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Cyproheptadine for Prevention of Neuropsychiatric Adverse Effects of Efavirenz: A Randomized Clinical Trial

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Abstract

Cyproheptadine prevention of the neuropsychiatric adverse effects of an antiretroviral regimen including efavirenz has been evaluated in a randomized clinical trial. Twenty-five patients (16 males and 9 females with mean ± SD ages of 36 ± 9 years) in a cyproheptadine group, and 26 patients (17 males and 9 females with mean ± SD ages of 34 ± 7 years) in a control group completed the trial. Sexual contact and injection drug use were the main routs of HIV infection in both groups. The patients' neuropsychiatric adverse effects were evaluated based on the Hamilton Depression Rating Scale, Hamilton Anxiety Rating Scale, Positive and Negative Syndrome Scale, Beck Depression Scale, Pittsburgh Sleep Quality Inventory, Positive and Negative Suicide Ideation, and Somatization Subscale of Symptom Checklist 90 at baseline and 4 weeks after treatment. Cyproheptadine significantly decreased the scores of Hamilton Depression Rating Scale, Hamilton Anxiety Rating Scale, Positive and Negative Syndrome Scale, Beck Depression Scale, Pittsburgh Sleep Quality Inventory, Positive and Negative Suicide Ideation of the patients after 4 weeks in comparison with control group. All of the scores increased in control group following antiretroviral therapy. Although short duration of the patients' follow-up was a major limitation of the study, the results of the study showed that cyprohepradine is effective in prevention of depression, anxiety, hallucination, aggressive behaviors, emotional withdrawal, poor rapport, poor impulse control, active social avoidance, suicidal ideation, and improved sleep quality of HIV-positive patients after initiation of antiretroviral therapy including efavirenz.

Introduction

Suppression of human immune deficiency virus (HIV) replication and decrease in morbidity and mortality of HIV-positive patients have been documented following antiretroviral therapy (ART), but this regimen has numerous adverse drug reactions (ADR).[1] Based on the severity of the ADR, modification or ending of treatment may be required.[1] Efavirenz is a potent non-nucleoside reverse transcriptase inhibitor (NNRTI) with favorable pharmacokinetic characteristics and few known ADR. These properties make it as a first-line drug in combination with other ART for treatment of HIV infection.[2,3] More than 50% of patients who take efavirenz will experience neuropsychiatric ADR of this drug.[4,5] Discontinuation of efavirenz due to its neuropsychiatric ADR has been reported in 2–13% of patients.[6–9] Interruption of efavirenz can promote viral resistance to this drug and other NNRTIs.[8] The neuropsychiatric ADR usually are mild to moderate and include dizziness, headache, nightmares, abnormal dreams, mild cognitive difficulty, sleep disturbance (somnolence, insomnia), impaired concentration, and fatigue.[1,10,11] Severe adverse effects have been reported in less than 2% of patients and include suicidal depression (one per 1000), hallucinations, delusions, paranoia, anxiety, agitation, aggressive behavior, mania, emotional lability, catatonia, melancholia, and psychosis.[4,6,10–13] These adverse effects often start after the first dose, peak at 14 days, and commonly disappear after one month of efavirenz treatment.[8,9,14] Several psychotropic categories including antidepressants (citalopram, sertraline, mirtazepine, reboxetine, venlafaxine), antipsychotics (olanzapine, risperidone, amisulpride, sulpiride), mood stabilizers (valproate, lamotrigine), and anxiolytics (oxazepam, lorazepam, temazepam, zopiclone) are proposed for relieving the neuropsychiatric ADR of efavirenz.[15,16] The

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interaction between psychotropic drugs and antiretroviral medications is a considerable problem.[14,16] Selection of an appropriate psychotropic agent with a broad spectrum activity and minimum drug interaction with ART is a challenge in the prevention or treatment of ART-associated neuropsychiatric ADR.

Cyproheptadine is an available, cheap, and relatively safe 5-hydroxytryptamine 2 (5-HT_2) receptor antagonist. Its affinity to interact with dopamine, histamine, and adrenergic and muscarinic receptors is relatively high.[17] The 5-HT 2 antagonists are beneficial in the treatment of psychiatric disorders such as schizophrenia, anxiety, and depression.[18–20] It does not have significant drug interaction via cytochrome P450 with ART (Lexi-Comp 2012, Micromedex Version 1514, 2010).[21] It is also used for treatment of recurrent and post-traumatic nightmares and prevention of vascular types of headache, especially migraine attack.[22–26] Cyproheptadine is a hypnotic drug that can used for sleep induction and also to improve sleep quantity and quality.[27] Common side effects of cyproheptadine are increased appetite and weight gain[28] that can be beneficial in HIV-positive individuals with decreased appetite and weight loss.[29,30] Based on this evidence, cyproheptadine could be a useful agent in prevention of neuropsychiatric ADR of efavirenz with beneficial effects on appetite and weight in HIV-positive patients. In this study, the effects of cyproheptadine in prevention of neuropsychiatric ADR of ART including efavirenz has been evaluated in a randomized clinical trial.

