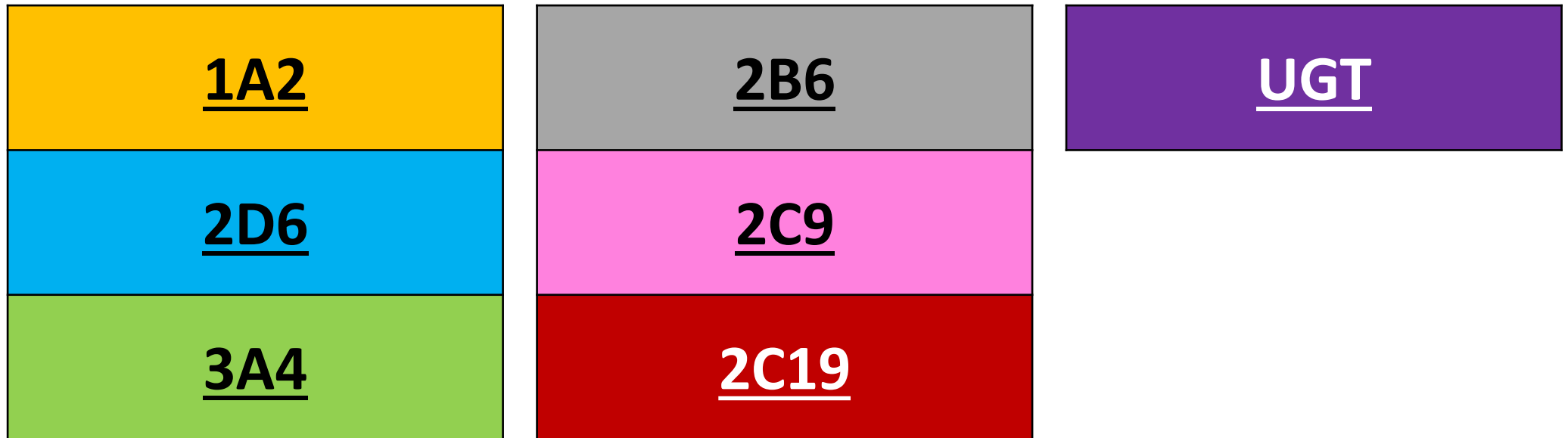


CYP Interactions

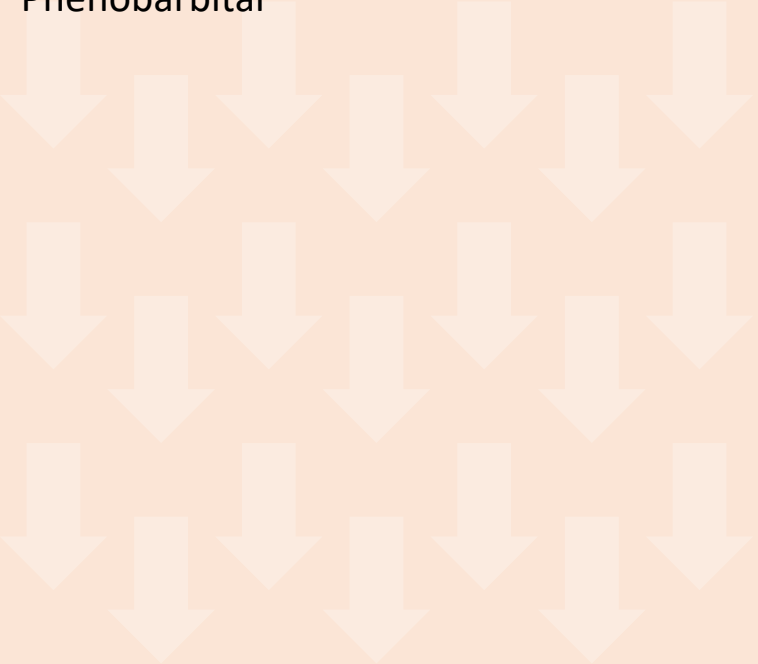


CYP1A2		
↓↓↓ Inducers (reduce levels) ↓↓↓	Substrate	↑↑↑ Inhibitor (increase levels) ↑↑↑
• Carbamazepine • Phenytoin • Phenobarbital • Secobarbital	• Fluvoxamine* • Duloxetine* • Mirtazapine* • TCAs • Agomelatine • Ropinirole • Clozapine* • Olanzapine* • Risperidone • Asenapine • Haloperidol • Carbamazepine	• Fluvoxamine +++ • Fluoxetine + • Paroxetine + • Sertraline +
• Rifampin • Ritonavir • Lansoprazole • Omeprazole • Montelukast • Tobacco/smoking • Charcoal-grilled meat	• Caffeine • Theophylline • Tacrine • Zolmitriptan • Naproxen • Warfarin	• OCP ++ • Estradiol ++ • Ciprofloxacin • Cimetidine + • Omeprazole • Fluoroquinolones + • Ticlopidine • Caffeine

CYP2D6		
↓↓↓ Inducers (reduce levels) ↓↓↓	Substrate	↑↑↑ Inhibitor (increase levels) ↑↑↑
• NO sig psychotropic inducers!!	• Citalopram • Escitalopram • Fluoxetine* • Fluvoxamine* • Paroxetine* • Sertraline • Venlafaxine* • Duloxetine • Vortioxetine • Atomoxetine • TCAs*	• Fluoxetine +++ • Paroxetine +++ • Sertraline + • Citalopram • Escitalopram • Duloxetine ++ • Venlafaxine • Bupropion +++ • Clomipramine • Asenapine • Haloperidol • Thioridazines
• Rifampin • Dexamethasone	• Codeine • Tramadol • Tamoxifen • Beta-blockers • Class 1C antiarrhythmics	• Methadone • Terbinafine • Quinidine • Cimetidine • Amiodarone • Ritonavir

CYP3A4			
