AIDS Rev. 2009;11:103-9

Neuropsychiatric Symptoms Associated with Efavirenz: Prevalence, Correlates, and Management. A Neurobehavioral Review

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Abstract

The non-nucleoside analog reverse transcriptase inhibitor efavirenz is one of the most common components of HAART. Neuropsychiatric symptoms are frequently reported in patients taking efavirenz-based regimens. These symptoms are usually transient, although they can sometimes persist for up to two years after initiation of treatment. This review describes in detail the most common neuropsychiatric symptoms related to efavirenz, outlines relevant and recent findings on this agent, and suggests possible interventions based on neurobehavioral results. Different recommendations on the assessment of efavirenz-related adverse events are also provided. **(AIDS Rev. 2009;11:103-9)**

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Key words

Efavirenz. Antiretroviral therapy. HIV infection.

Introduction

Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI) that was approved in Europe in 1999[1]. Its chemical characteristics enable it to penetrate the blood-brain barrier and it is therefore considered a neuroactive drug[2]. Concentrations of efavirenz in the central nervous system (CNS) are higher than those of other antiretroviral drugs, and its half-life is long, approximately 40-55 hours[3]. As part of highly active antiretroviral therapy (HAART) regimens, it can be prescribed once daily in one pill, has no food intake restrictions, and is suitable for treatment-naive patients[4]. It forms part of simplification strategies and is one of the three compounds that compose Atripla® (Bristol-Myers Squibb and Gilead Sciences, USA), which was approved in the USA in 2006[5] and recently introduced in Europe[6]. Atripla® is recommended for treatment-naive HIV-infected patients and is taken once daily as a single pill. Thus, efavirenz has become one of the most important drugs in current HAART regimens, and is a common choice for treatment-naive patients. However, clinical practice and research have shown efavirenz to induce neuropsychiatric symptoms[7].

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Neuropsychiatric symptoms

Prevalence

Despite the quantity of research evaluating the association between efavirenz and neuropsychiatric disturbances, data on the prevalence of symptoms are in part contradictory. Some authors have observed neuropsychiatric symptoms in as many as half of all patients who initiate therapy with efavirenz[8,9], or even in more than half[10]. The symptoms are mild to moderate and basically consist of dizziness, hallucinations, nightmares, abnormal dreams, and insomnia. Most authors show that reactions appear after the first dose, and that

they usually disappear by the end of the first month of treatment[8,11,12].

There have been reports of discontinuation of therapy in 4-10% of cases as a result of these symptoms, mainly after the first month on treatment[13-16]. Other authors, however, report discontinuation in 46% of cases[17], approximately half of which are due to neuropsychiatric symptoms[9,17].

Similarly, there is some disagreement concerning the persistence of efavirenz-related disorders involving the CNS. Most studies describe early neuropsychiatric symptoms, whereas others report long-term symptoms. The Sensio study[9] concluded that adverse events were more frequent in the first month, but that they have often been observed to persist for longer (in 10-59% of patients)[13,18-20]. One study showed that they may even be present two years after starting therapy[21]. In some cases, investigators have observed the same symptoms from the first month of treatment, although it is emphasized that most of the symptoms induced by efavirenz usually disappear with time, unlike the symptoms induced by protease inhibitors[22]. Table 1 shows the most common long-term efavirenz-related adverse events, and they have been compared between patients receiving a stable efavirenz-based regimen and those receiving a protease inhibitor-based regimen for at least one year[21].

Despite finding neuropsychiatric symptoms in the short and long term, our group demonstrated that there were no differences in virologic outcome between patients taking efavirenz or not, and no differences in adherence to antiretroviral treatment[19]. We also assessed patients who had been taking efavirenz for at least two years and found no differences in emotional status or quality of life, although certain symptoms did persist, mainly depression, mood changes, irritability, dizziness, nervousness, impaired concentration, abnormal dreams, and somnolence[21]. Adherence levels were maintained. Recent results have confirmed maintained adherence, especially in patients who initiated a first antiretroviral combination including efavirenz. Therefore, these results differ from the rates of discontinuation mentioned elsewhere[23].

One of the factors leading to such disparate results is the diversity of the assessment methods used. Most published studies have used different methodologies to evaluate possible CNS toxicity. Some authors have applied validated methods with low sensitivity, whereas others have adapted their own non-validated questionnaires. Therefore, it has been recommended to evaluate the range of effects associated with efavirenz in groups; first, anxiety, depression, stress, and problems with daily concentration; second, abnormal dreams and sleep disturbances; and finally, dizziness and confusion[24]. Study populations have also varied, although this is probably not one of the main disadvantages because baseline characteristics have been extensively described in most cases and potential confounding factors have also been controlled statistically.