Methods

This double-blind, randomized clinical trial was conducted in the HIV clinic of Imam Khomeini Hospital in Tehran, Iran, during 2011–2012. The clinical trial was registered at the Iranian Registry of Clinical Trials; its identity number is IRCT201103106026N. Patients with documented HIV infection (based on ELISA and Western Blot tests), aged between 18 and 65 years, and who were candidates for initiating ART including efavirenz were included in the trial. Patients with previous history of ART treatment including efavirenz, pregnancy, use of other medications that may affect the patients' mood, and history of major psychiatric disorders were excluded from the study. Sixty-four patients were screened, but 13 patients (8 patients in cyproheptadine group and 5 patients in placebo group) were excluded (Fig. 1). Fifty-one patients completed this trial. Stages of HIV infection was determined according to the 1993 revised classification of Centers for Disease Control and Prevention (CDC) definition.[31] The included patients were divided into two groups (cyproheptadine and placebo) using block randomization. Twenty-five patients were in the cyproheptadine group, and 26 patients were in the placebo group. The trial was approved by the ethical committee of Tehran University of Medical Sciences; each participant signed an informed written consent. Cyproheptadine was administered in a dose of 8 mg per day for 1 week, and 12 mg per day for the other 3 weeks in the cyproheptadine group; placebo patients received the same dose and frequency in control group. The patients were followed for 4 weeks. Neuropsychiatric ADR were evaluated on the day 0 and 28 of treatment by the following scales: Hamilton Depression Rating scale (HDRS), Hamilton Anxiety Rating Scale (HARS), Positive and Negative Syndrome Scale (PANSS), Beck Depression Inventory-2nd Edition (BDI-II), Pittsburgh Sleep Quality Inventory (PSQI), Positive and Negative Suicide Ideation (PANSI), and Somatization subscale of Symptom Checklist 90 (SCL 90). The expert interviewer completed HDRS, HARS, and PANSS questionnaires. HDRS, a validated Persian version,[32] was used to assess the patients' depression. The HDRS is a 17-item scale and rates from 0 (not present) to 4 (severe) for each item.[33] HARS, a validated Persian version,[32] was used for evaluation of the patients' anxiety status. The HARS includes 14 parameters and scores from 0 (not present) to 4 (severe) for each item.[34] PANSS, a validated Persian version[35–37] was used to assess the patients' positive symptoms such as hallucinatory behavior and hostility. This questionnaire includes 30 items and scores from 1 (absent) to 7 (extreme) for each item. Seven items for positive symptoms, 7 items for negative symptoms, and 16 items for general symptoms.[38,39] BDI-II, a validated Persian version,[40] was applied for evaluation of depression by patients. This self-report questionnaire includes 21 items and scores from 0 (absent) to 3 (severe) for each item.[41] Positive and Negative Suicide Ideation is a self- report questionnaire that includes 14 items and scores from 0 to 4 for each item. PANSI has two subscales: Positive Suicidal Ideation with 6 items and Negative Suicidal Ideation with 8 items.[42] The reliability of these two subscales was estimated using Cronbach's alpha reliability coefficient. This coefficient was 0.83 for Positive Suicidal Ideation and 0.94 for Negative Suicidal Ideation. PSQI, a validated Persian version,[43] used to evaluate sleep quality during the study period. PSQI is a self-measured, 7-component questionnaire (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction). Patients with a total score greater than 5 are classified as poor sleepers.[44] Somatization subscale of SCL-90, a validated Persian version,[45,46] was used for assessing physiological factors. Somatization dimension of SCL-90 represents physical morbidity. This self-reported questionnaire includes 12 items. This subscale represents distress in different systems such as cardiovascular, gastrointestinal, respiratory, and autonomic systems, and rated from 0 (none) to 4 (extreme)[47] for each item. Since increased appetite and sleep are common side effects of cyproheptadine, the sleep and appetite items of BDI-II and daytime dysfunction item of PSQI were deleted and the scores of these two questionnaires were re-analyzed.

The statistical package of social science (SPSS) version 16 was used for all analyses. The patients' demographic and laboratory data were evaluated by descriptive analysis. Two-tailed *t*-test and chi-square (or Fisher's exact test) was used to compare demographic, laboratory, and clinical data of the patients. We used two-way repeated measured analysis of variance to compute the effect of independent factors (cyproheptadine and efavirenz therapy) on the emerging neuropsychiatric adverse effects and changes in the patients' weight. Paired sample t-tests were used to calculate the changes in scores of the scales in each group. We considered p values less than 0.05 as statistically significant.

Results

From the included patients, 33 (64.7%) were male, and 18 (35.3%) were female. The most common opportunistic infection and concomitant disease in the patients were candidiasis (9.8 %) and hepatitis C infection (25.5 %). The major routes of