↓↓↓ Inducers (reduce levels) ↓↓↓		Substrate	↑↑↑ Inhibitor (increase levels) ↑↑↑
• Carbamazepine • Phenytoin • Phenobarbital • Felbamate • Topiramate – • St. John’s Wort –– • Morphine – • Nicotine –		• Escitalopram* • Sertraline* • Venlafaxine • Levomilnacipran • Mirtazapine* • Trazadone* • Vilazodone • Buspirone • Benzos (non-LOT) • Clozapine • Quetiapine* • Risperidone* • Aripiprazole* • Lurasidone* • Ziprasidone • Haloperidol • Pimozide • Carbamazepine	• Fluvoxamine +++ • Nefazodone +++ • Norfluoxetine
• Rifampin ––– • Efavirenz • Pioglitazone • Glucocorticoids		• Methadone* • Buprenorphine* • OCP • Acetaminophen • Tacrolimus • Cyclosporine • Tamoxifen • Statins • Macrolides • Quinidine • Ritonavir • Amlodipine • Diltiazem • Sildenafil • Erythromycin +++ (macrolides) • Ketoconazole +++ (azole antifungals) • Ritonavir ++ (HIV protease inhibitors) • Cimetidine + • Verapamil ++ • Diltiazem ++ • Amiodarone • Grapefruit juice	

CYP2C19		
↓↓↓ Inducers (reduce levels) ↓↓↓	Substrate	↑↑↑ Inhibitor (increase levels) ↑↑↑
• Carbamazepine • Phenytoin • Valproic acid • Phenobarbital • St. John's Wort	• Citalopram • Escitalopram • Sertraline • Amitriptyline • Benzos (non-LOT) • Clozapine • Antiepileptics	• Fluvoxamine +++ • Fluoxetine + • Sertraline
• Rifampin • Prednisone • Progestin	• Warfarin • PPIs • Propranolol	• Fluconazole +++ • Ketoconazole • Voriconazole • Cimetidine • Omeprazole ++ • Esomeprazole +++ • Lansoprazole

