

**Editor's Note:** Adverse drug reactions experienced by HMC, SCCA, or UWMC patients and reported via Patient Safety Net (PSN) are reviewed quarterly by the UW Pharmacy and Therapeutics Committee. Following the Committee's review, a literature-based companion article regarding some aspect of adverse drug reactions is published in this newsletter. It is hoped that these articles will be useful tools to remind prescribers of the fundamental principle of pharmacology that states, "No drug has only one action." By reminding prescribers to be alert to the appearance of undesired and unintended actions of drugs, therapeutic outcomes may be improved and adverse events minimized. If you have a patient you feel is experiencing an Adverse Drug Reaction, please report it via Patient Safety Net.

**ADR Focus** by Elizabeth Rudy, D.V.M., R.Ph.

## Antiretroviral Drugs and Neuropsychiatric ADRs

*An HIV-positive 40-year-old woman presents to the emergency department of a hospital with acute changes in her mental status. Her symptoms include disorientation, confusion, paranoid delusions, and insomnia. Following admission to the hospital, her laboratory values are found to be generally within the normal range, toxicological screens are negative, and no neurological abnormalities are found on exam. An MRI shows no evidence of cerebral atrophy, lymphoma, or toxoplasmosis. The woman has no previous history of mental illness. Six days prior to hospital admission, efavirenz (600mg/day) had been added to the woman's medication regimen, which also included zidovudine and lamivudine. Two days after starting the efavirenz, the woman first experienced episodes of confusion, agitation, and violent behavior. In the hospital, the efavirenz is discontinued and the patient is treated with haloperidol and lorazepam. Nevirapine is added to her HIV regimen in place of efavirenz. After 2 days in the hospital, the woman shows improvement in her mental status and is completely recovered by the seventh day of hospitalization. At a follow-up exam, 3 weeks after discharge, the woman, who had been previously removed from the psychotropic medications, shows no disturbances in mental status. In this case, the temporal association between the initiation of efavirenz therapy and the onset of the woman's psychotic symptoms may suggest a causal link.<sup>1</sup>*

With the current availability of potent antiretroviral drugs, such as the protease inhibitors (PIs), nucleoside reverse transcriptase inhibitors (NRTIs), and non-nucleoside reverse transcriptase inhibitors (NNRTIs) to treat HIV infection, the disease, in many cases, is considered a chronic condition that can be managed long term.<sup>2</sup> It has been postulated that neuropsychiatric complications from antiretroviral drug therapy may contribute to poor patient adherence to treatment regimens, result in changes to such regimens, cause treatment interruptions, and contribute to high-risk behaviors that may lead to the spread of HIV.<sup>2,3</sup> If such neuropsychiatric adverse drug reactions (ADRs) are not recognized and treated promptly, the patient's quality of life may be seriously affected. Additionally, the financial burden placed on the health care system will be significant, since HIV-infected patients with neuropsychiatric disorders usually require extensive health care resources to manage.<sup>2</sup> The purpose of this ADR Focus is to explore the association between antiretroviral drug therapy and neuropsychiatric adverse effects.

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Editor: Nelda A. Murri, Pharm.D. (206) 598-6612 – Asst. Editor: Elizabeth Rudy, D.V.M., R.Ph.  
Department of Pharmacy Services / School of Pharmacy

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**Neuropsychiatric complications may be secondary to the effect of the HIV virus itself, result from opportunistic infection, malignancy, unmasking of an underlying psychiatric disorder, or exposure to antiretroviral medications.**

**Neuropsychiatric adverse effects that have been observed in association with antiretroviral therapy range from sleep disorders to cognitive impairment to frank psychosis.**

**Nevirapine has been associated with adverse neuropsychiatric effects in only a few reports but is the NNRTI that exhibits the greatest CNS penetration (CSF/plasma ratio ~40%).**

**Both abacavir and zidovudine penetrate the CNS and have been associated with adverse neuropsychiatric effects in patients with HIV infection.**

Neuropsychiatric adverse effects have long been recognized as a complication of HIV infection.<sup>3</sup> These neuropsychiatric complications may be secondary to the effect of the HIV virus itself, result from opportunistic infection, malignancy, unmasking of an underlying psychiatric disorder, or exposure to antiretroviral medications.<sup>3,4</sup> The exact etiology of the patient's neuropsychiatric disorder may be difficult to determine because there could be overlap of the above-mentioned factors, making it difficult to determine the cause of the adverse symptoms observed in the patient. However, it is critical that the etiology of the patient's neuropsychiatric adverse symptoms be elucidated so that prompt and effective treatment can be instituted.

