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Potential benefits of cyproheptadine in HIV-positive patients under treatment with antiretroviral drugs including efavirenz

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Introduction: More than 50% of HIV-positive patients experience neuropsychiatric adverse reactions following efavirenz therapy. Discontinuation of efavirenz due to its neuropsychiatric side effects has been reported in 2 – 13% of patients. Dizziness, headache, nightmares, abnormal dreams, mild cognitive difficulty, sleep disturbance (somnolence and insomnia), impaired concentration, depression, hallucination, delusion, paranoia, anxiety, agitation, aggressive behavior, mania, emotional labiality, catatonia, melancholia, psychosis, and fatigue are the most reported efavirenz adverse reactions.

Areas covered: In this review, potential benefits of cyproheptadine in prevention and management of HIV/antiretroviral-associated neuropsychiatric complications are evaluated. The available evidence was collected by searching Scopus, PubMed, Medline, Cochrane central register of controlled trials, and Cochrane database systematic reviews.

Expert opinion: Cyproheptadine is a cheap and safe drug that does not have significant interactions with antiretroviral drugs. Cyproheptadine's common side effects including increasing appetite and weight gain can be useful in HIV-positive individuals with their decreased appetite and weight loss. There is limited evidence regarding the effectiveness of cyproheptadine in neuropsychiatric disorders. It is essential to evaluate cyproheptadine efficacy in the prevention and management of neuropsychiatric complications of HIV/antiretroviral infection in well-designed studies in the future.

Keywords: antiretroviral, cyproheptadine, efavirenz, HIV

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1. Introduction

Although antiretroviral therapy (ART) can suppress human immune deficiency virus (HIV) replication and decrease morbidity and mortality in HIV-positive individuals, they have numerous adverse drug reactions (ADR). Based on the severity of the ADR, modification or cession 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 [9]. Efavirenz ADRs usually

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Article highlights.

- Antiretroviral medications and HIV infection cause some neuropsychiatric complications such as dizziness, headache, nightmares, abnormal dreams, mild cognitive difficulty, sleep disturbances, depression, hallucination, delusion, paranoia, anxiety, agitation, aggressive behavior, mania, and psychosis.
- Cyproheptadine is an available, cheap, and relatively safe 5-hydroxytryptamine 2 (5-HT_2) receptors antagonist.
- Cyproheptadine showed beneficial effects in the treatment of nightmare, sleep disorders, acute and chronic schizophrenia, anxiety, depression, recurrent and posttraumatic nightmares, and in the prevention of vascular types of headache especially migraine attacks in non–HIV-positive individuals.
- It seems that cyproheptadine can be useful in the treatment of neuropsychiatric disorders that are related to ART and/or HIV infection.
- Common side effects of cyproheptadine are increase in appetite and weight gain which can be useful in HIV-positive patients.

This box summarizes key points contained in the article.