CYP2B6		
↓↓↓ Inducers (reduce levels) ↓↓↓	Substrate	↑↑↑ Inhibitor (increase levels) ↑↑↑
Phenobarbital 	- Sertraline* - Bupropion*	
Rifampin 		Thiotepa +++ (cancer alkylating agent) 

CYP2C9		
↓↓↓ Inducers (reduce levels) ↓↓↓	Substrate	↑↑↑ Inhibitor (increase levels) ↑↑↑
• Carbamazepine • Phenytoin • Secobarbital • Phenobarbital • Primidone • St. John's Wort	• Fluoxetine • Sertraline	• Valproic acid + • Fluoxetine • Fluvoxamine • Sertraline
• Rifampin • Ritonavir	• Warfarin • NSAIDs • OCPs • Glipizide • ARBs	• Fluconazole +++ • Miconazole ++ • Amiodarone • Fluvastatin • Lovastatin • Isoniazid • Trimethoprim

UGT		
↓↓↓ Inducers (reduce levels) ↓↓↓	Substrate	↑↑↑ Inhibitor (increase levels) ↑↑↑
• Carbamazepine • Phenytoin • Lamotrigine • Phenobarbital	• TCAs • Olanzapine • FGAs, SGAs • Lorazepam* • Oxazepam* • Lamotrigine • Temazepam*	• Valproic acid
• Rifampin • Carbapenems	• Morphine • NSAIDs • Carvedilol • Furosemide • Tramadol	• NSAIDs ++ • Diclofenac ++ • Cyclosporine • Probenecid • Tacrolimus

- <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4335312/table/T1/?report=objectonly>
- <https://journalce.powerpak.com/ce/psychotropic-drug-interactions-a-review>
- <http://primarypsychiatry.com/2010-guide-to-psychiatric-drug-interactions/>

CYP450 Substrates		Inhibitor		Inducer	
		Psychotropic	Other	Psychotropic	Other
1A2	Caffeine Theophylline TCAs Ropinirole Duloxetine Mirtazapine Clozapine Haloperidol Olanzapine Asenapine Tacrine Zolmitriptan	Fluvoxamine+++ Fluoxetine+ Paroxetine+ Sertraline+	Cimetidine+ Omeprazole Fluoroquinolones Ticlopidine	Phenobarbital Secobarbital Carbamazepine Phenytoin	Modafinil Tobacco Charcoal-grilled meat Rifampin
2C9	Warfarin Losartan NSAIDs Glipizide ARBs	Valproic acid+ Fluoxetine++	Fluconazole+++ Miconazole++ Amiodarone++	Secobarbital Carbamazepine	Rifampin
2C19	BZDs PPIs SSRIs (citalopram) Amitriptyline	Fluvoxamine+++ Fluoxetine+	Ketoconazole Cimetidine Omeprazole Lansoprazole	Carbamazepine Valproic acid Phenobarbital Phenytoin	Rifampin

CYP450 Substrates		Inhibitor		Inducer	
		Psychotropic	Other	Psychotropic	Other
2D6	β-blockers	Bupropion+++	Terbinafine++	None	None
	Class 1C antiarrhythmics	Fluoxetine+++	Quinidine+++		
	Codeine	Paroxetine+++	Cimetidine+		
	Amitriptyline	Duloxetine++	Amiodarone+		
	Sertraline	Sertraline+	Mibefradil+		
	Haloperidol	Citalopram+	Ritonavir+		
	TCAs	Escitalopram+			
	Risperidone	Haloperidol+			
	Iloperidone	Thioridazine+			
	Tramadol				
	Venlafaxine				
	Duloxetine				
	Aripiprazole				

