PSYCHIATRIC MEDICATIONS AND HIV ANTIRETROVIRALS
ADULT MANAGEMENT
Winter 2013

A DRUG INTERACTION GUIDE FOR CLINICIANS
Psychiatric Medications and HIV Antiretrovirals:
A Drug Interaction Guide for Clinicians
ADULT MANAGEMENT 2013
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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 adults being treated with psychiatric medications in conjunction with antiretrovirals. The information is intended for use in adult patients only. Additional/other references should be used when evaluating information for the treatment of adolescent and pediatric patients. These guidelines are for informational purposes only and cannot identify medical risks specific to an individual patient or recommend patient treatment. The absence of typographical errors is not guaranteed. These guidelines are not necessarily all-inclusive. Use of these guidelines indicates acknowledgement that neither NY/NJ AETC, nor the authors will be responsible for any loss or injury, sustained in connection with, or as a result of, the use of these guidelines. Users of this guide should consult other sources before prescribing medications or treatment. Data were compiled through February 2013. The NY/NJ AETC would like to acknowledge Ewald Horwath, MD and Christine Kubin, PharmD for their initial development work on this guide.

Pregnancy Category Definitions:
Within the Black Box Warnings/Caution sections of each medication category, medications that are Category D or X are noted. Category D medications are defined by the FDA as medications with positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. Category X medications are defined as medications where studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

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# Psychiatric Medications and HIV Antiretrovirals: A Drug Interaction Guide for Clinicians

## NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Route of Elimination/Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delavirdine, DLV</td>
<td>Rescriptor®</td>
<td>CYP 3A4 inhibitor</td>
</tr>
<tr>
<td>Efavirenz, EFV</td>
<td>Sustiva®</td>
<td>CYP 3A4 inducer and inhibitor</td>
</tr>
<tr>
<td>Nevirapine, NVP</td>
<td>Viramune®</td>
<td>CYP 3A4 inducer</td>
</tr>
<tr>
<td>Etravirine, ETV</td>
<td>Intelence TM</td>
<td>CYP 3A4 inducer, inhibitor of 2C9, 2C19</td>
</tr>
<tr>
<td>Rilpivirine, RPV</td>
<td>Edurant®</td>
<td>CYP 3A4 inducer</td>
</tr>
</tbody>
</table>

## NUCLEOSIDE/NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Route of Elimination/Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir, ABC</td>
<td>Ziagen®</td>
<td>Metabolized by alcohol dehydrogenase and glucuronyl transferase</td>
</tr>
<tr>
<td>Didanosine, ddl</td>
<td>Videx EC®</td>
<td>Renal excretion 50%</td>
</tr>
<tr>
<td>Emtricitabine, FTC</td>
<td>Emtriva®</td>
<td>Renal</td>
</tr>
<tr>
<td>Lamivudine, 3TC</td>
<td>Epivir®</td>
<td>Renal</td>
</tr>
<tr>
<td>Stavudine, d4T</td>
<td>Zerit®</td>
<td>Renal excretion 50%</td>
</tr>
<tr>
<td>Tenofovir, TDF</td>
<td>Viread®</td>
<td>Renal</td>
</tr>
<tr>
<td>Zidovudine, AZT</td>
<td>Retrovir®</td>
<td>Metabolized to AZT glucuronide, renal excretion</td>
</tr>
</tbody>
</table>

## PROTEASE INHIBITORS

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Route of Elimination/Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir, ATV</td>
<td>Reyataz®</td>
<td>CYP 3A4 inhibitor and substrate</td>
</tr>
<tr>
<td>Darunavir, DRV</td>
<td>Prezista®</td>
<td>CYP 3A4 inhibitor and substrate</td>
</tr>
<tr>
<td>Fosamprenavir, FPV</td>
<td>Lexiva®</td>
<td>CYP 3A4 inhibitor, inducer and substrate</td>
</tr>
<tr>
<td>Indinavir, IDV</td>
<td>Crixivan®</td>
<td>CYP 3A4 inhibitor</td>
</tr>
<tr>
<td>Lopinavir/ritonavir, LPV/r</td>
<td>Kaletra®</td>
<td>CYP 3A4 inhibitor and substrate</td>
</tr>
<tr>
<td>Nelfinavir, NFV</td>
<td>Viracept®</td>
<td>CYP 3A4 inhibitor and substrate</td>
</tr>
<tr>
<td>Ritonavir, RTV</td>
<td>Norvir®</td>
<td>CYP 3A4 and 2D6 inhibitor</td>
</tr>
<tr>
<td>Saquinavir, SQV</td>
<td>Invirase®</td>
<td>CYP 3A4 inhibitor and substrate</td>
</tr>
<tr>
<td>Tipranavir, TPV</td>
<td>Aptivus®</td>
<td>CYP 3A4 and 2D6 inhibitor</td>
</tr>
</tbody>
</table>
## Psychiatric Medications and HIV Antiretrovirals: A Drug Interaction Guide for Clinicians