Neuropsychiatric adverse effects that have been observed in association with antiretroviral therapy range from sleep disorders to cognitive impairment to frank psychosis (see Table 1).<sup>3</sup> In most cases, neuropsychiatric symptoms usually occur within the first few weeks of therapy.<sup>3</sup> The adverse reactions observed may be influenced by factors such as drug-drug interactions that may alter metabolism of the antiretroviral drug, potentially increase its concentrations in the blood, and thereby increase the likelihood that adverse effects will be seen. Other factors that may explain the patient's symptoms include patient pharmacogenetic differences, food-drug interactions, and the prevalence of drug polytherapy.<sup>2,3</sup> Additionally, the drug's ability to penetrate the blood-brain barrier (BBB) and the percentage of plasma protein drug binding are factors that affect drug concentrations in the central nervous system and thereby influence the likelihood that adverse neuropsychiatric symptoms will be seen.<sup>4</sup>

**Table 1: Incidence and Examples of Antiretroviral-induced Neuropsychiatric ADRs<sup>3</sup>**

Drug (Incidence)	Type	Examples
<b>Abacavir</b> (2%)	NRTI	<ul style="list-style-type: none"> <li>• Headache, depression, anxiety, auditory hallucinations</li> <li>• Mutism, catatonia, homicidal behavior, persecutory delusions</li> <li>• Headache, night terrors</li> </ul>
<b>Efavirenz</b> (40-70%)	NNRTI	<ul style="list-style-type: none"> <li>• Irritability, suicidal ideation, aggression, antisocial behavior</li> <li>• Excitability, anxiety, insomnia</li> <li>• Mental confusion, amnesia</li> <li>• Mania, disinhibition, grandiosity</li> <li>• Post-traumatic stress disorder, intrusive recollections</li> <li>• Severe psychosis, confusion, aggression</li> <li>• Disorientation, paranoid delusions, violent behavior</li> <li>• Suicidal ideation, anhedonia, agitation</li> </ul>
<b>Nevirapine</b>	NNRTI	<ul style="list-style-type: none"> <li>• Cognitive impairment, impulsive suicidal attempts, persecutory delusions</li> <li>• Depression</li> </ul>
<b>Ritonavir</b> (< 2%)	PI	<ul style="list-style-type: none"> <li>• Hallucinations, abnormal thinking</li> <li>• Depression</li> </ul>
<b>Zidovudine</b> (5%)	NRTI	<ul style="list-style-type: none"> <li>• Delusions, auditory hallucinations</li> <li>• Mania</li> <li>• Agitation, bizarre behavior, psychosis</li> </ul>

Nucleoside reverse transcriptase inhibitors such as zidovudine and abacavir have been associated with adverse neuropsychiatric adverse effects in patients with HIV infection. Both drugs exhibit good CNS penetration.<sup>4</sup> There are 3 reports in the literature describing zidovudine monotherapy associated with neuropsychiatric symptoms such as delusions, hallucinations, psychosis, mania, and depression.<sup>2,3</sup> It is important to note that the doses of zidovudine these patients received were higher than the doses generally prescribed today. Additionally, these patients all had a family or personal history of an affective disorder. The above factors may have contributed to the neuropsychiatric adverse effects that occurred in these patients.<sup>3</sup> Published data and data from the manufacturer of zidovudine estimate that the neuropsychiatric adverse event rate for zidovudine is approximately 5%.<sup>3</sup> A very small number of reports describe depression,

**The rate of adverse neuropsychiatric symptoms associated with abacavir therapy is thought to be about 2%.**

**The neuropsychiatric side effects associated with exposure to PIs tend to be less prominent than those seen with the NRTIs or NNRTIs.**

**Delavirdine and efavirenz are highly protein-bound and exhibit poor CNS penetration. Nevertheless, efavirenz is associated with a relatively high incidence of CNS side effects.**

**It has been suggested that psychiatric manifestations are more likely to occur in efavirenz-treated patients with a history of a psychiatric disorder or substance abuse.**

**23% of patients who receive efavirenz for  $\geq 3$  months report moderate-to-severe global neuropsychiatric discomfort.**

