



**PSYCHIATRIC MEDICATIONS**

**AND HIV ANTIRETROVIRALS**

**A GUIDE TO INTERACTIONS FOR CLINICIANS**

# Psychiatric Medications and HIV Antiretrovirals: A GUIDE TO INTERACTIONS FOR CLINICIANS

## Acknowledgements

This guide was developed and prepared by the following staff of the Columbia University HIV Mental Health Training Project.

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## Disclaimer:

The data in this guide are intended for use by clinicians and other health care providers as guidance to minimize drug interactions and toxicities among patients being treated with psychiatric medications in conjunction with antiretrovirals. Data were compiled from published studies and anecdotal reports as of March 2004.

*Produced and presented by the NY/NJ AETC and the Columbia University HIV Mental Health Training Project*



## CLASS

### Antipsychotics

## INDICATIONS

Antipsychotics can be used to treat psychotic disorders, mania, and behavioral disturbances, such as agitation, associated with dementia.

**CATEGORY** Third Generation Aripiprazole (Abilify)

**CAUTIONS** Side effects include somnolence, dizziness, and palpitations.

**PHARMACOKINETICS** Aripiprazole is metabolized by CYP 3A4 and 2D6. Drugs that induce CYP 3A4 (e.g. carbamazepine) could increase clearance of aripiprazole and lower blood levels. Inhibitors of CYP 3A4 (e.g. ketoconazole, ritonavir) or 2D6 (e.g. quinidine, fluoxetine, or paroxetine) can inhibit aripiprazole elimination and cause increased blood levels.

**NNRTIs** No published data about drug interactions specific to this combination.  
Delavirdine (Rescriptor)  
Efavirenz (Sustiva)  
Nevirapine (Viramune)

**NRTIs** No published data about drug interactions specific to this combination.  
Abacavir (ABC, Ziagen)  
Combivir (AZT/3TC)  
Didanosine (ddl, Videx)  
Emtricitabine (Emtriva)  
Lamivudine (3TC, Epivir)  
Stavudine (d4T, Zerit)  
Tenofovir (Viread)  
Trizivir (AZT/3TC/ABC)  
Zalcitabine (ddC, Hivid)  
Zidovudine (AZT,ZDV,Retrovir)

**Protease Inhibitors** No published data about drug interactions specific to this combination.  
Amprenavir (Agenerase)  
Atazanavir (Reyataz)  
Fosamprenavir (Lexiva)  
Indinavir (Crixivan)  
Lopinavir/Ritonavir (Kaletra)  
Nelfinavir (Viracept)  
Ritonavir (Norvir)  
Saquinavir (Fortovase)(Invirase)

## CLASS

### Herbal Preparations

## INDICATIONS

Self-prescribed by patients for multiple needs. Providers need to be aware of preparations used by their patients.

**St. John's Wort** (Hypericin, Hyperforin)  
Derived from the plant, Hypericum perforatum.

Inducer of CYP 3A4 and p-glycoprotein.

May reduce blood levels of NNRTIs.  
Induces metabolism of nevirapine; increased clearance - 35% (deMaat)

May reduce blood levels of PIs

Levels of indinavir were reported to fall by 50-80% in volunteers treated with St John's wort and indinavir. (Piscitelli)

## CLASS

### Antidepressants

## INDICATIONS

Many antidepressants (e.g., SSRIs) can be used to treat both depressive and anxiety disorders. Antianxiety drugs, such as benzodiazepines, however, are not a treatment for depression.



**CATEGORY** **Selective serotonin reuptake inhibitors (SSRIs)** Fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), citalopram (Celexa), escitalopram (Lexapro), fluvoxamine (Luvox)

**CAUTIONS** Serotonin syndrome (diaphoresis, hyperthermia, hypertension, tachycardia, papillary dilatation, nausea, diarrhea, shivering, hyperreflexia, myoclonus, restlessness, tremor, incoordination, rigidity, clonus, trismus, seizures, confusion, agitation, anxiety, insomnia, hallucinations, headache)  
Fluoxetine is also formulated as a combination with olanzapine (Symbyax); refer to olanzapine (atypical antipsychotics) for further information.