### COMBINATION PRODUCTS, SINGLE TABLET REGIMENS

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Route of Elimination/Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir and lamivudine</td>
<td>Epzicom®</td>
<td>See individual medications</td>
</tr>
<tr>
<td>Abacavir, zidovudine, and lamivudine</td>
<td>Trizivir®</td>
<td>See individual medications</td>
</tr>
<tr>
<td>Efavirenz, tenofovir, emtricitabine</td>
<td>Atripla®</td>
<td>See individual medications</td>
</tr>
<tr>
<td>Elvitegravir/cobicistat/tenofovir, and emtricitabine</td>
<td>Stribild®</td>
<td>See individual medications</td>
</tr>
<tr>
<td>Rilpivirine, tenofovir, and emtricitabine</td>
<td>Complera®</td>
<td>See individual medications</td>
</tr>
<tr>
<td>Tenofovir and emtricitabine</td>
<td>Truvada®</td>
<td>See individual medications</td>
</tr>
<tr>
<td>Zidovudine and lamivudine</td>
<td>Combivir®</td>
<td>See individual medications</td>
</tr>
</tbody>
</table>

### FUSION INHIBITOR

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Route of Elimination/Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enfuvirtide, ENF</td>
<td>Fuzeon®</td>
<td>Catabolism to amino acids</td>
</tr>
</tbody>
</table>

### CCR5 INHIBITOR

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Route of Elimination/Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maraviroc, MRV</td>
<td>Selzentry®</td>
<td>CYP 3A4 substrate</td>
</tr>
</tbody>
</table>

### INTEGRASE INHIBITOR

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Route of Elimination/Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raltegravir RAL</td>
<td>Isentress®</td>
<td>Metabolized by glucuronidation, not CYP 450</td>
</tr>
<tr>
<td>Elvitegravir EVG (available as combination with cobicistat, tenofovir, emtricitabine)</td>
<td>Stribild®</td>
<td>Metabolized by CYP3A4. Cobicistat is a potent CYP3A4 inhibitor used to boost levels of elvitegravir. See individual medications.</td>
</tr>
</tbody>
</table>

Abbreviations: PK - pharmacokinetics  
NNRTI - non-nucleoside reverse transcriptase inhibitor  
NRTI - nucleoside/tide reverse transcriptase inhibitor  
PI - protease inhibitor  
CCR5i - CCR5 inhibitor  
II - integrase inhibitor  
Black Box Warnings and medications which are Pregnancy Category D or X for psychiatric medications are listed in bold in the Caution section.
**CLASS**

Antidepressants

**INDICATIONS**

Many antidepressants 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)**, vilazodone (Viibryd) ***

**Tricyclics (TCAs)**

- nortriptyline (Pamelor), desipramine (Norpramin), amitriptyline (Elavil), imipramine (Tofranil), doxepin (Sinequan, Adapin, Silenor), clomipramine (Anafranil)**, protriptyline (Vivactil), maprotiline (Ludiomil) ****, amoxapine (Asendin)****, trimipramine (Surmontil)

### BLACK BOX

**WARNINGS/CAUTIONS**

**Increased suicide risk in <24 years old.**

Monitor for serotonin syndrome (diaphoresis, hyperthermia, hypertension, tachycardia, pupillary dilatation, nausea, diarrhea, shivering, hyperreflexia, myoclonus, restlessness, tremor, incoordination, rigidity, clonus, trismus, seizure, confusion, agitation, anxiety, insomnia, hallucinations, headache). Fluoxetine is also formulated as a combination with olanzapine (Symbyax); refer to olanzapine (atypical antipsychotics) for further information. Citalopram is associated with increased risk of sudden cardiac death. Paroxetine is Pregnancy Category D.

**Increased suicide risk in <24 years old.**

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. Nortriptyline is associated with increased risk of sudden cardiac death. Imipramine and nortriptyline are Pregnancy Category D.

### PK

**Fluoxetine:** Inhibitor of CYP 2D6, 3A4, 2C19.

**Fluvoxamine:** Inhibitor of CYP 3A4, 1A2, 2C19, 2C9.

**Citalopram, escitalopram, sertraline, and paroxetine:** Inhibitors of CYP 2D6.

**Vilazodone:** Metabolized mainly via CYP3A4, minor contribution from CYP2C19 and CYP2D6

**Metabolized by CYP 2D6**

* Patients with major depressive disorder (MDD) may experience worsening of depression and/or emergence of suicidal ideation/behavior and/or unusual changes in behavior.

