

ORIGINAL RESEARCH

Long-term assessment of neuropsychiatric adverse reactions associated with efavirenz

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Objectives

The Sensio study objectives were to assess the outcome of neuropsychiatric adverse reactions (NPAR) that develop after initiation of efavirenz (EFV) therapy, to ascertain the late NPAR after a 3-month treatment period, to evaluate the impact of NPAR on patients' quality of life (QoL) in a real-life population.

Methods

During a 6-month period, consecutive HIV-infected adult outpatients receiving an ongoing EFV therapy for at least 3 months were asked to fill in a specifically designed self-administered questionnaire addressing sleep disturbances, behavioural changes, mood disturbances, anxiety, cognitive disorders, hallucinations, dizziness and the general impact on patients' QoL.

Results

A total of 174 questionnaires were analyzed. The main late emergent NPAR were sleep disorders: abnormal dreams 24.7%, nocturnal waking 19.6%, trouble falling asleep 17.8%; cognitive disorders: memory disorders 23.0%, impaired concentration 18.9%; anxiety 15.5%; mood disorders: sadness 19.3%, suicidal ideations 9.2%. Global neuropsychic discomfort was moderate to severe in 23% of patients after a 3-month treatment period.

Conclusion

NPAR occur mainly during the first month of EFV therapy but often persist thereafter. A significant percentage of patients reported suicidal ideations at the time of the study. Our results suggest the need for routine screening for NPAR among patients receiving EFV therapy and better management.

Keywords: adverse reactions, depression, efavirenz, neuropsychiatric, quality of life

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Introduction

Neuropsychiatric adverse reactions (NPAR) commonly occur within the first days following initiation of treatment with efavirenz (EFV) and resolve in 2–4 weeks of EFV use [1]. NPAR have been reported in about 50% of the patients treated with this drug in clinical trials. Central nervous system disturbances range from dizziness to hallucinations, including frequent nightmares, unusual dreams and insomnia. Symptoms are usually mild to moderate [2]. The Sensio study was focused on the NPAR self-reported by

HIV-positive patients with an ongoing antiretroviral regimen including EFV in real-life conditions. The objectives were to assess the outcome of NPAR that develop after initiation of EFV therapy, to ascertain the late adverse reactions of EFV after a 3-month treatment period, and to evaluate the NPAR impact on patients' quality of life (QoL).

Patients and methods

During a 6-month period, in three HIV outpatient units, all consecutive HIV-infected adults receiving an ongoing EFV therapy for at least 3 months were concerned by the Sensio study. Capacity to understand and answer a questionnaire in the French language was required. Patients meeting these inclusion criteria were asked by investigators to complete

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the Sensio questionnaire (SQ) and left free to choose whether they accepted or not. Physicians or patients' relatives helped them to complete the questionnaire if necessary.

The SQ was an anonymous self-administered questionnaire specifically designed in order to characterize and measure NPAR related to EFV. The wording of the questions was chosen on the basis of EFV safety data in clinical trials [3–5], the Diagnostic and Statistical Manual of Mental Disorders (DSM IV) [6] and the General Health Questionnaire (GHQ-28) [7]. First, patients had to report their current antiretroviral treatment and the date of EFV initiation. Then, patients assessed their own psychological and physical status by completing the following items: sleep disturbances (trouble falling asleep, nocturnal waking, early morning waking, nightmares, perturbed dreams, day-time drowsiness, fatigue) behavioural changes (euphoria, irritability, tobacco alcohol and illicit drug use changes, agitation, aggressiveness) anxiety (restlessness, fits of anxiety) cognitive disorders (impaired concentration, memory disorders) mood disturbances (sadness, emotional instability, morning tiredness, eating disorders, suicidal ideation) hallucinations, dizziness (dizziness after receiving EFV, feeling of drunkenness) headaches, pharmacological management of NPAR. Neuropsychiatric symptoms were scored according to frequency, 1 = never, 2 = occasional (once or twice per month), 3 = frequent (three or four times per month), 4 = very frequent (more than four times per month). For each item, patients had to compare their health status before starting EFV therapy, during the first month of treatment and within the month previous to answering the SQ. Three items were assessed as follows: behavioural changes after receiving EFV during the first month (yes or no), at the time of the study (yes or no); sexual activity disturbances during the first month (yes or no), at the time of the study (yes or no); total sleep duration after receiving EFV (unchanged, diminished, increased). Finally, patients estimated the general impact on QoL scored according to severity (1 = absent, 2 = mild, 3 = moderate, 4 = severe) and asked whether they wish to stop EFV or not because of NPAR.

