonazepam are among the common benzodiazepines which are primarily metabolized by CYP3A4. Nefazodon, Fluoxetine, clarithromycin, telithromycin, Ketokonazole, itraconazole, fluvoxamine, nefinavir valerian, milk thistle, grape fruit juice and ginkgo biloba, are inhibitors of CYP3A4 enzyme. Phenytoin, carbamazepine, oxycarbazepine, phenobarbitone, prednisolone, john's wort, rifampicin and efavirnaz are common inducers of CYP3A4 enzyme.

Keywords: Cytochromes P450 (CYP) 3A4; Antipsychotics; Tricyclic antidepressants; Selective serotonin reuptake inhibitors; Benzodiazepines; Polymorphism; Antibiotics; Opiates

Introduction

Cytochromes P450 (CYPs) enzymes consist of a super family of heme-containing proteins localized within the endoplasmic reticulum of the liver as well as in the brain and periphery and are responsible for the metabolism of widest range of drugs [1-4].

Cytochrome P450 3A4 (CYP3A4) is the most prevalent of all Cytochromes P450 (CYPs) enzymes. It is found in large quantities in the liver and in the intestine and involved in the metabolism of hundred of drugs including antipsychotics, mood stabilizers, hypnotics, antianxiety drugs, antidepressants, calcium channel blockers, steroids and opiate analgesics [1,2].

Cytochrome P450 3A4 (CYP3A4) enzyme polymorphism is responsible for observed variations in drug response among patients of differing ethnic origins. Genetic variability (polymorphism) in these enzymes may influence a patient's response to commonly prescribed drug classes, including antipsychotics, beta blockers and antidepressants [5-8].

The CYP3A family is the most abundant subfamily of the CYP isoforms in the liver. CYP3A4 is mainly located in the liver and small intestine and is the most abundant cytochrome in these organs. Cytochrome CYP3A4 is responsible for the metabolism of more

than 50% of medicines. CYP3A4 activity is absent in new-borns but reaches adult levels at around one year of age [3-5].

The CYP3A4 protein localizes to the endoplasmic reticulum, and its expression is induced by glucocorticoids and some pharmacological agents. This enzyme is involved in the metabolism of approximately half the drugs that are used today [1-4].

Psychotropic and other Drugs Metabolized by CYP3A4**Antipsychotic medications metabolized by CYP3A4**

Both first generation and second generation antipsychotics are substrates of CYP3A4 enzyme. It metabolizes typical antipsychotic medications, such as haloperidol and perphenazine [9,10] and aripiprazole [12], quetiapine [13,14], risperidone [15-17] and ziprasidone [18] from second generation antipsychotics.

Antidepressant medications metabolized by CYP3A4

CYP3A4 metabolizes Selective Serotonin Reuptake Inhibitors (SSRIs) such as citalopram, escitalopram, paroxetine, and fluoxetine [19-23]. CYP3A4 also metabolizes selective Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) such as venlafaxine and trazodone [10,24].

Table 1: Common drugs metabolized by CYP3A4.

Group of drugs	Drug name
Antidepressants (tricyclics)	Amitriptyline, Imipramine, clomipramine
Antidepressants (SSRIs)	citalopram, escitalopram, paroxetine, fluoxetine
Antidepressants (SNRIs)	venlafaxine, trazodone
Antidepressants (others)	bupirone Nefazodone, Mirtazapine
Antipsychotics(first generations)	haloperidol, perphenazine
Antipsychotics(second generations)	aripiprazole, quetiapine, risperidone, ziprasidone
Benzodiazepines	Alprazolam, diazepam, medazolam, temazepam, lorazepam, clonazepam
Opiates	codeine, methadone, fentanyl, burenorphine
hypnotics	Zopiclone, Zaleplon, zolpidem
Antibiotics	erythromycin, clarithromycin, telithromycin
Phosphodiesterases (PDEs) inhibitors	sildenafil, tadalafil

Table 2: Summary cytochrome CYP3A4 substrates, inhibitors and inducers.

Substrate		Inhibitors	inducers
Aripiprazole	Erythromycin	Nefazodone	phenytoin
quetiapine	clarithromycin	Fluoxetine	carbamaepine
risperidone	telithromycin	clarithromycin	oxycarbazepine
ziprasidone	sildenafil	telithromycin	phenobarbitone
codeine	tadalafil	Ketokonazole	prednsolone
methadone	Amitriptyline	itraconazole	john's wort
fentanyl	Imipramine	fluvoxamine	rifampicin
burenorphine	clomipramine	nefinavir	efavirnaz
Alprazolam	citalopram	valerian	
Diazepam	escitalopram	milk thistle	
Medazolam	paroxetine	grape fruit juice	
Temazepam	fluoxetine	gingko biloba	
lorazepam	venlafaxine		
clonazepam	trazodone		
Zopiclone	bupirone		
Zaleplon	Nefazodone		
Zolpidem	Mirtazapine		
perphenazine	haloperidol		

Tricyclic Antidepressant (TCAs,) including amitriptyline, clomipramine and imipramine are metabolized by CYP3A4 enzymes [25-31].

Other Antidepressants such as bupirone Nefazodone and Mirtazapine are metabolized by CYP3A4 [32-34].

Mood stabilizer medications metabolized CYP3A4

From mood stabilizers carbamaepine is primarily metabolized by P450 3A4 [35-37] and other mood stabilizers including valproate, lamotrigine and topiramate are not metabolized by CYP3A4 [10,38-40]. Lithium is mood stabilizers which are purely renally excreted, with no hepatic metabolic component. It lacks any inhibitory or inductive capabilities.

Benzodiazepines metabolized by CYP3A4

CYP3A4 is also involved in metabolism of Benzodiazepines.

Alprazolam, diazepam, medazolam, temazepam, lorazepam and clonazepam are common benzodiazepine metabolized by CYP3A4 [10, 41,42].

Opiates metabolized by CYP3A4

Several of opiates including codeine, methadone, fentanyl and burenorphine are metabolized by CYP3A4 [41,42].

Hypnotics metabolized by CYP3A4

CYP3A4 is also involved in metabolism of hypnotics. Zopiclone, Zaleplon and zolpidem are commonly hypnotics called "Z" drugs are metabolized by CYP3A4 [10, 41,42].

Antibiotics metabolized by CYP3A4

The macrolide antibiotics such as erythromycin, clarithromycin and telithromycin are metabolized by CYP3A4 [41,42].

Phosphodiesterases (PDEs) inhibitors metabolized by CYP3A4

Phosphodiesterases (PDEs) inhibitors such as sildenafil and tadalafil are metabolized by CYP3A4 [10,41,42] (Table 1 & Table 2).

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