** fluvoxamine (Luvox) and clomipramine (Anafranil) are generally used for obsessive compulsive disorder.

*** vilazodone (Viibryd) is also a serotonin 1A receptor partial agonist

**** maprotiline and amoxapine are classified as a tetracyclic, and heterocyclic antidepressant, respectively

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*cont’d on next page*
### Antidepressants

**CLASS**

**Antidepressants**

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

<table>
<thead>
<tr>
<th>CLASS</th>
<th>CATEGORY (Continued)</th>
<th>Tricyclics (TCAs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Selective serotonin reuptake inhibitors (SSRIs)</td>
<td>nortriptyline (Pamelor), desipramine (Norpramin), amitriptyline (Elavil), imipramine (Tofranil), doxepin (Sinequan, Adapin, Silenor), clomipramine (Anafranil)<strong>, protriptyline (Vivactil), maprotiline (Ludiomil) *<strong>, amoxapine (Asendin)</strong></strong>, trimipramine (Surmontil)</td>
</tr>
<tr>
<td></td>
<td>fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Pexeva, Paxil), citalopram (Celexa), escitalopram (Lexapro), fluvoxamine (Luvox)**, vilazodone (Viibryd) ***</td>
<td></td>
</tr>
</tbody>
</table>

| NNRTIs | Fluoxetine increased trough levels of delavirdine ~ 50% Efavirenz and Nevirapine may reduce drug levels of vilazodone Efavirenz reduces sertraline levels by 39% No effect when efavirenz or etravirine are used with paroxetine | No published data about drug interactions specific to this combination. |

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

| PIs     | Ritonavir may increase levels of SSRIs and can lead to serotonin syndrome. Fluvoxamine increases levels of all PIs. Darunavir/ritonavir decreases sertraline levels by ~49% and decreases paroxetine levels by ~39%; monitor closely for antidepressant effect and increase dose as tolerated. Fosamprenavir/ritonavir decreases paroxetine levels 55%; monitor closely for antidepressant effect and increase dose as tolerated. All protease inhibitors may increase drug levels of vilazodone. Vilazodone dosage should be reduced to 20mg if used with strong CYP3A4 inhibitors. | Ritonavir is a CYP 2D6 inhibitor, and decreases desipramine clearance by 59% causing higher blood levels of desipramine; Ritonavir may also increase levels of all TCAs. When used in combination with ritonavir boosted protease inhibitors, caution is required. Reduced dosages may be required; monitor EKG and serum TCA levels. Use lowest dose of TCA and titrate based upon clinical assessment. |

**Fluvoxamine (Luvox) and clomipramine (Anafranil) are generally used for obsessive compulsive disorder.**

**Vilazodone (Viibryd) is also a serotonin 1A receptor partial agonist.**

**Maprotiline and amoxapine are classified as a tetracyclic, and heterocyclic antidepressant, respectively.**
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<tr>
<th>CATEGORY</th>
<th><strong>Selective serotonin reuptake inhibitors (SSRIs)</strong></th>
<th><strong>Tricyclics (TCAs)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Pexeva, Paxil), citalopram (Celexa), escitalopram (Lexapro), fluvoxamine (Luvox)**, vilazodone (Viibryd) ***</td>
<td>nortriptyline (Pamelor), desipramine (Norpramin), amitriptyline (Elavil), imipramine (Tofranil), doxepin (Sinequan, Adapin, Silenor), clomipramine (Anafranil)**, protriptyline (Vivactil), maprotiline (Ludiomil) <strong><strong>, amoxapine (Asendin)</strong></strong>, trimipramine (Surmontil)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>CCR5I</strong></th>
<th>No published data about drug interactions specific to this combination</th>
<th>No published data about drug interactions specific to this combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>Elvitegravir/cobicistat/tenofovir/emtricitabine</td>
<td>Elvitegravir/cobicistat/tenofovir/emtricitabine</td>
</tr>
<tr>
<td></td>
<td>may increase paroxetine levels and levels of other SSRIs. Use lowest dose.</td>
<td>increased desipramine levels 65%. May also increase amitriptyline, imipramine and nortriptyline levels. Reduced dosages may be required; monitor EKG and serum TCA levels.</td>
</tr>
</tbody>
</table>

***(Continued)***

Selective serotonin reuptake inhibitors (SSRIs)

- fluoxetine (Prozac)
- sertraline (Zoloft)
- paroxetine (Pexeva, Paxil)
- citalopram (Celexa)
- escitalopram (Lexapro)
- fluvoxamine (Luvox)**
- vilazodone (Viibryd) ***

Tricyclics (TCAs)

- nortriptyline (Pamelor)
- desipramine (Norpramin)
- amitriptyline (Elavil)
- imipramine (Tofranil)
- doxepin (Sinequan, Adapin, Silenor)
- clomipramine (Anafranil)**
- protriptyline (Vivactil)
- maprotiline (Ludiomil) ****
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- trimipramine (Surmontil)