The questionnaires with more than 60% of missing answers were removed. Two items addressing symptoms of the same kind were regrouped: nocturnal and early morning waking, restlessness and fits of anxiety. In the final analysis of NPAR, we excluded patients who presented frequent or very frequent (scores of 3 and 4) symptoms before initiation of EFV therapy. We then defined early emergent NPAR (i.e. occurring during the first month and not persisting thereafter), long-lasting NPAR (i.e. occurring during the first month and persisting thereafter) and late-onset NPAR (i.e. occurring for the first time at least 1 month after initiation of treatment).

Results

A total of 221 patients were asked to fill in the SQ between June and November 2001. Demographic features of the population were as follows: male [176 (79.6%)], median age 40 years (range 18–66), median duration of HIV infection 9.3 years (range 0.4–18.2). Median time between first HIV-positive test and first antiretroviral regimen was 4.2 years (range 0.1–14.7). For 33 patients, EFV was administered as first-line treatment.

Twenty-two SQ were left out for the following reasons: five were incomplete, 12 were not returned, five patients refused to answer. Of the 199 analyzable questionnaires, 174 met the 3-month treatment duration condition. Characteristics of these patients were as follows: male [136 (78.2%)], median age 40 years [range 23–65], median weight 66 kg [range 40–103]. Patients' antiretroviral regimens including EFV were: bitherapy [1 (0.5%)], tritherapy [124 (71.3%)], quadritherapy [41 (23.6%)], pentatherapy [8 (4.6%)]. EFV was associated with at least one protease inhibitor in 19% ($n=33$) regimens. Median duration of EFV therapy was 14.5 months (range 3–43.5).

The percentage of frequent or very frequent NPAR reported in our population before EFV initiation, during the first month and at the time of the study were shown in Table 1. The main late emergent NPAR related to EFV therapy reported were: abnormal dreams [42 (24.7%)], morning tiredness [44 (25.3%)], memory disorders [40 (23.0%)], nocturnal waking [34 (19.6%)], restlessness [31 (17.7%)], daytime drowsiness [35 (20.1%)], impaired concentration [33 (18.9%)], trouble falling asleep [31 (17.8%)], sadness [32 (18.3%)], irritability [25 (14.3%)], agitation [20 (11.5%)], emotional instability [21 (12.1%)], suicidal ideation [16 (9.2%)], aggressiveness [17 (9.8%)], headaches [13 (7.5%)], feeling of drunkenness [12 (6.9%)], euphoria [11 (6.3%)], hallucinations [10 (5.7%)]. The distribution of late-onset and long lasting NPAR is shown in Table 2. Most of the NPAR appeared during the first month of treatment and continued for at least 3 months afterwards.

At the time of the study, 13.2% ($n=23$) of patients reported having frequent or very frequent suicidal ideation (grade 3 and 4 according to our own scale). Among these 23 patients, 18 (10.3%) did not report having this symptom before starting EFV, four patients did and there was one missing answer. This depressive symptom was associated with other signs (scores of 3 and 4) such as fits of anxiety ($n=17$), sadness ($n=17$), trouble falling asleep ($n=13$), morning tiredness ($n=12$), impaired concentration ($n=12$) and memory disorders ($n=11$).