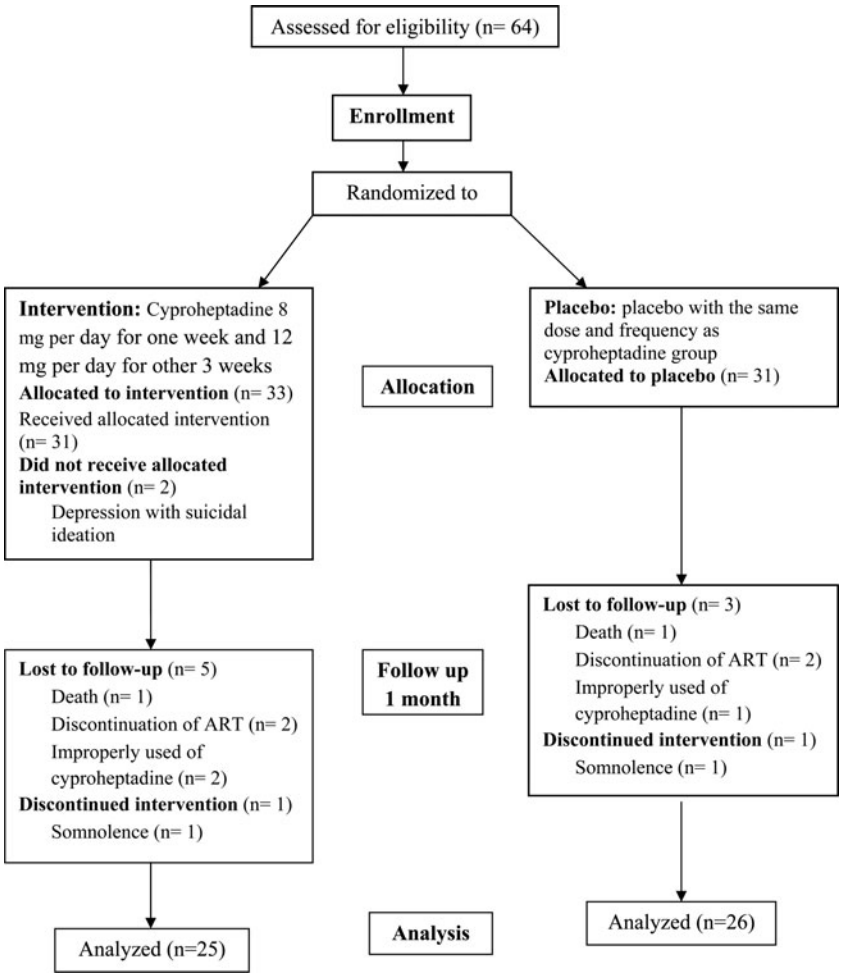

FIG. 1. Consort flowchart.

HIV transmission were sexual contact (39.2 %) and intravenous drug use (31.4 %). Most of the patients were in stage A (70.6 %) of HIV infection. Demographic characteristics of the patients have been summarized in Table 1. There was no significant difference regarding the patients' age, sex, route of HIV transmission, time between HIV infection to AIDS, job, education, stage of HIV infection, concomitant diseases, opportunistic infections, and concomitant medications between cyproheptadine and control groups.

The mean ± SD of the patients' laboratory data are shown in Table 2. There was no significant difference in patients' hematologic parameters, CD4 count, liver enzyme tests, renal function tests, lipid profile, and blood sugar at baseline and 4 weeks later between cyproheptadine and control groups.

Severities of the patients' neuropsychiatric problems are listed in Table 3. Based on HDRS, HARS, BDI-II, and BDI-II without sleep and appetite items scales, the patients' neuropsychiatric status were categorized as normal, minimal, mild, moderate, or severe. Most of the patients were in a mild, normal, and minimal category of HDRS, HARS, and BDI-II, respectively. There was not any significant difference in frequency of these scores between the groups at baseline and after 4 weeks except for HDRS score in the cyproheptadine group after 4 weeks ($p = 0.015$).

Based on the two-way repeated measure analysis of variance, mean ± SD of HDRS was decreased from 14.68 ± 7.32 to 8.00 ± 7.84 in the cyproheptadine group that was significantly ($p = 0.0001$) different from the control group after 4 weeks. Also, the mean ± SD of HARS decreased from 11.12 ± 6.29 to 5.36 ± 6.17 following 4 weeks of cyproheptadine therapy that was significantly ($p = 0.0001$) different from the control group. Positive ($p = 0.002$), negative ($p = 0.0001$), and general ($p = 0.001$) symptoms of the patients were also changed significantly in the cyproheptadine group compared with controls. The patients' BDI-II ($p = 0.004$), PANSI ($p = 0.047$), PSQI ($p = 0.0001$) scores were decreased significantly from 21.24 ± 13.51, 14.20 ± 11.56, and 7.64 ± 4.19 to 18.32 ± 15.67, 12.04 ± 12.08, and 5.76 ± 3.82, respectively, after 4 weeks treatment with cyproheptadine. Although the patients somatization status improved based on the SCL-90 scores, these changes were not significant in all patients. None of these scales changed significantly in the control group after 4 weeks in comparison with the cyproheptadine group.

The mean ± SD of the scales in each group at baseline and after 4 weeks of intervention are shown in Table 4.

Discussion

Both HIV infection and ART, including efavirenz, nevirapin, zidovudine, lamivudine, abacavir, and didanosine, have some neuropsychiatric adverse effects.[1,16,48] HIV infection causes psychiatric complications ranging from depression to mania

Table 1. Demographic Characteristics of the Patients

Characteristics	*Cyproheptadine Number (percent) or mean ± SD*	*Control Number (percent) or mean ± SD*	p *Value*[a]
Sex			
Male	16 (64%)	17 (65.4%)	0.918
Female	9 (36%)	9 (34.6%)	
Age	36 ± 9	34 ± 7	0.415
Time between HIV infection up to AIDS (months)	21 ± 30	12 ± 23	0.215
Education			
Illiterate	2 (8.0%)	1 (3.8%)	0.311
Elementary	3 (12.0%)	6 (23.1%)	
Guidance school	7 (28.0%)	2 (7.7%)	
High school	10 (40.0%)	12 (46.2%)	
More than diploma	3 (12.0%)	5 (19.2%)	
Transmission			
IV drug injection	9 (36.0%)	7 (26.9%)	0.692
Sex	11 (44.0%)	9 (34.6%)	
Needle	1 (4.0%)	2 (7.7%)	
IV drug injection and sex	2 (8.0%)	5 (19.2%)	
Unknown	2 (8.0%)	2 (7.7%)	
Blood	0 (0.0%)	1 (3.8%)	
Job			
Self-employed	10 (40.0%)	15 (57.7%)	0.209
House-hold	5 (20.0%)	5 (19.2%)	
Employee	1 (4.0%)	2 (7.7%)	
Student	1 (4.0%)	1 (3.8%)	
Taxi driver	4 (16.0%)	0 (0.0%)	
Unemployed	3 (12.0%)	0 (0.0%)	
Engineer	0 (0.0%)	1 (3.8%)	
Medical staff	1 (4.0%)	2 (7.7%)	
Opportunistic infections			
TB	0 (0.0%)	1(3.8%)	0.289
CMV	0 (0.0%)	2 (7.7%)	
Candidiasis	3 (12.0%)	2 (7.7%)	
None	20 (80.0%)	20 (76.9%)	
Zoster	2 (8.0%)	0 (0.0%)	
TB and candidiasis	0 (0.0%)	1 (3.8%)	
Concomitant diseases			
Diabetes	0 (0.0%)	1 (3.8%)	0.320
Depression	1 (4.0%)	0 (0.0%)	
HCV	7 (28.0%)	4 (15.4%)	
GI disease	2 (8.0%)	0 (0.0%)	
None	14 (56.0%)	20 (76.9%)	
HBV and HCV	1 (4.0%)	1 (3.8%)	
State of marriage			
Single	10 (40.0%)	8 (30.8%)	0.779
Married	12 (48.0%)	14 (53.8%)	
Divorced	3 (12.0%)	4 (15.4%)	
Stage of HIV infection			
A	19 (76.0%)	17 (65.4%)	0.068
B	5 (20.0%)	2 (7.7%)	
C	0 (0.0%)	4 (15.4%)	
Concomitant medication			
Cotrimaxazole	16 (64.0%)	12 (46.2%)	0.200
Gancyclovir	0 (0.0%)	2 (7.7%)	0. 255
Benzodiazepine	4 (16.0%)	2 (7.7%)	0.315
SSRI	1 (4.0%)	0 (0.0%)	0. 490
Fluconazole	3 (12.0%)	2 (7.7%)	0.481
INH, B_6	2 (8.0%)	4 (15.4%)	0.353
PPI	1 (4.0%)	1 (3.8%)	0.745
INH,RIF, PYZ,	0 (0.0%)	2 (7.7%)	0.255
ETM, B_6 Acyclovir	2 (8.0%)	0 (0.0%)	0.235
Insulin	0 (0.0%)	1 (3.8%)	0. 510