**Selective serotonin reuptake inhibitors (SSRIs)**

- **fluoxetine (Prozac)**
- **sertraline (Zoloft)**
- **paroxetine (Pexeva, Paxil)**
- **citalopram (Celexa)**
- **escitalopram (Lexapro)**
- **fluvoxamine (Luvox)**
- **vilazodone (Viibryd)**

**Tricyclics (TCAs)**

- **nortriptyline (Pamelor)**
- **desipramine (Norpramin)**
- **amitriptyline (Elavil)**
- **imipramine (Tofranil)**
- **doxepin (Sinequan, Adapin, Silenor)**
- **clomipramine (Anafranil)**
- **protriptyline (Vivactil)**
- **maprotiline (Ludiomil)**
- **amoxapine (Asendin)**
- **trimipramine (Surmontil)**

**Fluvoxamine (Luvox) and clomipramine (Anafranil) are generally used for obsessive compulsive disorder.**

**Vilazodone (Viibryd) is also a serotonin 1A receptor partial agonist.**

**Maprotiline and amoxapine are classified as a tetracyclic, and heterocyclic antidepressant, respectively.**
### Antidepressants

#### INDICATIONS
Many antidepressants can be used to treat both depressive and anxiety disorders. Antianxiety drugs, such as benzodiazepines, however, are not a treatment for depression.

#### CLASS

<table>
<thead>
<tr>
<th>BLACK BOX</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Increased suicide risk in &lt;24 years old.</strong></td>
</tr>
<tr>
<td><strong>Increased levels may induce seizures.</strong></td>
</tr>
<tr>
<td><strong>Caution should be observed when bupropion is administered concomitantly with drugs that may inhibit its metabolism (e.g., cimetidine, PIs), increasing bupropion levels and increasing the risk of drug-induced seizures.</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>WARNINGS/</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Increased suicide risk in &lt;24 years old.</strong></td>
</tr>
<tr>
<td><strong>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.</strong> This drug is usually avoided. Associated with somnolence and dizziness, especially at higher doses.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CAUTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Caution should be observed when bupropion is administered concomitantly with drugs that may inhibit its metabolism (e.g., cimetidine, PIs), increasing bupropion levels and increasing the risk of drug-induced seizures.</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolized by CYP 2D6, 3A4, 2B6.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NNRTIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz reduces bupropion levels by 55%, titrate bupropion based upon response.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NRTIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>No published data about drug interactions specific to this combination.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nelfinavir and ritonavir inhibit 2B6 and may increase bupropion levels, increasing risk of drug-induced seizures. Lopinavir/ritonavir has been demonstrated to reduce bupropion levels 57%. Avoid with high dose ritonavir. Tipranavir/ritonavir reduces bupropion levels 46%.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CCR5</th>
</tr>
</thead>
<tbody>
<tr>
<td>No published data about drug interactions specific to this combination.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Elvitegravir/cobicistat/tenofovir/emtricitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td>May increase bupropion levels.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Elvitegravir/cobicistat/tenofovir/emtricitabine</th>
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<tbody>
<tr>
<td>May increase nefazodone levels.</td>
</tr>
</tbody>
</table>

*Patients with major depressive disorder (MDD) may experience worsening of depression and/or emergence of suicidal ideation/behavior and/or unusual changes in behavior.*
### CLASS
**Antidepressants**

### INDICATIONS
Many antidepressants can be used to treat both depressive and anxiety disorders. Antianxiety drugs, such as benzodiazepines, however, are not a treatment for depression.

### CATEGORY
<table>
<thead>
<tr>
<th>Category</th>
<th>SELECTED REPRESENTATIVES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotonin norepinephrine reuptake inhibitors (SNRIs)</td>
<td>mirtazapine (Remeron)**, venlafaxine (Effexor, Effexor XR), duloxetine (Cymbalta), desvenlafaxine (Pristiq)</td>
</tr>
</tbody>
</table>

| Other | trazodone (Desyrel, Oleptro) |

### BLACK BOX
**WARNINGS/CAUTIONS**

<table>
<thead>
<tr>
<th>Combo</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trazodone has been associated with increased incidence of priapism and arrhythmias.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PK</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duloxetine: Metabolized by CYP 2D6, 1A2</td>
<td>Trazodone: substrate of CYP 3A4</td>
</tr>
<tr>
<td>Mirtazapine: Metabolized by CYP 2D6, 1A2, 3A4. Venlafaxine: Metabolized by CYP 2D6, 3A4. Desvenlafaxine: Metabolized primarily by conjugation and to a minor extent, oxidation via CYP 3A4 pathway. CYP 2D6 is not involved with desvenlafaxine metabolism.</td>
<td></td>
</tr>
</tbody>
</table>