**PHARMACOKINETICS** Metabolized by CYP 2D6, 3A4, 1A2, 2C19.  
Fluoxetine: potent inhibitor of CYP 2D6, 3A4, 2C19..  
Paroxetine: potent inhibitor of CYP 2D6.  
Fluvoxamine: potent inhibitor of CYP 3A4; inhibitor of 1A2, 2C19 and 2C9.  
Sertraline: weak inhibitor of 2D6.  
Citalopram: weak inhibitor of 2D6.  
Escitalopram: weak inhibitor of 2D6.

**NNRTIs** Fluoxetine increased through levels of delavirdine-50%

Delavirdine (Rescriptor)  
Efavirenz (Sustiva)  
Nevirapine (Viramune)

**NRTIs** No published data about drug interactions specific to this combination.

Abacavir (ABC, Ziagen)  
Combivir (AZT/3TC)  
Didanosine (ddl, Videx)  
Emtricitabine (Emtriva)  
Lamivudine (3TC, EpiVir)  
Stavudine (d4T, Zerit)  
Tenofovir (Viread)  
Trizivir (AZT/3TC/ABC)  
Zalcitabine (ddC, Hivid)  
Zidovudine (AZT, ZDV, Retrovir)

**Protease Inhibitors** Fluoxetine may lead to increased effects of ritonavir, but no dose adjustment of ritonavir is needed when used in combination (Ouellet et al.)

Amprenavir (Agenerase)  
Atazanavir (Reyataz)  
Fosamprenavir (Lexiva)  
Indinavir (Crixivan)  
Lopinavir/Ritonavir (Kaletra)  
Nelfinavir (Viracept)  
Ritonavir (Norvir)  
Saquinavir (Fortovase) (Invirase)

Ritonavir increases levels of fluoxetine, fluvoxamine, paroxetine and sertraline.

**Tricyclics (TCAs)** Nortriptyline (Pamelor), desipramine (Norpramin), amitriptyline (Elavil), imipramine (Tofranil), doxepin (Sinequan), clomipramine (Anafranil), protriptyline (Vivactil)

TCAs are associated with dry mouth, constipation, urinary retention, and blurred vision; toxic levels of TCAs may prolong the PR interval on EKG, and lead to atrioventricular (AV) block and cardiac arrhythmia; patients with an existing AV conduction disturbance are at increased risk. Note: CNS side effects are more prominent in patients with advanced AIDS. It is best to start with low doses and titrate slowly.

Metabolized by CYP 2D6.

No published data about drug interactions specific to this combination.

No published data about drug interactions specific to this combination.

Ritonavir is a moderately strong 2D6 inhibitor, and decreases desipramine clearance by 59% causing higher than anticipated blood levels (von Moltke, et al., 1998); may increase levels of amitriptyline, doxepin, imipramine, nortriptyline.

When used in combination with ritonavir, caution is required.

It is recommended to use lower doses, and regularly monitor EKG and serum TCA levels.

**CLASS**  
**Antidepressants**

**INDICATIONS**

Many antidepressants (e.g., SSRIs) can be used to treat both depressive and anxiety disorders. Antianxiety drugs, such as benzodiazepines, however, are not a treatment for depression.



**CATEGORY** Other Bupropion (Wellbutrin)

**CAUTIONS** Increased levels may induce seizures. Caution should be observed when bupropion is administered concomitantly with drugs that may inhibit its metabolism (e.g., cimetidine, protease inhibitors), increasing bupropion levels and increasing the risk of drug-induced seizures.