B_6, Vitamin B_6; CMV, cytomegalovirus; ETM, ethambutol; GI, gastrointestinal; HBV, hepatitis B virus; HCV, hepatitis C virus; INH, isoniazid; IV, intravenous; PYZ, pyrazinamide; RIF, rifampin; SSRI, selective serotonin reuptake inhibitor; TB, tuberculosis.

[a]Chi square or Fisher's exact test.

Table 2. Laboratory Data of Patients

Variable (mean ± SD)	*Cyproheptadine*	*Control*	p *Value*[a]
WBC	5160.461 ± 1665.98	5502.73 ± 2116.50	0.549
Neutrophils (percent)	57.82 ± 10.06	59.03 ± 9.28	0.687
CD4 count	148.57 ± 117.51	164.09 ± 121.23	0.665
Hemoglobin	12.98 ± 2.49	12.68 ± 1.84	0.644
Hematocrit	39.23 ± 6.25	38.15 ± 5.04	0.529
Platelets	205317.74 ± 114829.61	206981.82 ± 123155.68	0.963
Urea	23.00 ± 7.64	27.00 ± 10.12	0.156
Creatinine	1.25 ± 1.33	0.99 ± 0.25	0.382
ALT	44.91 ± 50.86	31.91 ± 27.24	0.294
AST	51.74 ± 67.17	32.86 ± 25.02	0.222
ALP	8973.09 ± 42078.45	207.18 ± 86.64	0.334
ESR	23.13 ± 20.71	29.31 ± 32.48	0.516
Cholesterol	139.32 ± 30.23	140.06 ± 32.52	0.943
Triglyceride	101.89 ± 43.42	162.39 ± 118.21	0.044
HDL	31.16 ± 11.17	30.11 ± 8.53	0.752
LDL	79.10 ± 23.13	78.11 ± 27.03	0.905
FBS	92.40 ± 14.45	112.60 ± 78.22	0.263

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ESR, erythrocyte sedimentation rate; FBS, fasting blood sugar; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SD, standard deviation; WBC, white blood cell.
[a]Two tailed *t*- test.

and psychosis.[1] Neuropsychiatric ADR of efavirenz are common[4,5] and cause up to 13% of ART discontinuation.[6–9] It must be considered that patient-reported symptoms as a whole in efavirenz-based ART regimens are less than other regimens.[51]

Psychotropic medications are used to relieve mild to moderate neuropsychiatric adverse effects.[16] Cessation of efavirenz therapy may be needed in severe cases.[1] Peyrierea and colleagues[10] reported three cases of efavirenz-induced CNS toxicity. One of these cases stopped efavirenz because of serious reactions. Other cases with efavirenz were managed with dose reduction. The authors proposed that administration of efavirenz regardless of patient's weight can cause high plasma concentration in low weight and patients with hypoalbuminemia. High serum concentration of free efavirenz will advance its neuropsychiatric adverse effects.[10] Gutierrez-Valencia et al.[5] used stepped-dose therapy of efavirenz over 2 weeks and concluded that this approach can reduce the severity and frequency of efavirenz-related neuropsychiatric adverse effects while its efficacy is maintained.[5] However, the efficacy and safety of dose escalation have not been established, and the manufacturer of efavirenz has discouraged this approach due to potential risk

Table 3. Severities of Patient Neuropsychiatric Status at Baseline and after 4 Weeks