Eighteen patients (10.3%) reported having needed symptomatic treatment for one or more NPAR at the time of the study: 11 from the first month, and seven after the first

Table 1 Frequent or very frequent neuropsychiatric symptoms in our population expressed as percentage, without excluding patients who presented frequent or very frequent symptoms before efavirenz (EFV) initiation

Neuropsychiatric symptoms	Before EFV initiation	During the first month	At the time of the study
Trouble falling asleep	17.2 (<i>n</i> = 30)	36.8 (<i>n</i> = 64)	28.7 (<i>n</i> = 50)
Nocturnal waking or early morning waking	19.5 (<i>n</i> = 34)	40.2 (<i>n</i> = 70)	33.9 (<i>n</i> = 59)
Nightmares	2.3 (<i>n</i> = 4)	33.9 (<i>n</i> = 59)	17.8 (<i>n</i> = 31)
Abnormal dreams	4 (<i>n</i> = 7)	43.7 (<i>n</i> = 76)	28.7 (<i>n</i> = 50)
Daytime drowsiness	14.4 (<i>n</i> = 25)	36.8 (<i>n</i> = 64)	30.5 (<i>n</i> = 53)
Fatigue	24.1 (<i>n</i> = 42)	44.3 (<i>n</i> = 77)	40.8 (<i>n</i> = 71)
Restlessness or fits of anxiety	24.1 (<i>n</i> = 42)	43.1 (<i>n</i> = 75)	39.1 (<i>n</i> = 68)
Aggressiveness	9.8 (<i>n</i> = 17)	19 (<i>n</i> = 33)	16.7 (<i>n</i> = 29)
Irritability	13.8 (<i>n</i> = 24)	32.8 (<i>n</i> = 57)	25.3 (<i>n</i> = 44)
Agitation	12.1 (<i>n</i> = 21)	21.8 (<i>n</i> = 38)	22.4 (<i>n</i> = 39)
Euphoria	5.2 (<i>n</i> = 9)	24.1 (<i>n</i> = 42)	10.3 (<i>n</i> = 18)
Sexual activity disturbances	–	23.6 (<i>n</i> = 41)	31.6 (<i>n</i> = 55)
Sadness	16.1 (<i>n</i> = 28)	31 (<i>n</i> = 54)	31 (<i>n</i> = 54)
Emotional instability	7.5 (<i>n</i> = 13)	20.7 (<i>n</i> = 36)	18.4 (<i>n</i> = 32)
Morning tiredness	12.6 (<i>n</i> = 22)	37.9 (<i>n</i> = 66)	34.5 (<i>n</i> = 60)
Suicidal ideations	5.7 (<i>n</i> = 10)	20.1 (<i>n</i> = 35)	13.2 (<i>n</i> = 23)
Impaired concentration	8.6 (<i>n</i> = 15)	29.3 (<i>n</i> = 51)	27 (<i>n</i> = 47)
Memory disorders	8.6 (<i>n</i> = 15)	27.6 (<i>n</i> = 48)	32.2 (<i>n</i> = 56)
Dizziness	–	29.9 (<i>n</i> = 52)	12 (<i>n</i> = 21)
Feelings of drunkenness	1.7 (<i>n</i> = 3)	21.8 (<i>n</i> = 38)	8 (<i>n</i> = 14)
Headaches	10.3 (<i>n</i> = 18)	19.5 (<i>n</i> = 34)	16.1 (<i>n</i> = 28)
Hallucinations	1.7 (<i>n</i> = 3)	13.2 (<i>n</i> = 23)	8 (<i>n</i> = 14)

Table 2 Frequent or very frequent neuropsychiatric symptoms in our population expressed as percentage, after excluding patients who presented frequent or very frequent symptoms before efavirenz (EFV) initiation