CYP450 Substrates		Inhibitor		Inducer	
		Psychotropic	Other	Psychotropic	Other
3A4	Acetaminophen	Fluvoxamine+++	Clarithromycin+++	Carbamazepine+++	Rifampin+++
	BZDs	Nefazodone+++	Erythromycin++	Phenytoin+++	Ritonavir++
	Statins		Troleandomycin++	Phenobarbital++	Indinavir++
	Macrolides		Fluconazole+++	St. John's Wort++	Efavirenz
	Quinidine		Ketoconazole+++	Morphine+	Pioglitazone
	Indinavir, Ritonavir		Itraconazole+++	Nicotine+	Glucocorticoids
	Amlodipine, Felodopine		Indinavir+++	Topiramate+	
	Diltiazem		Cimetidine+	Felbamate+	
	Atorvastatin		Verapamil++		
	Buspirone		Diltiazem++		
	Sertraline				
	Venlafaxine				
	Mirtazapine				
	Haloperidol				
	Iloperidone				
	Trazodone				

CYP450 Substrates		Inhibitor		Inducer	
		Psychotropic	Other	Psychotropic	Other
UGT	FGAs SGAs TCAs NSAIDs Carvedilol Furosemide Morphine Tramadol Lorazepam Oxazepam	Diclofenac+++ NSAIDs++ Probenecid++ Valproic acid+		Carbamazepine++ Phenytoin++ Phenobarbital++ Lamotrigine+	Rifampin+ Carbapenems+
OATP1A2	Atenolol Ciprofloxacin Pravastatin		Grapefruit juice Verapamil		
OATP2B1	Statins		Grapefruit juice Cyclosporine		
OAT1	Captopril Furosemide		Indomethacin Olmesartan Probenecid		
OAT3	Furosemide Olmesartan Pravastatin		Gemfibrozil Indomethacin		
OCT2	Amatadine Lamivudine Metformin Ranitidine		Bisoprolol Carvedilol Ranitidine		

CYP450 Substrates		Inhibitor		Inducer	
		Psychotropic	Other	Psychotropic	Other
MDR1 (P-gp)	Digoxin Fexofenadine Ritonavir TCAs Atypical antipsychotics SSRIs Topiramate Gabapentin Carbamazepine Lamotrigine	Trifluoperazine Fluphenazine Haloperidol Amitriptyline Flurazepam	Clarithromycin Cyclosporine Itraconazole Verapamil	Midazolam Phenobarbital Phenytoin Hypericum Morphine Nicotine	Clotrimazole Nifedipine Trogl