**PHARMACOKINETICS** Metabolized by CYP 2D6, 3A4, 2B6.

**NNRTIs** Efavirenz inhibits 2B6; may increase bupropion levels.  
Delavirdine (Rescriptor)  
Efavirenz (Sustiva)  
Nevirapine (Viramune)

**NRTIs** No published data about drug interactions specific to this combination.  
Abacavir (ABC, Ziagen)  
Combivir (AZT/3TC)  
Didanosine (ddl, Videx)  
Emtricitabine (Emtriva)  
Lamivudine (3TC, Epivir)  
Stavudine (d4T, Zerit)  
Tenofovir (Viread)  
Trizivir (AZT/3TC/ABC)  
Zalcitabine (ddC, Hivid)  
Zidovudine (AZT, ZDV, Retrovir)

**Protease Inhibitors** Nelfinavir and ritonavir inhibit 2B6; may increase bupropion levels, increasing risk of drug-induced seizures.  
Amprenavir (Agenerase)  
Atazanavir (Reyataz)  
Fosamprenavir (Lexiva)  
Indinavir (Crixivan)  
Lopinavir/Ritonavir (Kaletra)  
Nelfinavir (Viracept)  
Ritonavir (Norvir)  
Saquinavir (Fortovase) (Invirase)

**Other** Nefazodone (Serzone)

Cases of life-threatening hepatic failure have been reported with nefazodone; caution is indicated in patients with liver disease, such as hepatitis, or in combination with other potential hepatotoxins.

Associated with somnolence and dizziness, esp. at higher doses.

Metabolized by and potent inhibitor of CYP3A4.

No published data about drug interactions specific to this combination. (See Cautions)

No published data about drug interactions specific to this combination. (See Cautions)

Caution advised; combination of PI's and nefazodone may increase levels of both drugs.

## CLASS

### Antidepressants

## INDICATIONS

Many antidepressants (e.g., SSRIs) can be used to treat both depressive and anxiety disorders. Antianxiety drugs, such as benzodiazepines, however, are not a treatment for depression.



## CATEGORY Serotonin norepinephrine reuptake inhibitors (SNRIs)

Mirtazapine (Remeron); Venlafaxine (Effexor)

## CAUTIONS

Mirtazapine: Orthostatic hypotension, drowsiness.  
Venlafaxine: Hypertension.

## PHARMACOKINETICS

Mirtazapine: Metabolized by CYP 2D6, 1A2, 3A4.

Venlafaxine: Metabolized by CYP 2D6, 3A4.

## NNRTIs

Delavirdine (Rescriptor)  
Efavirenz (Sustiva)  
Nevirapine (Viramune)

No published data about drug interactions specific to this combination.

## NRTIs

Abacavir (ABC, Ziagen)  
Combivir (AZT/3TC)  
Didanosine (ddl, Videx)  
Emtricitabine (Emtriva)  
Lamivudine (3TC, EpiVir)  
Stavudine (d4T, Zerit)  
Tenofovir (Viread)  
Trizivir (AZT/3TC/ABC)  
Zalcitabine (ddC, Hivid)  
Zidovudine (AZT,ZDV,Retrovir)

No published data about drug interactions specific to this combination.

## Protease Inhibitors

Ampranavir (Agenerase)  
Atazanavir (Reyataz)  
Fosamprenavir (Lexiva)  
Indinavir (Crixivan)  
Lopinavir/Ritonavir (Kaletra)  
Nelfinavir (Viracept)  
Ritonavir (Norvir)  
Saquinavir (Fortovase)(Invirase)

Venlafaxine may decrease Indinavir levels. An in vivo study (n=9) showed a 28% decrease in the AUC and a 36% decrease in the C<sub>max</sub> of Indinavir. The clinical significance of this interaction is unknown.

## Other Trazadone (Desyrel)

Increased plasma levels may cause nausea, hypotension and syncope and drowsiness.

In vitro drug metabolism studies reveal that trazadone is a substrate of the CYP3A4 enzyme and trazadone metabolism can be inhibited by the CYP3A4 inhibitors ketoconazole, ritonavir, and indinavir. The effect of short-term administration of ritonavir (200 mg twice daily, 4 doses) on the pharmacokinetics of a single dose of trazadone (50 mg) has been studied in 10 healthy subjects. The C<sub>max</sub> of trazadone increased by 34%, the AUC increased 2.4-fold, the half-life increased by 2.2-fold, and the clearance decreased by 52%. Adverse effects including nausea, hypotension, and syncope were observed when ritonavir and trazadone were co-administered.