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<thead>
<tr>
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** Mirtazapine (remeron) is also classified as a tetracyclic compound.
### Antidepressants

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

### CLASS

**Antidepressants**

### CATEGORY

**Serotonin norepinephrine reuptake inhibitors (SNRIs)**

- Mirtazapine (Remeron),
- Venlafaxine (Effexor, Effexor XR),
- Duloxetine (Cymbalta),
- Desvenlafaxine (Pristiq)

### Cautions

<table>
<thead>
<tr>
<th>PI</th>
<th>PIs</th>
<th>Short-term administration of ritonavir (200 mg twice daily, 4 doses) increased the Cmax of trazodone by 34%, AUC increased 2.4 - fold, half-life increased by 2.2-fold, trazodone clearance decreased by 52%. Lopinavir/ritonavir increased trazodone levels 2.4 fold. Potential for drug interactions when trazodone is co-administered with PIs, especially ritonavir boosted PIs. If trazodone is used with CYP 3A4 inhibitor, a lower dose of trazodone should be considered. Use caution when combining; if using concurrently, initiate trazodone at lowest available dosage and monitor for adverse effects as listed in the cautions section.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCR5</td>
<td>No published data about drug interactions specific to this combination</td>
<td>No published data about drug interactions specific to this combination.</td>
</tr>
<tr>
<td>I</td>
<td>No published data about drug interactions specific to this combination.</td>
<td>Elvitegravir/cobicistat/tenofovir/emtricitabine likely to increase trazodone levels. If using concurrently, initiate trazodone at lowest available dosage and monitor for adverse effects.</td>
</tr>
</tbody>
</table>
CLASS
Antidepressants

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

CATEGORY
Monoamine oxidase inhibitors (MAOIs) isocarboxide (Marplan), tranylcypromine (Parnate), phenelzine (Nardil), selegiline transdermal (Emsam)

BLACK BOX
Increased suicide risk in <24 years old.* Other antidepressants, meperidine, tramadol, sumatriptan, dextromethorphan and linezolid should be avoided during concurrent MAOI treatment due to potential for serotonin syndrome or hypertensive crisis. Patients should also be counseled to avoid tyramine containing foods and beverages. Consult additional references for a complete list of medications and foods to be avoided with concurrent MAOI use. A 14 day washout period is recommended after discontinuation of an MAOI before initiating any therapy that may interact. Also a 14 day washout is required before initiating an MAOI when patients are discontinuing medications likely to interact.

WARNINGS/CAUTIONS
PK
Isocarboxide: Hepatic metabolism by oxidation via monoamine oxidase
Phenelzine: Hepatic metabolism by oxidation via monoamine oxidase
Selegiline: Metabolism via various CYP450 isoenzymes
Tranylcypromine: Hepatic metabolism by oxidation via monoamine oxidase

NNRTIs
No published data about drug interactions specific to this combination

NRTIs
No published data about drug interactions specific to this combination

PIs
No published data about drug interactions specific to this combination. Data with ketoconazole (a potent CYP 3A4 inhibitor) and transdermal selegiline demonstrated no effect on ketoconazole or selegiline levels.

CCR5
No published data about drug interactions specific to this combination

* Patients with major depressive disorder (MDD) may experience worsening of depression and/or emergence of suicidal ideation/behavior and/or unusual changes in behavior.
### CLASS
Anxiolytics and Sedative-Hypnotics

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

### CATEGORY

<table>
<thead>
<tr>
<th>Benzodiazepines</th>
<th>Non-Benazezapine sedative/hypnotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam (Niravam, Xanax), clonazepam (Klonopin), clorazepate (Tranxene), diazepam (Valium), flurazepam (Dalmane), lorazepam (Ativan), midazolam (Versed)*, oxazepam, temazepam (Restoril), triazolam (Halcion)</td>
<td>Buspirone (BuSpar), diphenhydramine (Benadryl) eszopiclone (Lunesta), ramelteon (Rozerem), zaleplon (Sonata), zolpidem (Ambien, Ambien CR, Edluar, Intermezzo, Zolpimist)</td>
</tr>
</tbody>
</table>

### BLACK BOX WARNINGS/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. **Alprazolam, clonazepam, clorazepate, diazepam and lorazepam are Pregnancy Category D. Temazepam and Triazolam are Pregnancy Category X.**

### PK

| Alprazolam, flurazepam, clonazepam, and diazepam are metabolized by CYP 3A4 | Buspirone: Substrate for CYP 3A4 |
| Midazolam, triazolam extensively metabolized by CYP 3A4 | Diphenhydramine: CYP2D6 |
| Clorazepate, lorazepam, oxazepam, temazepam are metabolized by glucuronidation and are free of drug interactions with inhibitors of CYP 3A4. Please see PI section for contraindications and caution with use. | Eszopiclone: Metabolized by CYP 3A4 and 2E1 |

### NNRTIs

Concurrent etravirine and diazepam may increase diazepam plasma concentrations. A decrease in diazepam dosage may be needed when using etravirine

### NRTIs

No published data about drug interactions specific to this combination.