Table 1

Psychotropic Drugs and Potential Drug-Interaction Pathways

Enzyme	Substrates		Inhibitors				Inducers
	Antidepressants	Anxiolytics	Antipsychotics	Antidepressants	Antiepileptics	Other Common Drugs	Common Drugs
CYP1A2	Duloxetine ^a Fluvoxamine ^a Mirtazapine ^a	N/A	Clozapine ^a Olanzapine ^a	Fluoxetine ^a Fluvoxamine ^b Paroxetine ^a Sertraline	N/A	Contraceptives ^c Estradiol ^b Fluoroquinolones ^d	Carbamazepine Lansoprazole Montelukast Omeprazole Phenobarbital Phenytoin Rifampin Ritonavir St. John's wort
CYP2B6	Bupropion ^a	N/A	N/A	N/A	N/A	Thiotepa ^b	Phenobarbital Rifampicin
CYP2C9	Fluoxetine ^a Sertraline	N/A	N/A	Fluoxetine ^c Fluvoxamine ^b Sertraline	Valproic acid	Amiodarone ^c Fluconazole ^c Fluvastatin Isoniazid Lovastatin Miconazole ^c Trimethoprim	Carbamazepine Phenobarbital Phenytoin Primidone Rifampicin Ritonavir Secobarbital St. John's wort
CYP2C19	Citalopram ^a Escitalopram ^a Sertraline	Alprazolam Chlordiazepoxide Clonazepam Diazepam Midazolam	Clozapine	Fluoxetine ^a Fluvoxamine ^b Sertraline	N/A	Cimetidine Esomeprazole ^b Fluconazole ^b Lansoprazole Omeprazole ^c Voriconazole ^c	Carbamazepine Norethindrone Phenobarbital Phenytoin Prednisone Rifampin St. John's wort
CYP2D6	Citalopram Duloxetine Escitalopram ^a Fluoxetine ^a Fluvoxamine Mirtazapine ^a Paroxetine ^a TCAs ^a Venlafaxine ^a	N/A	Aripiprazole Clozapine Olanzapine Risperidone ^a	Bupropion ^c Citalopram Duloxetine ^c Escitalopram Fluoxetine ^b Mirtazapine ^b Paroxetine ^b Sertraline	Haloperidol ^d Thioridazine ^d	Amiodarone Chlorphenamine Cimetidine Clomipramine Methadone Mibefradil Quinidine ^b Ticlopidine	Dexamethasone Rifampicin
CYP3A4	Escitalopram ^a Mirtazapine ^a Sertraline ^a Trazodone ^a Venlafaxine	Alprazolam ^a Chlordiazepoxide Clonazepam ^a Diazepam ^a Midazolam ^a	Aripiprazole ^a Clozapine Lurasidone ^a Quetiapine ^a Risperidone ^a	Fluvoxamine ^c Nefazodone ^b Norfluoxetine	N/A	Amiodarone Cimetidine Ciprofloxacin Diltiazem ^c Fluconazole ^c Grapefruit juice ^b HIV protease inhibitors (indinavir, nelfinavir, ritonavir, saquinavir) ^{b,c} Itraconazole ^b Ketoconazole ^b Macrolides (clarithromycin, erythromycin) ^{b,c} Posaconazole ^b Verapamil ^d Voriconazole ^b	Barbiturates Carbamazepine Phenytoin Rifampicin St. John's wort
UGT	TCAs	Lorazepam ^a Oxazepam ^a Temazepam ^a	Olanzapine	N/A	Valproic acid	Cyclosporine Diclofenac ^c NSAIDs ^c Probenecid Tacrolimus	Carbamazepine Carbapenems Lamotrigine Phenytoin Phenobarbital Rifampin

^a Primary metabolic pathway.^b High strength of inhibition.^c Moderate strength of inhibition.^d Low strength of inhibition.

N/A: not applicable; NSAID: nonsteroidal anti-inflammatory drug; TCA: tricyclic antidepressant; UGT: uridine 5'-diphosphate glucuronosyltransferase.

Source: References 5, 15, 16, 19, 59.

Table I Antidepressants and CYP enzymes

Antidepressants	Major elimination pathway	Other elimination pathways	Inhibitory effect on CYP isoenzyme
SSRI			
Citalopram	CYP2C19	CYP3A4, CYP2D6	CYP1A2, CYP2B6, CYP2C19, CYP2D6
Escitalopram	CYP2C19	CYP3A4, CYP2D6	CYP2D6, CYP2C9
Fluoxetine (active metabolite norfluoxetine)	CYP2D6	CYP2C9, CYP2C19, CYP3A4	CYP2D6,** CYP2C9,* CYP2C19,* CYP3A4,* CYP1A2
Fluvoxamine	CYP1A2, CYP2D6		CYP1A2,** CYP2C19,** CYP2C9,* CYP3A4,* CYP2D6
Paroxetine	CYP2D6	CYP3A4	CYP2D6,** CYP1A2, CYP2C9, CYP2C19, CYP3A4
Sertraline	CYP2B6	CYP2C19, CYP2C9, CYP3A4, CYP2D6	CYP2D6,* CYP1A2, CYP2C9, CYP2C19, CYP3A4
SNRI			
Desvenlafaxine	Renal	UGT, CYP3A4	None
Duloxetine	CYP1A2	CYP2D6	CYP2D6*
Levomilnacipran	Renal	CYP3A4, CYP2C8, CYP2C19, CYP2D6, CYP2J2, UGT	None
Milnacipran	Renal	UGT, CYP3A4	CYP3A4
Venlafaxine (active metabolite desvenlafaxine)	CYP2D6	CYP3A4	CYP2D6, CYP3A4
Others			
Agomelatine	CYP1A2	CYP2C9, CYP2C19	None
Bupropion (active metabolite hydroxybupropion)	CYP2B6		CYP2D6*
Mirtazapine	CYP2D6, CYP3A4	CYP1A2, UGT	None
Reboxetine	CYP3A4		None
Vilazodone	CYP3A4	CYP2C19, CYP2D6, carboxylesterase	CYP2C8 [?]
Vortioxetine	CYP2D6	CYP3A4, CYP2C19, CYP2C9, CYP2A6, CYP2C8, CYP2B6	None