Scoring		*Group (base) Number (percent)*		*Group (after 4 weeks) Number (percent)*		p *Value (base)*[a]	p *Value (after 4 weeks)*[a]
		Cyproheptadine	*Control*	*Cyproheptadine*	*Control*		
Hamilton Depression Rating Scale	Normal (0–7)	3 (12.0%)	8 (30.8%)	15 (60.0%)	5 (19.2%)	0.372	0.015
	Mild (8–13)	9 (36.0%)	10 (38.5%)	6 (24.0%)	9 (34.6%)		
	Moderate (14–18)	4 (16.0%)	4 (15.4%)	2 (8.0%)	9 (34.6%)		
	Severe (19–22)	5 (20.0%)	2 (7.7%)	0 (0.0%)	2 (7.7%)		
	Very Severe (≥ 23)	4 (16.0%)	2 (7.7%)	2 (8.0%)	1 (3.8%)		
Hamilton Anxiety Rating Scale	Normal (0–13)	16 (64.0%)	24 (92.3%)	22 (88.0%)	21(80.8%)	0.095	0.445
	Mild (14–17)	7 (28.0%)	2 (7.7%)	2 (8.0%)	4 (15.4%)		
	Moderate (18–24)	1 (4.0%)	0(0.0%)	1(4.0%)	0 (0.0%)		
	Severe (25–30)	1 (4.0%)	0 (0.0%)	0(0.0%)	1 (3.8%)		
Beck Depression inventory-2nd Edition	Minimal l (0–13)	9 (36.0%)	11 (42.3%)	13 (52.0%)	9 (34.6%)	0.059	0.537
	Mild (14–19)	6 (24.0%)	2 (7.7%)	1 (4.0%)	3 (11.5%)		
	Moderate (20–28)	4 (16.0%)	11(42.3%)	4 (16.0%)	6 (23.1%)		
	Severe (29–63)	6 (24.0%)	2 (7.7%)	7 (28.0%)	8 (30.8%)		
Beck Depression inventory- 2nd Edition (without sleep and appetite scores)	Minimal l (0–13)	10 (40.0%)	12 (46.2%)	14 (56.0%)	11(42.3%)	0.619	0.516
	Mild (14–19)	5 (20.0%)	5 (19.2%)	3 (12.0%)	4 (15.4%)		
	Moderate (20–28)	5 (20.0%)	7 (26.9%)	1 (4.0%)	4 (15.4%)		
	Severe (29–63)	5 (20.0%)	2 (7.7%)	7 (28.0%)	7 (26.9%)		

[a]Based on Chi-square or Fisher-exact test analysis.

Table 4. Comparison of Weight and Neuropsychiatric Characteristics of the Patients at Baseline and Following Cyproheptadine (A) or Placebo (B) Intervention

Variable	*Group*	*Baseline mean ± SD*	*After 4 weeks mean ± SD*	p *Value within groups*[a]	p *Value between groups*[b]
Weight (kg)	A	65.02 ± 12.32	66.34 ± 12.45	0.452	0.297
	B	67.73 ± 13.17	68.38 ± 13.00	0.569	
HDRS	A	14.68 ± 7.32	8.00 ± 7.84	0.072	0.0001
	B	11.15 ± 6.37	12.65 ± 5.67	0.018	
HARS	A	11.12 ± 6.29	5.36 ± 6.17	0.008	0.0001
	B	6.92 ± 4.46	8.50 ± 4.83	0.048	
PSS	A	9.08 ± 1.78	8.00 ± 1.38	0.255	0.002
	B	8.54 ± 1.58	9.38 ± 2.08	0.008	
NSS	A	9.16 ± 2.19	7.76 ± 1.33	0.013	0.0001
	B	7.85 ± 1.35	8.96 ± 2.37	0.031	
GSS	A	25.16 ± 4.39	20.72 ± 4.23	0.082	0.001
	B	23.11 ± 3.83	23.77 ± 5.66	0.035	
BDI-II	A	21.24 ± 13.51	18.32 ± 15.67	0.140	0.004
	B	16.31 ± 9.73	20.77 ± 12.35	0.537	
BDI_II Without questions 16 and 18	A	19.08 ± 12.54	16.00 ± 14.44	0.150	0.003
	B	14.61 ± 9.05	18.69 ± 11.83	0.469	
Suicidal ideation	A	14.20 ± 11.56	12.04 ± 12.08	0.044	0.047
	B	8.77 ± 6.68	10.81 ± 7.49	0.662	
Somatization	A	14.48 ± 7.73	15.76 ± 10.37	0.014	0.224
Subscale of SCL 90	B	9.31 ± 6.81	13.69 ± 9.44	0.460	
PSQI	A	7.64 ± 4.19	5.76 ± 3.82	0.006	0.0001
	B	4.50 ± 3.58	7.04 ± 4.62	0.288	
PSQI	A	7.32 ± 4.03	5.36 ± 3.68	0.009	0.0001
Without question 7	B	4.42 ± 3.57	6.69 ± 4.42	0.249	

BDI-II, Beck Depression Inventory-2nd Edition; GSS, General Symptoms Scale; HARS, Hamilton Anxiety Rating Scale; HDRS, Hamilton Depression Rating Scale; NSS, Negative Symptoms Scale; PSQI, Pittsburg Sleep Quality Inventory; PSS, Positive Symptoms Scale; PSS, Positive Symptoms Scale; SD, Standard Deviation; SCL 90, Symptom Check List 90.

[a]Paired *t*-test; [b]two way repeated measure analysis of variance.

of resistance.[2] We have not found any effective and safe intervention for prevention of neuropsychiatric adverse effects of ART in our literature review. Appropriate prevention of these ADR can minimize ART discontinuation and improve patients' adherence to therapy. In the limited studies, cyproheptadine showed beneficial effects on the treatment of acute and chronic schizophrenia,[49–51] anxiety,[19] depression,[52] and recurrent and post-traumatic nightmares.[22,23,53] It can also improve quantity and quality of sleep.[27] Common side effects of cyproheptadine (appetite improvement and weight gain)[28] can be useful in HIV-positive patients.