*Midazolam is used for pre-procedural sedation or for use in ICU settings

**cont'd on next page**
### Class
**Anxiolytics and Sedative-Hypnotics**

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

<table>
<thead>
<tr>
<th>Benzodiazepines</th>
<th>Non-Benzodiazepine sedative/hypnotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam (Niravam, Xanax), chlordiazepoxide (Librium), clonazepam (Klonopin), clorazepate (Tranxene), diazepam (Valium), flurazepam (Dalmane), lorazepam (Ativan), midazolam (Versed)*, oxazepam, temazepam (Restoril), triazolam (Halcion)</td>
<td>buspirone (BuSpar), diphenhydramine (Benadryl), eszopiclone (Lunesta), ramelteon (Rozerem), zaleplon (Sonata), zolpidem (Ambien, Ambien CR, Edluar, Intermezzo, Zolpimist)</td>
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</table>

#### PIs
Oral midazolam and triazolam are metabolized by CYP 3A4, and are CONTRAINDICATED in combination with PIs due to the potential for serious and life-threatening reactions such as prolonged or severe sedation or respiratory depression. Single dose IV midazolam in controlled settings for sedation is acceptable. Flurazepam and clonazepam are also metabolized by CYP 3A4, and should be used with caution in combination with PIs due to the potential for serious reactions such as prolonged or severe sedation or respiratory depression. Alprazolam and diazepam likely to be increased by PIs, consider alternatives such as lorazepam, oxazepam or temazepam. Lorazepam, temazepam, and oxazepam are metabolized by glucuronidation and are free of interactions with PIs.

#### CCR5I
No published data about drug interactions specific to this combination.

#### Elvitegravir/cobicistat/tenofovir/emtricitabine
Elvitegravir/cobicistat/tenofovir/emtricitabine likely to increase levels of buspirone and zolpidem. Monitor for excess sedation.

*Midazolam is used for pre-procedural sedation or for use in ICU settings.*
### Mood Stabilizers and Anticonvulsants

#### Indications

Lithium carbonate (Eskalith, Lithobid) and divalproex sodium (Depakote, Depakote ER, Stavzor), gabapentin (Neurontin, Gabarone and Gralise), lamotrigine (Lamictal), levetiracetam (Keppra), oxcarbazepine (Trileptal), phenobarbital, phenytoin (Dilantin), pregabalin (Lyrica), tiagabine (Gabitril), and valproic acid (Depakene) are used as monotherapy and in combination with other drugs (ie atypical antipsychotics) for the treatment of acute mania and as maintenance treatment for bipolar disorder.

### Black Box Warnings/CAUTIONS

**Lithium toxicity** occurs above therapeutic serum levels. Long-term use can impair renal or thyroid function: regularly monitor serum lithium levels, creatinine, electrolytes and thyroid function tests. **Lithium is Pregnancy Category D**

**Divalproex sodium and valproic acid** have three black box warnings: hepatotoxicity (including fatalities) can occur usually within the first 6 months of therapy; teratogenicity, including neural tube defects; and life threatening pancreatitis. Lamotrigine has a black box warning for life threatening rashes, including Stevens-Johnson Syndrome, toxic epidermal necrolysis, and rash related fatalities. Carbamazepine, divalproex sodium, phenobarbital and valproic acid are Pregnancy Category D. Carbamazepine has two black box warnings: bone marrow suppression including aplastic anemia and agranulocytosis; and serious dermatologic reactions including severe and fatal cases of Stevens-Johnson Syndrome and toxic epidermal necrolysis. Monitor LFTs and CBC, and use caution when prescribing medications with overlapping toxicities.

### PK

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

Carbamazepine: CYP 3A4 enzyme inducer

Gabapentin: renal elimination.

Lamotrigine: undergoes glucuronidation

Phenobarbital: CYP 450 inducer

Phenytoin: metabolised by and induces CYP 2C9, CYP 2C19; also inducer CYP 2D6 and CYP 3A4

Topiramate: inhibits CPY 2C19

Valproic acid: inhibitor of glucuronidation

### NNRTIs

No published data about drug interactions specific to this combination.

Carbamazepine, phenobarbital, phenytoin: CYP 3A4 inducers, may decrease levels of PIs and NNRTIs. Avoid if possible.

Carbamazepine, phenobarbital, and phenytoin may decrease etravirine and rilpivirine drug levels and should not be used together.