Nevertheless, despite the disparities observed in the data, there is a general consensus that neuropsychiatric effects are associated with efavirenz, at least in a considerable proportion of patients shortly after initiation of therapy, and in a variable proportion in the long term.

Table 1. List of the most common adverse events associated with efavirenz in the long term (compared with protease inhibitor-based regimens)

Adverse Events	EFV Group n (%)	PI Group n (%)	*P value*
Dizziness	13 (21.7)	3 (5)	**0.008**
Nephrolithiasis	–	4 (6.7)	0.118
Polineuropathy	15 (25)	11 (18.3)	0.402
Perioral paresthesia	–	1 (1.7)	0.999
Gastrointestinal disorders	11 (18.3)	18 (30)	0.122
Fatigue	22 (36.7)	15 (25)	0.185
Difficulty in erection	12 (20)	11 (18.3)	0.817
Loss of libido	14 (23.3)	11 (18.3)	0.530
Headaches	14 (23.3)	8 (13.3)	0.170
Sadness	22 (36.7)	9 (15)	**0.008**
Mood changes	16 (26.7)	7 (11.7)	**0.041**
Irritability	18 (30)	6 (10)	**0.007**
Euphoria	2 (3.3)	1 (1.7)	0.157
Lightheadedness	17 (28.3)	5 (8.3)	**0.005**
Nervousness	18 (30)	7 (11.7)	**0.015**
Impaired concentration	16 (26.7)	7 (11.7)	**0.041**
Abnormal dreams	29 (48.3)	1 (1.7)	**< 0.001**
Difficulty in sleeping	17 (28.3)	11 (18.3)	0.213
Somnolence	15 (25)	6 (10)	**0.034**
Nausea	9 (15)	6 (10)	0.427

Statistically significant differences in univariate comparisons between the EFV group and the PI group are shown in bold.
EFV: efavirenz; PI: protease inhibitor.
Extracted from Fumaz, et al., 2005[21].

Correlates

It has been suggested that elevated plasma concentrations of efavirenz could be responsible for the onset of neuropsychiatric symptoms[13-15]. Fumaz, et al.[21] assessed this hypothesis after two years of treatment with efavirenz and did not find such an association. However, the pharmacokinetic evaluation was performed two years after initiation of therapy; therefore, only those patients who adequately tolerated therapy until that time were included in data analyses, unlike those who could have presented major intolerance to efavirenz and interrupted treatment early. Similarly, a recent study in Japan observed no association between efavirenz and the onset of neuropsychiatric symptoms, or differences in symptoms between patients with high and low plasma drug levels[25]. It is relevant that, in both studies, data were not compared at different time points after initiation of therapy.

One interesting point is the well-established relationship observed between insomnia and exposure to efavirenz, since some authors have revealed a strong association between higher efavirenz levels in plasma and the onset of insomnia[26,27]. Similarly, other authors have suggested that sleep disturbances could explain the presence of neuropsychiatric symptoms[16].

The A5097s study[12], a substudy of protocol ACTG 5095[28], prospectively evaluated the existence of CNS symptoms in 303 patients, 283 of whom completed the study. The primary endpoint was an assessment of CNS toxicity associated with efavirenz by evaluating anxiety, depression, sleep disturbances, symptoms associated with efavirenz, and neurocognitive functioning. Plasma concentrations of efavirenz were also monitored. Clifford, et al.[12] published the results of this study and showed that anxiety levels increase to the same degree in both the efavirenz and the non-efavirenz arms, observing no significant differences between groups or in global outcome, although the rates were high, especially at six months of follow-up. The plasma concentrations of efavirenz did not correlate with anxiety scores at any time during the study and the rates for depression were also similar between groups, with no significant differences. This correlated with plasma concentrations only at week 4. As for sleep disturbances, patients taking efavirenz showed worse scores at week 1, and no relationship with efavirenz levels in plasma was observed. The authors also found differences in the global score, including characteristic symptoms associated with efavirenz at week 1, and detected a link with drug concentrations. Finally, in neurocognitive functioning, the results were similar between groups: antiretroviral treatment improved functioning in the whole sample (in the efavirenz arm and the non-efavirenz arm). Nonetheless, there were some limitations in the study design. First, the existence of emotional disorders was not assessed at baseline. Second, switching to nevirapine in patients the clinician considered suitable candidates for this drug was not monitored. Third, neurocognitive functioning was explored using an excessively brief neuropsychological battery, which probably did not include relevant information related to possible deficits in other neurocognitive areas.