Notes: **Potent; *moderate; [?]undetermined; no symbol, weak. Data from Flockhart,³³ Gelenberg et al,²³ and Spina et al.³⁴

Abbreviations: CYP, cytochrome P450; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin-reuptake inhibitor; UGT, uridine diphosphate glucuronosyltransferases.

SSRI	Significant pharmacokinetic interactions (increased plasma levels and potential adverse effects)	Significant pharmacodynamic interactions
Fluvoxamine – a potent inhibitor of CYP 1A2, 2C19 and weak inhibitor of 3A4 and 2C9	Agomelatine* Some benzodiazepines (eg diazepam, alprazolam and bromazepam) Caffeine + Clozapine* Duloxetine* Haloperidol Melatonin Olanzapine + Proton pump inhibitors Phenytoin* Quetiapine Theophylline* Tricyclic antidepressants* (eg amitriptyline, clomipramine, desipramine, imipramine, maprotiline and trimipramine) Warfarin*	Potential serotonin syndrome when combined with: Other serotonin-enhancing antidepressants Tramadol Fentanyl Buspirone St John’s Wort Lithium Ondansetron Linezolid Increased risk of bleeding (particularly upper GI bleed) with: NSAIDs Warfarin and other anticoagulants Antiplatelets
Fluoxetine, paroxetine – potent inhibitor of CYP 2D6	Aripiprazole Atomoxetine Carvedilol Clozapine + Donepezil Galantamine Metoprolol Risperidone + Tricyclic antidepressants* (eg amitriptyline, clomipramine, desipramine, imipramine, maprotiline and trimipramine)	Other pharmacodynamic interactions to consider: Other drugs which can also cause sexual dysfunction (antipsychotics), GI effects (acetylcholinesterase inhibitors) or hyponatraemia (thiazide diuretics).
Sertraline	Clozapine+ Unlikely to cause other clinically significant pharmacokinetic drug interactions	
Citalopram, escitalopram	Unlikely to cause clinically significant pharmacokinetic drug interactions but contra-indicated with other drugs which can prolong QT interval.	
*Avoid – high risk combination either due to the clinical significance or the potential toxicity of the affected drug + Use with caution – monitor the combination closely for any adverse effects		

TABLE: Antidepressant CYP450 drug interactions and management

Antidepressant	Major CYP450 Metabolism	Drug Interactions	Management of Antidepressant
Levomilnacipran (Fetzima®)	3A4	Inhibitors • Ketoconazole Inducers • Carbamazepine^a	Reduce dosage to max 80 mg daily and/or monitor for side effects Monitor patient response
Vortioxetine (Brintellix®)	2D6	Inhibitors • Ketoconazole • Fluconazole • Bupropion Inducers • Rifampin • Carbamazepine^a • Phenytoin^a • Barbiturates^a	Reduce dosage by half and/or monitor for side effects (gastrointestinal, dizziness) Monitor patient response
Vilazodone (Viibryd®)	3A4	Inhibitors • Ketoconazole • Erythromycin^a Inducers • Carbamazepine^a	Reduce dosage to max 20 mg daily and/or monitor for side effects Increase dosage to max 80 mg daily and/or monitor response
Venlafaxine (Effexor®)	2D6	Inhibitors • Bupropion	Decrease dosage of venlafaxine and/or monitor for side effects
Duloxetine (Cymbalta®)	2D6 and 3A4	Inhibitors • Bupropion^a • Paroxetine • Fluvoxamine	Monitor for side effects; avoid long-term use of paroxetine or fluvoxamine with duloxetine
Mirtazapine (Remeron®)	2B6	Inhibitors • Fluvoxamine Inducers • Carbamazepine^a • Phenytoin^a	Monitor for side effects; may need to decrease mirtazapine dose May need to increase dose; monitor for patient response
Bupropion (Wellbutrin®)		Inducers • Carbamazepine • Phenytoin^a • Rifampin^a • Phenobarbital^a	Monitor patient response

^aNo supporting evidence for interaction from in vivo studies.