**Some authorities recommend therapeutic drug monitoring for patients with a previous psychiatric history who are taking efavirenz.**

hallucinations, and suicidal ideation in patients on abacavir therapy.<sup>3</sup> The manufacturer reports a 2% rate of adverse neuropsychiatric symptoms associated with abacavir therapy.<sup>3</sup>

Protease inhibitors such as ritonavir are often used in combination with other antiretroviral agents to treat HIV infection. This class of drugs generally has very poor penetration into the CNS.<sup>4</sup> The manufacturer of ritonavir reports a  $<2\%$  incidence of psychiatric disorders, including hallucinations, depression, and abnormal thinking in patients taking the drug.<sup>3</sup> Treisman and Kaplin report that the neuropsychiatric side effects seen with exposure to PIs tend to be variable and less prominent than those seen with the NNRTIs or NRTIs.<sup>2</sup>

Non-nucleoside reverse transcriptase inhibitors include delavirdine, nevirapine, and efavirenz. Because delavirdine and efavirenz are highly protein-bound in the plasma, they exhibit poor CNS penetration. Of the NNRTIs, nevirapine has the greatest penetration into the CNS, with a CSF/plasma ratio reaching 40%.<sup>4</sup> Nevirapine has been associated with adverse neuropsychiatric effects in a few reports in the literature. Delirium and psychosis starting within the first 2 weeks of nevirapine therapy were reported in 3 patients.<sup>3</sup> However, these reports did not mention other factors, such as concurrently administered medications, that may have contributed to the magnitude of the adverse symptoms.<sup>3</sup> Another HIV-infected patient who was tolerating nevirapine developed mania and cognitive impairment when he was concurrently given clarithromycin for a respiratory infection.<sup>3</sup> When the clarithromycin was discontinued, the patient's neuropsychiatric symptoms resolved. It was theorized that because both drugs are metabolized by the same hepatic cytochrome P450 isoenzyme, a pharmacokinetic interaction was the underlying cause of the adverse symptoms.

In many cases, efavirenz is the preferred NNRTI for combination HIV treatment regimens. Reports in the literature suggest that 40–70% of patients receiving efavirenz experience an adverse CNS effect, with the most commonly observed being sleep disturbances.<sup>3</sup> However, only about 4% of patients on efavirenz therapy discontinue the drug because of CNS-associated adverse effects.<sup>3</sup> Although relatively rare, more serious neuropsychiatric complications, including depression, mania, aggressive behavior, paranoia, and psychosis, have been reported with efavirenz therapy.<sup>5</sup> It has been suggested that psychiatric manifestations are more likely to occur in efavirenz-treated patients with a history of a psychiatric disorder or substance abuse.<sup>2,4</sup> Two studies that looked at long-term (drug administration  $\geq 3$  months) neuropsychiatric complications in patients on efavirenz-based regimens reported mixed results. The first study compared 60 patients on efavirenz-based regimens to a similar number of patients who had been on a PI-based regimen for at least 1 year and found no significant difference in psychological status or quality of life between the 2 groups.<sup>6</sup> However, neuropsychiatric symptoms persisted in more than half of the individuals on long-term therapy, although the symptoms were generally mild and well tolerated. In the second study, results from a questionnaire designed to assess quality-of-life issues given to 174 patients who received efavirenz for  $\geq 3$  months showed that 23% of patients suffered moderate-to-severe global neuropsychiatric discomfort.<sup>7</sup>

Controversy exists as to the merits of therapeutic drug monitoring (documenting peripheral blood-drug concentrations), particularly in patients with a previous psychiatric history who are taking efavirenz. Some authors recommend the practice, citing a study by Marzolini et al. that showed a correlation between efavirenz drug plasma levels and adverse CNS effects.<sup>8</sup> In a 2005 study, Gutierrez et al. also linked plasma concentrations of

**Other authorities argue against therapeutic drug monitoring for efavirenz because of the potential for virological failure and resistance should patients receive stepped-down dosing in response to adverse CNS symptoms.**

**In some cases, genetic variation in the CYP2B6 G516T allele may contribute to the development of neuropsychiatric disorders following exposure to efavirenz.**

**Patients homozygotic for the CYP2B6 G516T allele have a median efavirenz AUC almost 3 times as high as patients without the mutation (wild type) and more than twice that of patients heterozygotic for the allele.**

**Health care providers need to be aware that neuropsychiatric complications have been attributed to all classes of antiretroviral drugs.**

efavirenz to adverse neuropsychiatric events.<sup>9</sup> Treisman and Kaplin point out that such monitoring may allow patients with psychiatric disorders such as depression to remain on efavirenz therapy while being treated for their psychiatric symptoms.<sup>2</sup>