Table 2 summarizes the most relevant characteristics of the published studies that focus on this controversial association between plasma drug levels and neuropsychiatric symptoms.

The existence of interindividual variables has also been proposed as one explanation for the discordant data. First, genetic differences have been suggested as determinants for the appearance of symptoms (e.g. hypersensitivity reaction to efavirenz)[29]. Indeed, efavirenz-induced neuropsychiatric symptoms have been revealed in African American patients, in contrast to European American or Hispanic patients who presented low rates[30]. Another example is seen in data derived from study ACTG 5095[31], which showed racial differences between white and black patients for virologic failure after initiating therapy with efavirenz. Higher rates of treatment failure were found in black patients, and this may have been due to poor adherence. Reduced quality of life was also observed, although that finding did not correlate with poor adherence. In an interesting study carried out on mice, O'Mahony, et al.[32] found biological correlates that linked efavirenz to a major presence of depression and stress, as well as a certain genetic predisposition. The connections found seemed to be mediated by high concentrations of proinflammatory chemokines, and by an increase in levels of tumor necrosis factor-alpha. The main conclusion of this study was the existence of evidence of disease, which might explain the association between efavirenz and emotional changes, thus revealing the potential usefulness of antidepressant therapy.

Some authors have suggested female sex as a risk factor for toxicity induced by efavirenz[33]. This has been confirmed by Spire, et al.[16], who only evaluated patients who discontinued therapy with efavirenz. They found that the variables most related to this change were female sex, unemployment, steady partner, and,

Table 2. Summary of previous reports assessing efavirenz-containing regimens: efficacy, plasma concentrations, and neuropsychiatric symptoms

	Molina, et al.	Hartmann, et al.	Marzolini, et al.	Núñez, et al.	Gallego, et al.	Lochet, et al.	Fumaz, et al.	Gutiérrez, et al.	Rihs, et al.	Takahashi, et al.
Study characteristics										
Design	Open-label study	Open-label, multicenter study	Open-label study	Open-label study	Open-label	Open-label, multicenter study	Randomized, two-arm, controlled study	Open-label study	Retrospective, case-control study	Open-label study
Patients receiving EFV	40	314	130	51	18	174	60	17	33	69
Age (years) mean ± SD	33 ± 6	–	–	–	42 ± 7	40[a]	41 ± 8	40*	43 ± 10	40 ± 11
Male (n %)	35 (88%)	33 (73%)	93 (72%)	–	15 (84%)	136 (78%)	45 (75%)	14 (82%)	–	60 (87%)
Follow-up (weeks) mean ± SD	24	80	12-72†	12-24†	24 ± 12	58*	91 ± 39	72*	56 ± 20	76 ± 64
Efficacy										
Treatment success (n %)	38 (95%)	Experienced: 56% Naive: 82%	99 (76%)	–	–	–	44 (73%)	13 (76%)	–	61 (88%)
Treatment discontinuation associated with EFV (n %)	0 (0%)	37 (12%)	–	–	–	–	–	4 (23%)	–	4 (6%)
Plasma concentrations										
EFV plasma levels (µg/ml) mean ± SD	–	–	2.19* (0.12-15.23)†			–	0.64-6.0†	4.12 ± 2.51	–	2.43 ± 1.31
With CNS side effects (µg/ml) mean ± SD	–	–	–	Patients with insomnia, 4.9 (0.3-12.5)†	Patients with insomnia, 4.3 ± 2.9	–	2.5 ± 1.1	5.10 ± 2.15	–	2.45 ± 1.08
Without CNS side effects (µg/ml) mean ± SD	–	–	–	Controls, 3.7 (3-35)†	Controls, 2.7 ± 0.7	–	2.7 ± 0.7	2.79 ± 1.31	–	2.42 ± 1.40
Neuropsychiatric assessment										
Assessment method	–	–	–	–	Insomnia: PSQI	Self-reported questionnaire	Self-reported questionnaire	Semistructured interview	DASS, CFQ, Self-reported questionnaire	SCL-90-R, Psychological interview
Patients with neuropsychiatric symptoms (n %)	29 (73%)	75 (24%)	13 (10%)	–	Insomnia: 13 (72%)	71 (41%)	32 (54%)	10 (59%)	Anxiety, 6 (19%); depression, 3 (9%); unusual dreams, 19 (58%)	19 (28%)
Neuropsychiatric symptoms	Insomnia, abnormal dreaming, depression, mood changes, dizziness, asthenia	Dizziness, headache, depression, nightmare, nervousness	Light-headedness, feeling faint, dizzy, drunk, 'out of control', or restless, nightmares, dreams, impaired concentration	–	–	Morning tiredness, abnormal dreams, memory disorders, daytime drowsiness, nocturnal waking, impaired concentration, sadness	Dizziness, sadness, mood changes, irritability, lightheadedness, nervousness, impaired concentration, abnormal dreams, somnolence	Dizziness, insomnia, impaired concentration, depression, obsessive disorder, drowsiness, irritability, light-headedness	–	Abnormal dreams, dizziness, nervousness, difficulty in sleeping, loss of libido, hallucinations