No published data about drug interactions specific to this combination.

No published data about drug interactions specific to this combination.

In vitro drug metabolism studies suggest that there is a potential for drug interactions when trazadone is co-administered. Adverse effects including nausea, hypotension, and syncope were observed when ritonavir and trazadone were co-administered. It is likely that ketoconazole, indinavir, and other CYP3A4 inhibitors such as itraconazole or nefazodone may lead to substantial increases in trazadone plasma concentrations with the potential for adverse effects. If trazadone is used with a potent CYP3A4 inhibitor, a lower dose of trazadone should be considered.

## CLASS

**Anxiolytics  
and Sedative-  
Hypnotics**

## INDICATIONS

Anxiolytics  
& Sedative-  
Hypnotics  
can be used  
to treat  
anxiety  
disorders  
and sleep  
disorders.



## CATEGORY **Benzodiazepines**

### CAUTIONS

Some caution advised in patients with history of drug dependence, in order to avoid additional dependency.  
Note: CNS side effects are more prominent in patients with advanced AIDS. In these patients, start with lower doses and titrate slowly.

### PHARMACOKINETICS

Some benzodiazepines are metabolized by CYP 3A4, and their levels may be increased by CYP 3A4 inhibitors, such as protease inhibitors, causing excessive sedation, or respiratory depression.  
The following are contraindicated in combination with protease inhibitors: midazolam; triazolam.  
The following should be used with caution in combination with protease inhibitors: alprazolam, flurazepam, estazolam, diazepam, clonazepam.  
The following are metabolized by glucuronidation and are free of drug interactions with inhibitors of CYP 3A4: lorazepam, temazepam, and clorazepate.

### NNRTIs

Delavirdine (Rescriptor)  
Efavirenz (Sustiva)  
Nevirapine (Viramune)

No published data about drug interactions specific to this combination.

### NRTIs

Abacavir (ABC, Ziagen)  
Combivir (AZT/3TC)  
Didanosine (ddl, Videx)  
Emtricitabine (Emtriva)  
Lamivudine (3TC, Epivir)  
Stavudine (d4T, Zerit)  
Tenofovir (Viread)  
Trizivir (AZT/3TC/ABC)  
Zalcitabine (ddC, Hivid)  
Zidovudine (AZT,ZDV,Retrovir)

No published data about drug interactions specific to this combination.

### Protease Inhibitors

Amprenavir (Agenerase)  
Atazanavir (Reyataz)  
Fosamprenavir (Lexiva)  
Indinavir (Crixivan)  
Lopinavir/Ritonavir (Kaletra)  
Nelfinavir (Viracept)  
Ritonavir (Norvir)  
Saquinavir (Fortovase)(Invirase)

Benzodiazepines with possible interactions: midazolam, triazolam these drugs are metabolized by CYP450 3A4, and are CONTRAINDICATED in combination with protease inhibitors due to the potential for serious and life-threatening reactions such as prolonged or severe sedation or respiratory depression.

Benzodiazepines with potential interactions: alprazolam, flurazepam, clonazepam, diazepam: these drugs are metabolized by CYP3A4, and should be used with caution in combination with protease inhibitors due to the potential for serious reactions such as prolonged or severe sedation or respiratory depression.

Benzodiazepines without problematic interactions: lorazepam, temazepam, clorazepate. These drugs are metabolized by glucuronidation and are free of the serious interactions with protease inhibitors found with other benzodiazepines.

**Non-Benzodiazepine sedative/hypnotics** Zolpidem (Ambien), zaleplon (Sonata)

Should be used as a second therapeutic choice once sleep hygiene is established.

Metabolized by by CYP3A4.

No published data about drug interactions specific to this combination.

No published data about drug interactions specific to this combination.

Zolpidem and zaleplon should be used with caution in combination with protease inhibitors due to the potential for serious reactions such as prolonged or severe sedation or respiratory depression.