However, Cespedes and Aberg discuss some of the problems associated with therapeutic drug monitoring.<sup>3</sup> They report that there is no established direct correlation between plasma efavirenz concentrations and adverse neuropsychiatric symptoms. They also point out that patients could potentially be placed at risk for virological failure and resistance if they receive suboptimal doses of the drug due to concern for the development of adverse CNS symptoms. Additionally, they mention that such testing is expensive and not always readily available in the United States. Finally, they state that therapeutic drug monitoring does not measure intracellular or CSF efavirenz drug concentrations, and that these levels are of particular importance in relation to a drug's propensity to cause neuropsychiatric effects.

Patient genetic factors that potentially influence the hepatic metabolism of efavirenz have been addressed in the recent medical literature. Pharmacogenetic studies show that individual genetic variations may play a significant role in neuropsychiatric disorders with exposure to efavirenz.<sup>10-12</sup> Efavirenz is metabolized primarily by the liver CYP isoenzyme 2B6 with some involvement of CYP3A4. Studies show that the single nucleotide polymorphism CYP2B6 G516T mutation is associated with significantly reduced function of the CYP2B6 enzyme.<sup>3</sup> This mutation has been shown to affect efavirenz concentrations in both Caucasians and African-Americans.<sup>3</sup>

Hasse et al. describe a case of psychosis attributed to impaired hepatic metabolism of efavirenz in a patient homozygous for the CYP2B6 G516T allele.<sup>13</sup> The patient's symptoms developed 1 month after the start of an efavirenz-containing medication regimen. Because the patient was also taking fluconazole at the time, her symptoms were thought to result from an interaction with this antifungal. However, when the fluconazole dose was reduced, the symptoms persisted. When the patient's efavirenz plasma concentration was measured, it was found to be >30 times the normal limit. Efavirenz was discontinued and the patient's symptoms resolved. Later, efavirenz was restarted at one-third of the recommended daily dose with no recurrence of the previously observed symptoms.

Results from another study that examined genetic variation with the CYP2B6 G516T allele showed that individuals homozygotic for the allele had a statistically significant median efavirenz area under the curve (AUC) almost 3 times as high as individuals without the mutation (wild type) and more than twice that of individuals heterozygotic for the allele.<sup>11,12</sup> The association of the CYP2B6 G516T allele and alterations in efavirenz concentrations with the drug's potential CNS toxicity was substantiated in a 2005 study by Rotger et al.<sup>10</sup> The homozygous variant of the allele was shown to be linked with both increased plasma and intracellular efavirenz concentrations—these 2 factors being strong predictors of the drug's potential to produce neuropsychiatric symptoms in treated individuals.

Health care providers need to be aware that neuropsychiatric complications have been attributed to all classes of antiretroviral drugs, although reports have occurred most commonly with the NNRTI efavirenz. Various strategies exist to help providers prevent and manage such adverse effects (see Figure 1). Prevention and management begin with educating both providers and patients about the potential for antiretroviral drugs to cause neuropsychiatric effects. Providers need to obtain detailed medication and psychiatric histories from patients prior to the initiation of therapy.<sup>3</sup> Obtaining such histories may aid in the proper selection of medications to minimize the likelihood that neuropsychiatric

**Patients on antiretroviral therapy need to be closely monitored for the development of symptoms that might indicate neuropsychiatric complications.**