In the present study, cyproheptadine significantly decreased the scores of 6 scales (HDRS, HARS, PANSS, PANSI, BDI-II, and PSQI) after 4 weeks. All of these scores increased in the control (placebo) group following 4 weeks, and increase in HARS, HDRS, and PANSS were statistically significant. Greenway and others[52] reported antidepressant effects of cyproheptadine in 6 patients with major depression in a double-blind, crossover trial. The HDRS scores of 4 patients decreased after 8 weeks treatment with cyproheptadine.[52] Akhondzadeh and colleagues[50] reported the results of a randomized double-blind placebo controlled study of cyproheptadine in 30 patients with chronic schizophrenia. Patients were randomly treated with 30 mg haloperidol and 24 mg cyproheptadine per day or 30 mg haloperidol daily plus placebo for 8 weeks. PANSS scores were higher in the placebo group in comparison with the cyproheptadine group at weeks 4, 6, and 8.[50] Silver et al.[54] also investigated the effect of cyproheptadine augmentation therapy with haloperidol in 10 patients with chronic schizophrenia. The authors concluded that cyproheptadine can be effective on ameliorating both positive and negative symptoms in the patients.[54] Our finding showed that cyproheptadine can prevent depression, anxiety, positive symptoms (hallucination and aggressive behaviors), negative symptoms (emotional withdrawal and poor rapport), and general symptoms (poor impulse control and active social avoidance) of HIV-positive patients who starting ART including efavirenz.

The sleep quality, which was evaluated by PSQI, significantly improved in the cyproheptadine group. Tokunaga et al.[27] evaluated the effects of some H1-antagonists, including oral cyproheptadine, on the sleep-wake cycle in sleep-disturbed rats in comparison with oral nitazepam in an experimental study. In this study, cyproheptadine decreased the total waking time and increased the total nonrapid eye movement (non-REM) sleep time, slow wave sleep, and delta activity.[27] The score of PSQI increased in placebo group but was not statistically significant. Sleep disturbance is a common neuropsychiatric adverse effect of efavirenz.[1,10,55] When sleep and appetite items of BDI-II and daytime dysfunction of PSQI were excluded, the results of repeated analyses did not differ significantly than the BDI-II and PSQI scales. Although there are not enough data regarding correlation between efavirenz and risk of suicide,[8] this study showed that the mean of suicidal ideation scores increased

after 4 weeks in placebo group, although it was not significant. The mean of PANSI was decreased in the cyproheptadine group significantly. This finding showed that cyproheptadine is effective in prevention of suicidal ideation following initiation of ART including efavirenz. Cyproheptadine was not effective in preventing or decreasing the physical morbidity in various systems of the patients. The mean of somatization subscale of SCL-90 was increased significantly within the cyproheptadine group and insignificantly in the control group, but these changes was not significant in comparison between groups. The common side effects of ART are nausea, vomiting, headache, dizziness, malaise, myalgia, and peripheral neurologic complications such as neuropathic pain, neuropathic weakness, and denervation syndromes.[14,56] These side effects increased somatization subscale of SCL-90 scores.

The mean of patients' weight was increased after 4 weeks in both groups, but it was not significant within and between groups. Sense of well-being and improvement in general condition of HIV-positive patients following ART, can increase patients' appetite and weight.

Stiel et al.,[57] Daviss et al.,[28] Homnick et al.,[58] Epifanio et al.,[59] and Rerksuppaphol et al.[60] investigated the effect of cyproheptadine on weight gain in healthy people, ADHD individuals, patients with cystic fibrosis, and malnourished children, respectively. They concluded that cyproheptadine can increase weight in these populations. Cyproheptadine did not cause significant weight gain in our HIV-positive patients, which may be due to small sample size and short duration of intervention in this study.

The main route of HIV transmission in the Iranian population is injection drug use.[61–63] In the present study, the most common route of HIV transmission in the patients was sexual contact. We excluded IDU patients who were under treatment with methadone because of efavirenz–methadone interaction. Efavirenz can increase metabolism of methadone and results in occurrence of withdrawal symptoms that may be mistaken with efavirenz neuropsychiatric adverse effects.[5]

Although the results of this study showed that cyproheptadine is effective in prevention of neuropsychiatric adverse effects of ART including efavirenz, the study had some limitations. Small sample size and short duration of the patients' follow-up were major limitations of the study. Seven different questionnaires were used for evaluation of the patients' neuropsychiatric status. In average, about 1 h was needed for each patient's interview and complementation of the questionnaires that was boring for some patients. It may have influenced the accuracy of the patients' responses. The results of this study must be confirmed in future clinical trials with sufficient sample size and long term follow-up. As neuropsychiatric effects of EFV often resolve spontaneously within 4 weeks, additional studies at shorter (2 week) and longer (several month) intervals with cyproheptadine might be tried.

This is first study that has evaluated the efficacy of an intervention (cyproheptadine) in prevention of ART-induced neuropsychiatric adverse effects. The results showed that cyprohepradine is effective in prevention of anxiety, depression, hallucination, aggressive behaviors, emotional withdrawal, poor rapport, poor impulse control, active social avoidance, suicidal ideation, and improved sleep quality of HIV-positive patients following initiation of ART including efavirenz.