## CLASS

### Mood Stabilizers

**INDICATIONS**  
Mood Stabilizers are used as monotherapy and in combination with other drugs (e.g. atypical antipsychotics) for treatment of acute mania, and as maintenance treatment for bipolar disorder.



**CATEGORY** **Lithium carbonate** (Eskalith, Lithobid)

**CAUTIONS** Long-term use can impair renal or thyroid function: regularly monitor serum lithium levels, creatinine, electrolytes and thyroid function tests.

**PHARMACOKINETICS** Lithium is cleared exclusively by the kidneys; renal impairment requires lower doses to avoid toxicity.

**NNRTIs** No published data about drug interactions specific to this combination.  
Delavirdine (Rescriptor)  
Efavirenz (Sustiva)  
Nevirapine (Viramune)

**NRTIs** No published data about drug interactions specific to this combination.  
Abacavir (ABC, Ziagen)  
Combivir (AZT/3TC)  
Didanosine (ddI, Videx)  
Emtricitabine (Emtriva)  
Lamivudine (3TC, Epivir)  
Stavudine (d4T, Zerit)  
Tenofovir (Viread)  
Trizivir (AZT/3TC/ABC)  
Zalcitabine (ddC, Hivid)  
Zidovudine (AZT, ZDV, Retrovir)

**Protease Inhibitors** No published data about drug interactions specific to this combination.  
Amprenavir (Agenerase)  
Atazanavir (Reyataz)  
Fosamprenavir (Lexiva)  
Indinavir (Crixivan)  
Lopinavir/Ritonavir (Kaletra)  
Nelfinavir (Viracept)  
Ritonavir (Norvir)  
Saquinavir (Fortovase) (Nirvase)

**Anticonvulsants** Divalproex sodium (Depakote), carbamazepine (Tegretol), phenytoin (Dilantin), oxcarbazepine (Trileptal), gabapentin (Neurontin), lamotrigine (Lamictal), topiramate (Topamax), tiagabine (Gabitrin)

Valproic acid: inhibitor of glucuronidation  
Carbamazepine: powerful CYP3A4 enzyme inducer, may decrease levels of PIs and NNRTIs  
Phenytoin: known to be powerful CYP3A4 enzyme inducer, may decrease levels of PIs and NNRTIs.  
Lamotrigine: undergoes glucuronidation.  
Gabapentin: renal elimination.  
Topiramate: inhibits 2C19

Carbamazepine: known to be powerful CYP3A4 enzyme inducer, may decrease levels of PIs and NNRTIs.  
Phenytoin: known to be CYP 450 3A4 enzyme inducer, may decrease levels of PIs and NNRTIs.

Valproic acid: inhibitor of glucuronidation; study showed 100% increase in AUC of zidovudine, but dosage adjustment not recommended (Lertora et al.)  
Long term clinical implications not known; monitor for zidovudine toxicity.

Carbamazepine: known to be powerful CYP3A4 enzyme inducer, may decrease levels of PIs and NNRTIs. Known to decrease indinavir levels with loss of viral suppression. Carbamazepine levels increased by ritonavir (Kato).  
Phenytoin: Co-administration of lopinavir/ritonavir (LPV/r) and phenytoin results in a 2-way drug interaction whereby both LPV/r and phenytoin concentrations are decreased. - 30%. (Lim et al.)  
Phenytoin: Co-administration of nelfinavir (NFV) with phenytoin resulted in a 30% reduction in the phenytoin AUC and a 20% reduction in the AUC of the major NFV metabolite, M8, but had no effect on the NFV AUC (Shelton).



## CLASS

**Antipsychotics**

## INDICATIONS

Antipsychotics can be used to treat psychotic disorders, mania, and behavioral disturbances, such as agitation, associated with dementia.