Omitted information is not reported by authors or not applicable in this table.
*Median; †range.
EFV: efavirenz; SD: standard deviation; CNS: central nervous system; PSQI: Pittsburgh Sleep Quality Index; DASS: Depression, Anxiety and Stress Scale; CFQ: Cognitive Failures Questionnaire; SCL-90-R: Symptoms Check List-90-Revised.

Table 3. Factors associated with discontinuation among patients taking efavirenz

	Continuing EFV (n = 175) n (%)	Discontinued EFV (n = 152) n (%)	OR	IC [50%]	AOR	IC [50%]
Female gender	30 (17)	46 (30)	2.1	[1.2-3.7]	2.2	[1.2-3.8]
Unconfortable housing	94 (54)	102 (67)	1.8	[1.1-2-8]		
Unemployment	67 (38)	83 (55)	1.9	[1.2-3.1]	1.8	[1.1-2.8]
Principal partner (pp)						
No pp	85 (49)	60 (40)	1		1	
Not living with the pp	26 (15)	27 (18)	1.5	[0.8-2.8]		
Living with the pp	62 (36)	62 (42)	1.4	[0.9-2.3]	1.6	[1.0-2.6]
Cocaine or heroine use	10 (6)	22 (14)	2.2	[0.9-5.4]		
Episodes of depression						
No	96 (55)	55 (36)	1		1	
Once	51 (29)	47 (31)	1.6	[0.9-2.8]	1	
Several times	28 (16)	50 (33)	3.1	[1.7-5.7]	2.6	[1.5-4.5]

EFV: efavirenz; OR: odds ratio; IC: interval of confidence; AOR: adjusted odds ratio.
Extracted from Spire, et al., 2004[17].

to an even greater extent, a history of depression (see table 3). Other investigators have reached the same conclusion[7,34]. However, the study by Spire, et al. had important limitations: data were self-reported, and the design was cross-sectional, which made it impossible to observe efavirenz-related depressive episodes at the beginning of treatment. In any case, the above-mentioned studies continue to be relevant when attempting to determine possible differences in the consequences of treatment with efavirenz.

In summary, the most recent reviews indicate that although neuropsychiatric complications may lead patients to discontinue therapy with efavirenz, the nightmares, irritability, and problems of concentration usually disappear after the first weeks of treatment[7]. Nevertheless, although some complications may be associated with long-term administration of this drug, the factors explaining the onset of neuropsychiatric symptoms could be related to previous psychological disorders, or to the neuropathogenic effect of the virus itself. Therefore, these issues should be considered in the evaluation of patients receiving efavirenz, and may help us to determine whether there is an association with this antiretroviral drug.