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References

1. Bartlett JA, Ferrando SJ. Identification and management of neurologic and psychiatric side effects associated with HIV and HAART. http://www.medscape.com/viewprogram/2960_pnt. Accessed February 26, 2010.
2. Boyle B, Goldenberg D. Current issues in antiretroviral and psychiatric therapy for HIV-infected patients. AIDS Read 2000;10:508–513.
3. Sütterlin S, Vögele C, Gauggel S. Neuropsychiatric complications of efavirenz therapy: Suggestions for a new research paradigm. J Neuropsychiatry Clin Neurosci 2010;22:361–369.
4. Blanch J, Martínez E, Rousaud A, et al. Preliminary data of a prospective study on neuropsychiatric side effects after initiation of efavirenz. J Acquir Immune Defic Syndr 2001;27:336–343.
5. Gutiérrez-Valencia A, Viciana P, et al. Stepped-dose versus full-dose efavirenz for HIV infection and neuropsychiatric adverse events: A randomized trial. Ann Intern Med 2009;151:149–156.
6. Puzantian T. Central nervous system adverse effects with efavirenz: Case report and review. Pharmacotherapy 2002;22:930–933.
7. Rihs T, Begley K, Smith D, et al. Efavirenz and chronic neuropsychiatric symptoms: A cross-sectional case control study. HIV Med 2006;7:544–548.
8. Kenedi CA, Goforth HW. A systematic review of the psychiatric side-effects of efavirenz. AIDS Behav 2011;15:1803–1818.
9. Muñoz-Moreno JA, Fumaz CR, Ferrer MJ, et al. Neuropsychiatric symptoms associated with efavirenz: prevalence, correlates, and management. A neurobehavioral review. AIDS Rev 2009;11:103–109.
10. Peyriere H, Mauboussin JM, Rouanet I, Fabre J, Reynes J, Hillaire-Buys D. Management of sudden psychiatric disorders related to efavirenz. AIDS 2001;15:1323–324.
11. Bernard EJ. Does efavirenz cause depression? AIDS Treat Update 2006;158:3.
12. Sabato S, Wesselingh S, Fuller A, Ray J, Mijch A. Efavirenz-induced catatonia. AIDS 2002;16:1841–1842.
13. Von Giesen HJ, Koller H, de Nocker D, Haslinger BA, Arendt G. Long-term safety and efficacy of NNRTI within the central nervous system. HIV Clin Trials 2003;4:382–390.
14. Treisman GJ, Kaplin AI. Neurologic and psychiatric complications of antiretroviral agents. AIDS 2002;16:1201–1215.
15. Thompson A, Silverman B, Dzeng L, Treisman G. Psychotropic medications and HIV. Clin Infect Dis 2006;42:1305–1310.
16. Turjanski N, Lloyd GG. Psychiatric side-effects of medications: Recent developments. Adv Psychiatr Treat 2005;11:58–70.
17. Goudie AJ, Cooper GD, Cole JC, Sumnall HR. Cyproheptadine resembles clozapine in vivo following both acute and chronic administration in rats. J Psychopharmacol 2007;21:179–190.