*cont'd on next page*
**CLASS**

**Mood Stabilizers and Anticonvulsants**

**INDICATIONS**

Mood Stabilizers (lithium, anticonvulsants) are used as monotherapy and in combination with other drugs (ie atypical antipsychotics) for the treatment of acute mania and as maintenance treatment for bipolar disorder.

---

<table>
<thead>
<tr>
<th>CLASS</th>
<th>CATEGORY</th>
<th>NRTIs</th>
<th>PIs</th>
<th>CCR5I</th>
<th>II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lithium carbonate (Eskalith, Lithobid)</td>
<td>No published data about drug interactions specific to this combination.</td>
<td>Valproic acid: inhibitor of glucuronidation; study showed 100% increase in AUC of zidovudine, but dosage adjustment not recommended; monitor for zidovudine toxicity.</td>
<td>No published data about drug interactions specific to this combination.</td>
<td>Increase maraviroc dosage to 600mg twice daily when combined with carbamazepine, phenobarbital or phenytoin in the absence of a strong CYP3A4 inhibitor.</td>
</tr>
</tbody>
</table>

|       | Anticonvulsants | No published data about drug interactions specific to this combination. | Carbamazepine: may decrease levels of PIs; decreases indinavir levels resulting in virologic failure. Ritonavir increases carbamazepine levels. Avoid with PIs if possible. Phenytoin: Co-administration of LPV/r and phenytoin results in a 2-way drug interaction whereby both LPV/r and phenytoin concentrations are decreased ~ 30%. Once daily Kaletra not recommended with 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. Lamotrigine: When combined with LPV/r, lamotrigine levels were markedly decreased; increased lamotrigine dosage may be required. | No published data about drug interactions specific to this combination. | Carbamazepine, oxcarbazepine, phenobarbital and phenytoin may significantly reduce elvitegravir concentrations and should be avoided. |
### Antipsychotics

**CLASS**

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

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>First Generation - Typical</th>
<th>Atypical Antipsychotics</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>chlorpromazine (Thorazine), fluphenazine (Prolixin), haloperidol (Haldol), loxapine (Loxitane), mesoridazine (Serentil), molindone (Moban), perphenazine (Trilafon), pimozide (Orap)*, thioridazine (Mellaril), thiothixene (Navane), trifluoperazine (Stelazine)</td>
<td>aripiprazole (Abilify), asenapine (Saphris), clozapine (Clozaril, FazaClo), iloperidone (Fanapt), olanzapine (Zyprexa), lurasidone (Latuda), paliperidone (Invega), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon)</td>
</tr>
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</table>

### BLACK BOX WARNINGS/CAUTIONS

Pimozide side-effects are prominent in patients with HIV illness. In these patients, start with low doses and titrate slowly. 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).

**Elderly patients with dementia-related behavioral disorders are at increased risk of death compared to placebo.**

All drugs in class: Elderly patients with dementia-related behavioral disorders are at increased risk of death compared to placebo. Clozapine contains 5 black box warnings, which include seizures, myocarditis, cardiovascular effects, respiratory effects, and the risk of life-threatening agranulocytosis; avoid with other medications that 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 with prolongation of the QT interval, recent acute myocardial infarction, or uncompensated heart failure. Also CONTRAINDICATED in combination with other drugs that prolong the QT interval, such as pentamidine, mesoridazine, thioridazine, chlorpromazine, droperidol, or pimozide (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 CYP 3A4; caution is indicated when ziprasidone is co-administered with drugs that inhibit CYP 3A4.

*Pimozide (Orap) is indicated for severe Tourette’s syndrome.*

*cont’d on next page*
### Antipsychotics

**CLASS**

**Antipsychotics**

**INDICATIONS**

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

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<td>aripiprazole (Abilify), asenapine (Saphris), clozapine (Clozaril, FazaClo), iloperidone (Fanapt), olanzapine (Zyprexa), lurasidone (Latuda), paliperidone (Invega), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon)</td>
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**PK**

- Chlorpromazine: Metabolized by CYP 1A2, 2D6, 3A4; inhibits CYP 2D6.
- Fluphenazine: Metabolized by CYP 2D6; inhibits CYP 2D6.
- Haloperidol: Metabolized by CYP 2D6; inhibits CYP 2D6.
- Loxapine: metabolized via glucuronidation.
- Mezoridazine: renal elimination.
- Molindone: Metabolized by CYP 2D6.
- Perphenazine: Metabolized by CYP 2D6; inhibits CYP 2D6.
- Pimozide: metabolized via N-dealkylation.
- Thioridazine: Metabolized by CYP 1A2, 2D6; inhibits CYP 2D6.
- Trifluoperazine: Metabolized by CYP 1A2.

**NNRTIs**

No published data about drug interactions specific to this combination.

**NRTIs**

No published data about drug interactions specific to this combination.

*Pimozide (Orap) is indicated for severe Tourette’s syndrome.