## CATEGORY

**First Generation - Typical** Haloperidol (Haldol), fluphenazine (Prolixin), perphenazine (Trilafon), chlorpromazine (Thorazine), pimozide (Orap), trifluoperazine (Stelazine), mesoridazine (Sereniti), thioridazine (Mellaril), molindone (Moban), loxapine (Loxitame)

**Second Generation - Atypical** Clozapine (Clozaril), risperidone (Risperdal), quetiapine (Seroquel), olanzapine (Zyprexa); aripiprazole (Abilify), ziprasidone (Geodon)

## CAUTIONS

Pimozide side-effects are prominent in patients with HIV illness. In these patients, start with low doses and titrate slowly. Orap (pimozide): prolongs the QT interval on EKG, and is CONTRAINDICATED in combination with protease inhibitors. Mesoridazine and thioridazine should not be used in individuals who have known cardiac conduction defects (e.g. AV block, bundle-branch block, cardiac arrhythmia, QT prolongation).

Clozapine: because of the risk of life-threatening agranulocytosis associated with clozapine, it should be avoided in combination with other medications having a known potential to suppress bone marrow function. Inhibitors of CYP 3A4 and 2D6 may increase plasma levels of clozapine & increase the risks for seizures, orthostatic hypotension & other adverse effects. Ziprasidone: 1) Causes a dose-related prolongation of the QT interval, and is CONTRAINDICATED in patients with known prolongation of the QT interval, with recent acute myocardial infarction, or with uncompensated heart failure. It is also CONTRAINDICATED in combination with other drugs that prolong the QT interval, such as pentamidine, mesoridazine, thioridazine, chlorpromazine, droperidol, or pimozide (this is not a complete list). 2) An in vivo study showed a 35-40% increase in the AUC and Cmax of ziprasidone when co-administered with ketoconazole, a potent inhibitor of CYP3A4; caution is indicated when ziprasidone is co-administered with drugs that inhibit CYP3A4, such as ritonavir.

## PHARMACOKINETICS

Chlorpromazine: Metabolized by 1A2, 2D6, 3A4; inhibits 2D6.  
Fluphenazine: Metabolized by 2D6; inhibits 2D6.  
Haloperidol: Metabolized by 2D6; inhibits 2D6.  
Molindone: Metabolized by 2D6.  
Perphenazine: Metabolized by 2D6; inhibits 2D6.  
Thioridazine: Metabolized by 1A2, 2D6; inhibits 2D6.  
Trifluoperazine: Metabolized by 1A2.

Clozapine: Metabolized by CYP3A4, 2D6, 1A2, 2C19.  
Quetiapine: Metabolized by CYP3A4.  
Ziprasidone: Metabolized by CYP3A4.  
Risperidone: Metabolized by 2D6, 3A4; inhibits 2D6.  
Olanzapine: Metabolized by 1A2, 2D6.

## NNRTIs

Delavirdine (Rescriptor)  
Efavirenz (Sustiva)  
Nevirapine (Viramune)

No published data about drug interactions specific to this combination.

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## NRTIs

Abacavir (ABC, Ziagen)  
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Lamivudine (3TC, EpiVir)  
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Trizivir (AZT/3TC/ABC)  
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## Protease Inhibitors

Amprenavir (Agenerase)  
Atazanavir (Reyataz)  
Fosamprenavir (Lexiva)  
Indinavir (Crixivan)  
Lopinavir/Ritonavir (Kaletra)  
Nelfinavir (Viracept)  
Ritonavir (Norvir)  
Saquinavir (Fortovase) (Invirase)

Pimozide: prolongs the QT interval on EKG, and is CONTRAINDICATED in combination with protease inhibitors due to potential for serious and life-threatening reactions, such as cardiac arrhythmia.

Ritonavir may increase levels of antipsychotics.

Protease Inhibitors may inhibit CYP 3A4 and 2D6 and may increase plasma levels of clozapine & increase the risk for seizures & orthostatic hypotension.

Olanzapine: one study showed an increased clearance of olanzapine, when used in combination with ritonavir, which induces CYP 1A2 (Penzak et al.), but the clinical significance of this is not clear.

Ziprasidone: caution is indicated when ziprasidone is co-administered with drugs that inhibit CYP3A4, such as ritonavir.

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