18. Barnes NM, Sharp T. A review of central 5-HT receptors and their function. Neuropharmacology 1999;38:1083–1152.
19. Koek W, Jackson A, Colpaert FC. Behavioral pharmacology of antagonists at 5-HT2/5-HT1C receptors. Neurosci Biobehav Rev 1992;16:95–105.
20. Bourgeois J, Bourgeois JA, Hales RE, Young JS. The American Psychiatric Publishing board review guide for psychiatry: Amer Psychiatric Pub Incorporated, Washington, DC, 2009, p. 442.
21. *Drug Interaction Facts.*Tatro DS, editor. Wolters Kluwer Health, Inc., 2012.
22. Harsch HH. Cyproheptadine for recurrent nightmares. Am J Psychiatry 1986;143:1491–1492.
23. Brophy MH. Cyproheptadine for combat nightmares in post-traumatic stress disorder and dream anxiety disorder. Mil Med 1991;156:100–101.
24. Rijnders RJ, Laman DM, Van Diujn H. Cyproheptadine for posttraumatic nightmares. AM J Psychiatry 2000;157:1524–1525.
25. Yonker ME. Pharmacologic treatment of migraine. Curr Pain Headache Rep 2006;10:377–381.
26. Stark RJ, Stark CD. Migraine prophylaxis. Med J Aust 2008;189:283–288.
27. Tokunaga S, Takeda Y, Shinomiya K, Hirase M, Kamei C. Effects of some H1-antagonists on the sleep-wake cycle in sleep-disturbed rats. J Pharmacol Sci 2007;103:201–206.
28. Daviss WB, Scott J. A chart review of cyproheptadine for stimulant-induced weight loss. J Child Adolesc Psychopharmacol 2004;14:65–73.
29. Koethe JR, Heimburger DC. Nutritional aspects of HIV-associated wasting in sub-Saharan Africa. Am J Clin Nutr 2010;91:1138S–1142S.
30. Polsky B, Kotler D, Steinhart C. HIV-associated wasting in the HAART era: Guidelines for assessment, diagnosis, and treatment. AIDS Patient Care STDs 2001;15:411–423.
31. From the Centers for Disease Control and Prevention. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Recomm Rep 1992;18:1–19.
32. Shams J, Gudarzi SSP, Ghorbani B, Habibi LK, Yasami MT. The efficacy and safety of add-on ginko TD (Ginkgo biloba) treatment for PTSD: Results of a 12-week double-blind placebo-controlled study. Iran J Psychiatry 2007;2:58–64.
33. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62.
34. Bruss GS, Gruenberg AM, Goldstein RD, Barber JP. Hamilton Anxiety Rating Scale Interview guide: Joint interview and test-retest methods for interrater reliability. Psychiatry Res 1994;53:191–202.
35. Malakouti SK, Nojomi M, Panaghi L, et al. Case-management for patients with schizophrenia in Iran: A comparative study of the clinical outcomes of mental health workers and consumers' family members as case managers. Community Ment Health J 2009;45:447–452.
36. Malakouti SK, Panaghi L, Foroughan M, Salehi M, Zandi T. Farsi version of the Neuropsychiatric Inventory: Validity and reliability study among Iranian elderly with dementia. Int Psychogeriatr 2012;24:223–230.
37. Khazaie H, Tahmasian M, Younesi G, et al. Evaluation of dream content among patients with schizophrenia, their siblings, patients with psychiatric diagnoses other than schizophrenia, and healthy control. Iran J Psychiatry 2012;7:26–30.
38. Kay SR, Flszbein A, Opfer LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophrenia Bull 1987;13:261.
39. Kay SR, Opler LA, Lindenmayer JP. Reliability and validity of the positive and negative syndrome scale for schizophrenics. Psychiatry Res 1988;23:99–110.
40. Ghassemzadeh H, Mojtabai R, Karamghadiri N, Ebrahimkhani N. Psychometric properties of a Persian-language version of the Beck Depression Inventory-Second edition: BDI-II-PERSIAN. Depress Anxiety 2005;21:185–192.
41. Beck AT, Steer RA, Brown GK. Manual for the Beck depression inventory-II. San Antonio, TX: Psychological Corporation. 1996;1:82.
42. Muehlenkamp JJ, Gutierrez PM, Osman A, Barrios FX. Validation of the Positive and Negative Suicide Ideation (PANSI) Inventory in a diverse sample of young adults. J Clin Psychol 2005;61:431–345.
43. Farrahi Moghaddam J, Nakhaee N, Sheibani V, Garrusi B, Amirkafi A. Reliability and validity of the Persian version of the Pittsburgh Sleep Quality Index (PSQI-P). Sleep Breath 2012;16:79–82.
44. Wibbeler T, Reichelt D, Husstedt IW, Evers S. Sleepiness and sleep quality in patients with HIV infection. J Psychosom Res 2012;72:439–442.
45. Hedayati-Moghaddam M, Mashhadi IE, Zibaee R, Hosseinpoor A, Fathi-Moghaddam F, Bidkhori H. Assessment of psychiatric symptoms using SCL-90-R among HIV/AIDS individuals in Razavi Khorasan Province, Iran. Iran Red Crescent Med J 2011;13:58–59.
46. Mirzai R. Standardizing and validating of SCL-90-R in Iran. Arch Iran Med 2009;12:9.
47. Derogatis L. Symptoms checklist-90: Administration, scoring and procedures manual for the revised version. Baltimore, Md: Clin Psychomet Res 1977:2.
48. Morlese JF, Qazi NA, Gazzard BG, Nelson MR. Nevirapine-induced neuropsychiatric complications, a class effect of non-nucleoside reverse transcriptase inhibitors? AIDS 2002;16:1840–1841.
49. Edelman EJ, Gordon K, Rodriguez-Barradas MC, Justice AC; Vacs Project Team. Patient-reported symptoms on the antiretroviral regimen efavirenz/emtricitabine/tenofovir. AIDS Patient Care STDS 2012 26:312–319.
50. Akhondzadeh S, Mohammadi M, Amini-Nooshabadi H, Davari-Ashtiani R. Cyproheptadine in treatment of chronic schizophrenia: A double-blind, placebo-controlled study. J Clin Pharm Ther 2001;24:49–52.
51. Pangalila-Ratu Langi E, Jansen A. Ritanserin in the treatment of generalized anxiety disorders: A placebo-controlled trial. Hum Psychopharmacol 1988;3:6.
52. Greenway SE, Pack AT, Greenway FL. Treatment of depression with cyproheptadine. Pharmacotherapy 1995;15:357–360.
53. Gupta S, Popli A, Bathurst E, Hennig L, Droney T, Keller P. Efficacy of Cyproheptadine for nightmares associated with posttraumatic stress disorder. Compr Psychiatry 1998;39:160–164.
54. Silver H, Blacker M, Weller MP, Lerer B. Treatment of chronic schizophrenia with cyproheptadine. Biol Psychiatry1989;25:502–504.
55. Arendt G, de Nocker D, von Giesen HJ, Nolting T. Neuropsychiatric side effects of efavirenz therapy. Expert Opin Drug Saf 2007;6:147–154.
56. Sapkota S, Shakya R, Pandey B. Study on highly active antiretroviral therapy: Prescription pattern and side effects. JNPA 2012;26:12–18.
57. Stiel JN, Liddle GW, Lacy WW. Studies of mechanism of cyproheptadine-induced weight gain in human subjects. Metabolism 1970;19:192–200.

58. Homnick DN, Homnick BD, Reeves AJ, Marks JH, Pimentel RS, Bonnema SK. Cyproheptadine is an effective appetite stimulant in cystic fibrosis. Pediatr Pulmonol 2004;38: 129–134.
59. Epifanio M, Marostica PC, Mattiello R, et al. Ensaio clínico randomizado, duplo-cego e controlado por placebo de ciproheptadina para estímulo do apetite na fibrose cística; (A randomized, double-blind, placebo-controlled trial of cyproheptadine for appetite stimulation in cystic fibrosis). J Pediatria 2012;88:155–160.
60. Rerksuppaphol S. Effect of cyproheptadine on weight gain in malnourished children: a randomized, controlled trial. Asian Biomed 2011;4:977–982.
61. Etminani-Esfahani M, Khalili H, Soleimani N, et al. Serum vitamin D concentration and potential risk factors for its deficiency in HIV positive individuals. Curr HIV Res 2012;10: 165–170.
62. Khalili H, Dashti-Khavidaki S, Mohraz M, Etghani A, Almasi F. Antiretroviral induced adverse drug reactions in Iranian human immunodeficiency virus positive patients. Pharmacoepidemiol Drug Saf 2009;18:848–857.
63. National AIDS Committee Secretariat, Ministry of Health and Medical Education. Islamic Republic of Iran AIDS Progress Report, March 2012. Available at. http://www.unaids.org/en/dataanalysis/knowyourresponse/countryprogressreports/2012countries/IRIran%20AIDS%20Progress%20Report%202012%20English%20final1_1.pdf. Accessed December 27, 2012.

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