Neuropsychiatric symptoms	Early emergent NPAR*	Long-lasting NPAR [†]	Late Onset NPAR [‡]
Early morning waking	9.2 (<i>n</i> = 16) [§]	7.5 (<i>n</i> = 13)	4.6 (<i>n</i> = 8)
Trouble falling asleep	12.6 (<i>n</i> = 22)	10.9 (<i>n</i> = 19)	6.9 (<i>n</i> = 12)
Nightmares	21.8 (<i>n</i> = 38)	9.8 (<i>n</i> = 17)	4.0 (<i>n</i> = 7)
Abnormal dreams	18.4 (<i>n</i> = 32)	20.7 (<i>n</i> = 36)	4.0 (<i>n</i> = 7)
Nocturnal waking	9.8 (<i>n</i> = 17)	14.4 (<i>n</i> = 25)	5.2 (<i>n</i> = 9)
Daytime drowsiness	9.2 (<i>n</i> = 16)	14.9 (<i>n</i> = 26)	5.2 (<i>n</i> = 9)
Anxiety	8.0 (<i>n</i> = 14)	9.8 (<i>n</i> = 17)	5.7 (<i>n</i> = 10)
Restlessness	8.6 (<i>n</i> = 15)	12.0 (<i>n</i> = 21)	5.7 (<i>n</i> = 10)
Aggressiveness	4.6 (<i>n</i> = 8)	6.9 (<i>n</i> = 12)	2.9 (<i>n</i> = 5)
Irritability	11.5 (20)	10.3 (<i>n</i> = 18)	4.0 (<i>n</i> = 7)
Agitation	5.7 (<i>n</i> = 8)	7.5 (<i>n</i> = 13)	4.0 (<i>n</i> = 7)
Euphoria	13.8 (<i>n</i> = 24)	5.2 (<i>n</i> = 9)	1.1 (<i>n</i> = 2)
Sexual activity disturbances	1.1 (<i>n</i> = 2)	22.4 (<i>n</i> = 39)	6.9 (<i>n</i> = 12)
Sadness	5.7 (<i>n</i> = 10)	12.6 (<i>n</i> = 22)	5.7 (<i>n</i> = 10)
Emotional instability	5.7 (<i>n</i> = 10)	9.2 (<i>n</i> = 16)	2.9 (<i>n</i> = 5)
Morning tiredness	8.0 (<i>n</i> = 14)	19.0 (<i>n</i> = 33)	6.3 (<i>n</i> = 11)
Suicidal ideations	10.9 (<i>n</i> = 19)	4.6 (<i>n</i> = 8)	4.6 (<i>n</i> = 8)
Impaired concentration	8.0 (<i>n</i> = 14)	13.2 (<i>n</i> = 23)	5.7 (<i>n</i> = 10)
Memory disorders	8.6 (<i>n</i> = 15)	16.1 (<i>n</i> = 28)	6.9 (<i>n</i> = 12)
Dizziness	19.5 (<i>n</i> = 34)	10.3 (<i>n</i> = 18)	4.6 (<i>n</i> = 8)
Feelings of drunkenness	13.8 (<i>n</i> = 24)	6.3 (<i>n</i> = 11)	0.6 (<i>n</i> = 1)
Headaches	7.5 (<i>n</i> = 13)	2.9 (<i>n</i> = 5)	4.6 (<i>n</i> = 8)
Hallucinations	6.9 (<i>n</i> = 12)	4.0 (<i>n</i> = 7)	1.7 (<i>n</i> = 3)

*Early emergent NPAR were symptoms occurring during the first month and not persisting thereafter. [†]Long-lasting NPAR were symptoms occurring during the first month and persisting thereafter. [‡]Late-onset NPAR were symptoms occurring for the first time at least 1 month after initiation of treatment.

month. Eleven patients reported using benzodiazepines to manage anxiety or sleep disturbances alone or in combination with antidepressants. Patients were also asked to assess the global neuropsychic discomfort on their QoL. Fifty-five (31.6%) and 40 (23%) patients described a moderate to severe impairment during the first month of EFV therapy and at the time of the study, respectively. Eleven patients (6.3%) wished to stop EFV because of NPAR.

Discussion

Our study shows that NPAR occur mainly during the first month of EFV therapy and can persist for 3 months or more. It is an accepted fact that EFV induces frequent early NPAR that sometimes may be severe [8–9]. There have been reports of inappropriate behaviour and severe acute depression developing after 1 month of treatment [10]. To our knowledge, few studies have assessed the long-term side-effects of EFV. The Sensio study is original insofar as it addresses NPAR to EFV from the patients' point of view, and evaluates the impact of this medication on the QoL of a 'real-life' population. The study assessed mainly six neuropsychiatric domains (sleep disturbances, behavioural disorders, cognitive disorders, anxiety, mood disorders and dizziness). Patients self-evaluated retrospectively their own psychiatric and physical status. By comparing self-reported status of patients before EFV treatment initiation, after 1 month of treatment and at the time of the study, we hoped to identify NPAR presumably related solely to EFV, i.e. occurring under treatment. Thus we excluded patients who presented frequent or very frequent neuropsychiatric symptoms before initiation of EFV therapy and focused on those for whom the symptoms appeared under treatment.