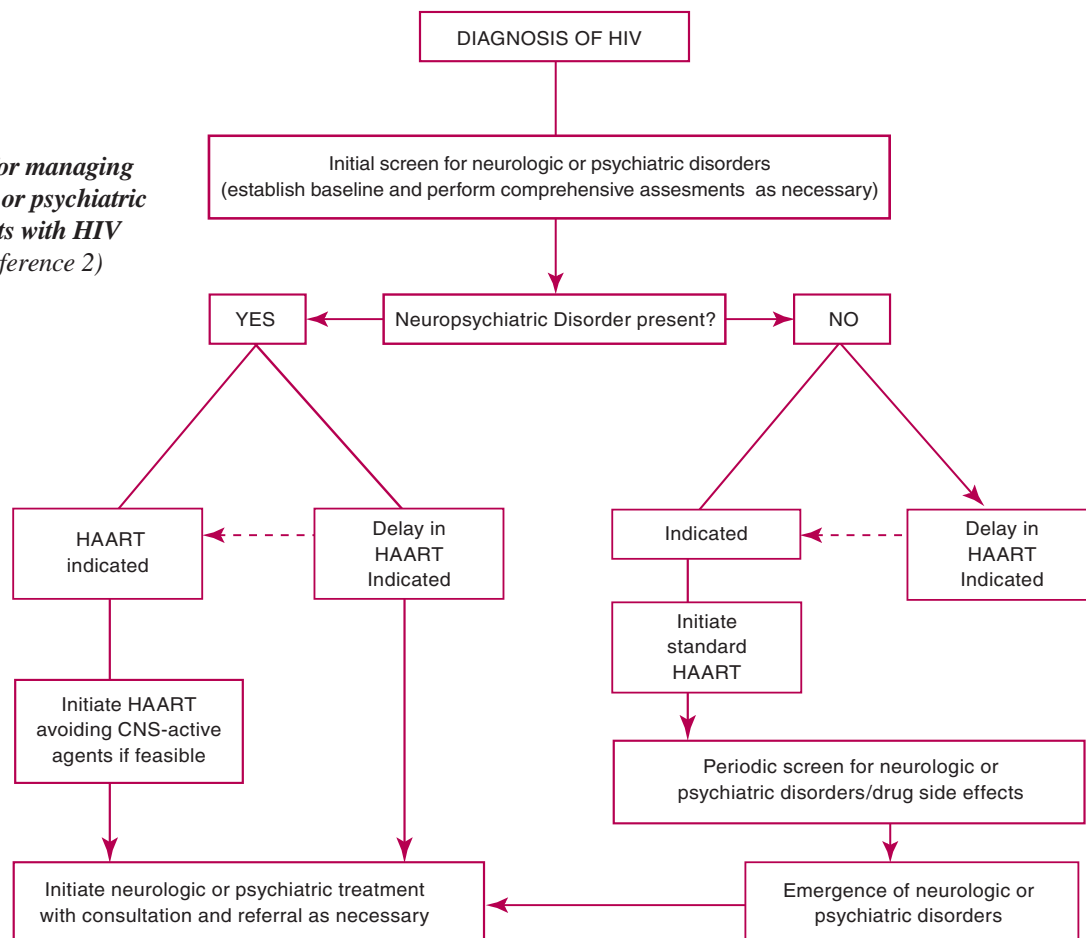
**Treatment options for neuropsychiatric complications of HIV therapy include monitoring the patient without changing the drug regimen, adding treatment for the neuropsychiatric symptoms without a change to the HIV regimen, and removing the offending medication from the patient's treatment regimen.**

symptoms will develop. Providers with patients on antiretroviral therapy need to closely monitor their patients for the development of symptoms that might indicate neuropsychiatric complications. If symptoms develop, determination of the specific etiology (disease-induced, drug-induced, etc.) of the symptoms is necessary in order to formulate and institute an effective treatment plan. If the symptoms are determined to be drug-induced, then the provider needs to determine the best approach for dealing with the symptoms.

Multiple options are available to treat drug-induced neuropsychiatric complications, depending upon the nature and the severity of the patient's symptoms and disease state. Some of the treatment options include monitoring the patient without changing the treatment regimen, treating the patient's neuropsychiatric symptoms while maintaining the current therapeutic drug regimen, and removing the offending medication from the patient's treatment regimen.

There is no single best approach to preventing and treating adverse neuropsychiatric reactions caused by antiretroviral drugs in HIV-infected patients.<sup>4</sup> Proper antiretroviral drug selection is a complex and critical matter that must be based on multiple factors.<sup>4</sup> The primary goal of treatment with antiretroviral medications is to provide the patient with the most clinically effective treatment regimen to manage the disease state while maintaining good quality of life. If neuropsychiatric symptoms occur during treatment, the risks versus benefits of continuing the current treatment regimen must be weighed, based on the medication's effectiveness at treating the infection, against the severity of the patient's neuropsychiatric symptoms.

*Figure 1: Strategy for managing comorbid neurologic or psychiatric disorders in patients with HIV (adapted from Reference 2)*



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# Antiretroviral Drugs and Neuropsychiatric ADRs (continued)

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**Newsletter:**

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**P&T Committee Actions, No meeting was held in Dec '06**



**DRUG INFORMATION CENTER  
Box 354735  
Seattle, WA 98195-4735**

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