Neurobehavioral interventions

To date, very little has been published on the use of neurobehavioral strategies for the management of adverse events related to efavirenz. Most evidence comes from presentations at international conferences and from studies examining the neurobehavioral aspects of antiretroviral therapy. At the International AIDS Conference held in Bangkok in 2004, Thomas, et al.[35] presented a study in which they examined the response to a psychological intervention program in groups of patients who initiated therapy with efavirenz. Although the authors did not specifically describe the program applied, they reported that it was based on psychoanalytic orientation and consisted of techniques for coping with CNS-related adverse events, mainly sleep disturbances. A total of 89 patients initiated treatment with efavirenz and 30 were included in the follow-up. Table 4 shows

Table 4. Results of the continuation of therapy with efavirenz in patients exposed and not exposed to the psychological program

	Exposed (n = 30)	Non-exposed (n = 59)	*P value*
Rate of drop-out			
Overall	7 (23.3%)	24 (40.7%)	0.081
At 1 week	0 (0.0%)	1 (1.7%)	0.663
At 1 month	0 (0.0%)	6 (10.2%)	0.078
At 3 months	1 (3.3%)	3 (25.0%)	0.009
At 6 months	3 (10.3%)	20 (51.3%)	0.000
Time on Efavirenz (days)	363 ± 153	182 ± 153	0.000

Extracted from Thomas, et al., 2004[35].

Table 5. Comparison of adherence and undetectable viral load between experimental and control groups

	Patients with adherence ≥ 95% N (% intention to treat) (% as treated)			Patients with HIV-RNA ≤ 400 copies N (% intention to treat) (% as treated)		
	Experimental group	**Control group**	***P* value**	**Experimental group**	**Control group**	***P* value**
Week 4	37	35		12	15	
	(67)	(57)	NS	(22)	(25)	NS
	(92.5)	(87.5)	NS	(48)	(75)	NS
Week 24	28	24		22	17	
	(51)	(39)	NS	(40)	(28)	NS
	(90)	(75)	NS	(79)	(65)	NS
Week 48	32	25		32	25	
	(58)	(41)	0.064	(58)	(45)	0.062
	(94)	(69)	0.008	(89)	(66)	0.026

NS: Not significant.
Extracted from Tuldrà, et al., 2000[36].

the results obtained. Patients who had received psychological intervention responded better to therapy with efavirenz, and this fact correlated with the continuity of the treatment. A total of 31 patients from the total sample interrupted treatment (23.3% of patients in the experimental group, and 40.7% of the control group; p = 0.081). The greater benefit associated with discontinuation was observed after the first month of therapy, although the clearest difference between groups was observed in month 6 (month 1, 0 vs. 10.2%, respectively; month 3, 3.3 vs. 25%; month 6, 10.3 vs. 51.3%; p < 0.001). The mean time on therapy with efavirenz was also significantly higher in the experimental group (363 vs. 182 days; p < 0.001).

These data show that, both in research and in clinical practice, neurobehavioral strategies can significantly improve tolerability to antiretroviral treatment. In a previous study, we showed how the use of a psychological therapy, more specifically an approach-based cognitive-behavioral therapy, could improve adaptation to antiretroviral therapy[36]. The intervention induced better adherence to treatment, and this correlated with a greater rate of virologic success in those patients who underwent psychological therapy. Table 5 displays these results. Thus, the hypothesis that neurobehavioral interventions can improve tolerability to antiretroviral treatments seems valid, and the literature contains ample evidence of how psychological interventions, which may not necessarily be systematic or structured, can improve adherence[37,38].

Several neurobehavioral strategies could prove effective for improving adaptation to antiretroviral therapy and tolerability of adverse events. Such strategies might include providing information on antiretroviral treatment and HIV infection, consideration of patient attitude to therapy, examination of the effect of the disease on the patient's daily life, prevention and management of adverse events, and resolution of concomitant psychological problems. In any case, an evaluation of emotional status appears to be vital, as does prevention as a means of managing adherence. Therefore, structured neurobehavioral programs and other psychological interventions of all types could prove effective when administering antiretroviral therapy.

Conclusions

Neuropsychiatric adverse events are not infrequent in patients taking efavirenz. They consist mainly of sleep disturbances, mood disorders, and symptoms such as dizziness or confusion. In most patients, these effects appear throughout the first month of treatment and generally disappear in the short term. However, they may also persist over time, and the results of the studies evaluating adverse effects are partially disparate. A correct assessment of these effects requires an evaluation of previous emotional status and of other relevant variables such as emotional disorders and assessment methods.

Neurobehavioral interventions can improve tolerability and adherence. Given that most adverse events occur during the first month of treatment, neurobehavioral interventions, which may be as simple as providing

suitable information, can help patients adapt to their treatment.

Long-term results are available. Although they do not only apply to efavirenz-based antiretroviral regimens, they do provide evidence that psychological interventions can improve adherence. Our experience is consistent with these results and highlights the value of neurobehavioral follow-up, both in patients starting therapy and in those who have been taking it for many years.

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