Sleep disturbances and dizziness occurred mostly at the beginning of EFV therapy. More specifically, abnormal dreams, nightmares, and feelings of drunkenness seem to be associated with EFV and, respectively, 4%, 2.3% and 1.7% of the patients reported having these symptoms before EFV initiation. The proportions rose to 43.7%, 33.9% and 21.8% after 1 month of treatment and did not recede after 1 month for 23.6%, 12%, 6.9% of the patients (Table 1). These results are notably different from early published data [11], but are consistent with those found by Fumaz *et al.* [12].

NPAR which persisted or worsened over the 3-month treatment period were: anxiety (restlessness, fits of anxiety), behavioural troubles (agitation, aggressiveness, sexual activity disturbances), sadness and cognitive disorders (impaired concentration, memory disorders).

The most frequent late NPAR were abnormal dreams (24.7%) and nocturnal waking (19.6%), memory disorders (23.0%) and concentration difficulty (18.9%), morning tiredness (25.3%) and daytime drowsiness (20.1%). These

results suggest that EFV-related NPAR can persist for more than 3 months. In a cross-sectional cohort study comparing EFV and protease inhibitors, Hawkins *et al.* showed that EFV was responsible for central nervous system side-effects persisting for 1 year [13]. HIV infection is associated with a greater risk for major depressive disorders [14]. A high percentage of our patients (10.3%) reported suicidal ideations at the time of the study whereas none of them did before EFV initiation. This symptom was associated with other depressive symptoms such as demoralization, neurovegetative features and cognitive disorders. Even though this result had no clinical diagnostic value, it was notably higher than in previous studies in which severe acute depression was reported in 1–2/1000 EFV-treated patient [4].

In a prospective study by Blanch *et al.*, no significant changes on patients' QoL was observed after 3 months of EFV therapy in comparison with baseline [15]. In contrast, our results showed that NPAR related to EFV seriously affected patients' QoL: 23% of patients evaluated their global neuropsychic discomfort as moderate to severe after at least a 3-month treatment period, and 6.3% of patients wished to discontinue the EFV therapy because of NPAR. The severity of NPAR might induce spontaneous break of treatment by patients. It would be interesting to examine the impact of an EFV-containing regimen on adherence, tolerability and antiretroviral efficacy.

There are several limitations to our study. The first is intrinsic to uncontrolled studies: factors other than EFV possibly influencing neuropsychiatric features such as HIV disease progression and life stresses could not be accounted for [15]. A second limitation comes from the self-administered questionnaire: patients receiving EFV for more than 1 year may have had difficulties remembering their health status during the first month of EFV therapy, thus introducing a memorization bias. Loss of information may have happened: by excluding from analysis questionnaires with more than 60% missing answers, we aimed to reduce this problem. In spite of questions being formulated as statements (with no direct causality implied), one cannot exclude a subjectivity bias in the answers given. Finally, the SQ being anonymous, there was no possibility to refer to the patients' medical file for additional information such as mental health status or substance use history. Both factors are known to be predictive of NPAR to EFV [16]. It was not possible to know if other antiretroviral agents were added with EFV during the study which could interfere with NPAR. Despite these limitations, we believe our study yields important information on long lasting and late onset adverse reactions to EFV, such as experienced by patients in 'real life' conditions. EFV plasma levels monitoring might help to ascertain the relationship with NPAR. Recently published studies demonstrated a dose dependence correlation between some NPAR

and EFV plasma levels [17, 18]. Pharmacokinetics were not considered in the present study but should be the object of further investigation.

Our results suggest that the duration of NPAR could be longer than 2–4 weeks. They warrant routine screening for NPAR among patients receiving EFV therapy. Nonpharmacological and pharmacological interventions for the management of long-lasting NPAR should be improved. Despite the high rate of long-lasting NPAR related to EFV and their impact on QoL, most patients are able to maintain EFV. This tolerance to adverse reactions may be explained by the will to keep an effective antiretroviral therapy or by the convenience of a once daily dosing treatment.

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