**cont’d on next page**
## Antipsychotics

### CLASS

**Antipsychotics**

### INDICATIONS

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

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</table>

### PIs

- Pimozide: Prolongs the QT interval on EKG, and is CONTRAINDICATED in combination with PIs due to potential for serious and life-threatening reactions, such as cardiac arrhythmia. Ritonavir may increase levels of antipsychotics; caution with other PIs and ritonavir-boosted PIs. Dosage reductions may be required.
- Ritonavir may increase levels of antipsychotics; caution with other PIs and ritonavir-boosted PIs. Dosage reductions may be required.

### CCR5i

- No published data about drug interactions specific to this combination

### II

- Elvitegravir/cobicistat/tenofovir/emtricitabine may increase perphenazine and thioridazine levels. Use lowest dose.
- Elvitegravir/cobicistat/tenofovir/emtricitabine may increase risperidone levels. Use lowest dose.

*Pimozide (Orap) is indicated for severe Tourette’s syndrome.*
### CATEGORY

**Stimulants**
- amphetamine and dextroamphetamine (Adderall), armodafinil (Nuvigil), atomoxetine (Strattera), dexamphetamine (Dexedrine, ProCentra), lisdexamfetamine (Vyvanse), methamphetamine (Desoxyn), methylphenidate (Concerta, Metadate, Methylin, Ritalin), methylphenidate transdermal (Daytrana), modafinil (Provigil)

### WARNINGS/CAUTIONS

**All drugs in class except for armodafinil, modafinil**: Potential for drug dependency exists; avoid abrupt discontinuation in patients who have received for prolonged periods.

Adderall, Dexedrine: Use has been associated with serious cardiovascular events including sudden death in patients with pre-existing structural cardiac abnormalities or other serious heart problems (sudden death in children and adolescents; sudden death, stroke and MI in adults).

**PK**
- Amphetamine, dextroamphetamine: CYP 2D6 substrate and weak inhibitor
- Atomoxetine: Metabolized via CYP 2D6 and glucuronidation
- Methylphenidate: CYP 2D6 inhibitor
- Modafinil: Substrate for CYP 3A4

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

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

**PIs**
- Use of ritonavir may increase drug concentrations of modafinil, methylphenidate, amphetamine, and dextroamphetamine.

**CCR5**
- No published data about drug interactions specific to this combination.

**II**
- No published data about drug interactions specific to this combination.
## ST. JOHN’S WORT
(Hypericin, Hyperforin)
Derived from the plant, Hypericum perforatum.

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th><strong>BLACK BOX WARNINGS/CAUTIONS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>St. John’s Wort is contraindicated with concurrent PI therapy.</td>
<td></td>
</tr>
</tbody>
</table>

### PK
Inducer of CYP 3A4 and p-glycoprotein.

### NNRTIs
May reduce blood levels of NNRTIs. Induces metabolism of nevirapine; increased clearance ~35%. Do not co-administer with NNRTIs.

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

### PIs
May reduce levels of PIs, Indinavir levels reduced by 50-80% in volunteers treated with St. Johns Wort and indinavir. Do not co-administer with PIs.

### CCR5i
No published data about drug interactions specific to this combination.

### II
May reduce levels of elvitegravir and cobicistat. Do not co-administer with elvitegravir/cobicistat/tenofovir/emtricitabine
RESOURCES

The National AETC Program also includes the following services:

**National HIV/AIDS Clinicians Consultation Center:** 1-800-933-3413
Offering treating clinicians current HIV clinical and drug information and individualized, expert case consultation.

**Post-Exposure Prophylaxis hotline:** 1-888-448-4911
Providing consultation for occupational exposures.

**Perinatal HIV Hotline:** 1-888-448-8765

Providing resources (including curricula and lecture slide sets) on HIV disease treatment, education and data.

The following websites may be helpful in managing HIV infected patients:

- NY/NJ AIDS Education and Training Center [www.nynjaetc.org](http://www.nynjaetc.org)
- NYSDOH AIDS Institute Clinical Resources [www.hivguidelines.org](http://www.hivguidelines.org)
- Substance Abuse and Mental Health Services Administration [www.samhsa.gov](http://www.samhsa.gov)
- Addiction Technology Transfer Center [www.nattc.org](http://www.nattc.org)
- Harm Reduction Coalition [www.harmreduction.org](http://www.harmreduction.org)
RESOURCES

Data supporting this guide was gathered from various sources including:

Micromedex® Health Care Series
Lexicomp® Online
Facts and Comparisons 4.0®
Food and Drug Administration Approved Product Labels
Various HIV related conference abstracts, posters and oral presentations

Additional Information

For detailed references, training requests, or to order additional guides, please contact the NY/NJ AETC Central Office: (212) 304-5530.