Table 8. Some Clinically Significant Drug-Drug Interactions Resulting from Inhibition of Cytochrome P450 (CYP) Isoenzymes.

Cytochrome P450 Inhibition of			Increases Serum Levels of These CYP Substrates	
CYP1A2	•	Agomelatine	•	Naproxen
		Caffeine		Olanzapine
	•	Clozapine	•	Risperidone
		Duloxetine		Tacrine
	•	Mexiletine	•	Theophylline
				Warfarin
CYP2C19	•	Antiarrhythmics	•	Omeprazole
		Antiepileptics (diazepam, phenytoin, phenobarbital)		Primidone
	•	Indomethacin	•	Propanolol
				Warfarin
CYP2D6	•	Tricyclic antidepressants	•	Risperidone
		Beta-blockers (metoprolol, propranolol)		Vortioxetine
	•	Codeine and other opioids (reduces effect)	•	Tamoxifen (reduces effect)
		Olanzapine		Tramadol
CYP3A4	•	Amiodarone	•	Levomilnacipran
		Antiarrhythmics (quinidine)		Macrolide antibacterials (clarithromycin, erythromycin)
	•	Antihistamines (astemizole, chlorpheniramine)	•	Methadone
		Calcium channel antagonists (e.g., diltiazem, verapamil)		Phenothiazines
	•	Haloperidol	•	Quetiapine
		HIV protease inhibitors		Sildenafil
	•	Statins	•	Tamoxifen
		Immune modulators (cyclosporine, tacrolimus)		Vilazodone

Table 9. Potential Drug-Drug Interactions Involving Newer Antidepressants and Atypical Antipsychotics.

Potential for Drug-Drug Interaction	Antidepressants	Atypical Antipsychotics
Minimal or low potential	• Citalopram • Desvenlafaxine • Escitalopram • Mirtazapine • Venlafaxine	• Paliperidone
Moderate potential	• Agomelatine (1A2 substrate^a) • Bupropion (2D6 inhibitor) • Duloxetine (2D6 inhibitor; 1A2 substrate^a) • Levomilnacipran (3A4 substrate) • Sertraline (2D6 inhibitor) • Vilazodone (3A4 substrate) • Vortioxetine (2D6 substrate)	• Aripiprazole (2D6, 3A4 substrate) • Olanzapine (1A2 substrate^b) • Risperidone (2D6, 3A4 substrate)
Higher potential	• Fluoxetine (2D6, 2C19 inhibitor) • Fluvoxamine (1A2, 2C19, 3A4 inhibitor) • Moclobemide (MAO inhibitor precautions^c) • Paroxetine (2D6 inhibitor) • Selegiline (MAO inhibitor precautions^c)	• Clozapine (3A4, 1A2 substrate) • Lurasidone (3A4 substrate) • Quetiapine (3A4 substrate)

Moderate and higher potential interactions are noted in parentheses. MAO, monoamine oxidase.

^aCoadministration with CYP1A2 inhibitors (e.g., cimetidine, ciprofloxacin and other fluoroquinolone antimicrobials, ticlopidine) should be avoided because serum antidepressant levels will be higher, leading to increased potential for side effects.

^bAlso metabolized through the uridine diphosphate glucuronosyltransferase (UGT) pathway.

^cPrecautions similar to those of older MAO inhibitors. Avoid coadministration of other antidepressants, serotonergic drugs (e.g., meperidine), and sympathomimetic drugs (e.g., pseudoephedrine, stimulants).