are mild to moderate and they generally include dizziness, headache, nightmares, abnormal dreams, mild cognitive difficulty, sleep disturbance (somnolence, insomnia), impaired concentration, and fatigue [10]. Depression following efavirenz therapy was reported in 2% of patients [11]. Severe neuropsychiatric ADR such as severe depression with suicidal attempt (1 per 1,000), hallucination, delusion, paranoia, anxiety, agitation, aggressive behavior, mania, emotional labiality, catatonia, melancholia, and psychosis were detected in less than 2% of patients [5,6,10,12,13]. There are some case reports of recurrence of posttraumatic stress disorders after starting efavirenz-based ART [14]. Typically, these ADR begin after first doses and relive within 1 month of efavirenz therapy [8,15]. In 13% of patients, these ADR persisted for 1 year period [7,16]. Severe psychiatric disorders are more likely in patients with underlying mental illnesses or history of drug abuse [4]. Female sex can be a risk factor for efavirenz-induced central nervous system toxicity [8]. The mechanism of these ADR is not well described [17]. Some mechanisms were proposed in the different studies [10,13,17]. Efavirenz may inhibit creatine kinase (CK), an enzyme responsible for cellular energy production in tissues with high energy consumption such as brain. Decreased CK activity can cause brain ischemia and neuronal loss [18]. CYP2B6 polymorphism can play essential role in slowing clearance of efavirenz and following high plasma level of this drug [19]. Efavirenz is administrated with dose of 600 mg per day regardless of the body weight in the adult patient. In patient with low body weight, it causes a higher concentration of efavirenz in blood and CNS and may lead to CNS toxicity [10]. The protein binding of efavirenz is very high, and in patient with hypoalbuminemia, unbound fraction of efavirenz is increased in plasma, and efavirenz diffusion to CNS becomes more readily that can cause ADR [10]. In addition, high-fat meals can increase plasma level of efavirenz and CNS toxicity [20]. The severity of these ADR often is dose-dependent and ameliorated with dose reduction [10,13]. Increasing the efavirenz doses slowly over 2 weeks, reduced incidence and intensity of its neuropsychiatric ADR while maintaining its efficacy [5]. The safety of dose escalation has not been established, and the efavirenz manufacturer does not recommend this approach due to risk of drug resistance [2]. Nevirapine is another drug in NNRTI class. There are some reports of psychiatric ADR such as vivid dream with this drug [21]. Zidovudine, lamivudine, and didanosine also may cause psychiatric complications. Abacavir can induce psychosis and mania when used in combination with other ART [22]. Neuropsychiatric ADR of ART and neuropsychiatric complications of HIV infection may overlap significantly, and it may be difficult to differentiate them from each other. Psychiatric complications of HIV infection varies from depression to mania and psychosis [1]. The neuropsychiatric complications of HIV may be related to immune system activation and viral infection of the brain macrophages and microglia [22].

1.1 Management of ART-associated neuropsychiatric complications

ART-associated neuropsychiatric complications should be managed with regard to the severity. Mild complications usually are well tolerated and self-limited [22,23]. If these ADR do not resolve spontaneously within 2 weeks of therapy, psychotropic medication can be useful [6]. In patients with severe reactions, modification or discontinuation of offending drug may be necessary [22,23]. 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 neuropsychiatric ADR of efavirenz [24]. The interaction between psychotropic drugs and antiretroviral medications is a considerable problem [15,22]. Selection of an appropriate psychotropic agent with a broad spectrum activity and minimum drug interaction with ART is a challenging point in prevention or treatment of ART-associated neuropsychiatric ADR.

Cyproheptadine is an available, cheap, and relatively safe 5-hydroxytryptamine 2 (5-HT_2) receptors antagonist. Also its affinity to interact with dopamine, histamine, adrenergic, and muscarinic receptors is relatively high [25]. Cyproheptadine is extensively metabolized in the liver and principally excreted as inactive metabolites in the urine and feces. The principal metabolite found in human urine has been identified as a quaternary ammonium glucuronide conjugate of cyproheptadine. Cyproheptadine may have additive effects with alcohol and other CNS depressant such as hypnotics, sedative, tranquilizers, and antianxiety agents. Monoamino oxidase inhibitors can prolong and intensify anticholinergic

effects of cyproheptadine. It does not have significant drug interaction through cytochrome P450 isoenzymes [26-28].

Some neuropsychiatric effects of cyproheptadine are same as clozapine [25]. Also, cyproheptadine and clozapine have the similar mechanism in food intake-enhancing effect in an experimental study [29]. Cyproheptadine has beneficial effects in the treatment of acute and chronic schizophrenia, anxiety, and depression [30-34]. It also may be effective in treatment of recurrent and posttraumatic nightmares and in the prevention of vascular-type headaches, especially migraine attacks [35-39]. Cyproheptadine is a hypnotic drug that can induce sleep and also improves its quantity and quality [40]. Common side effects of cyproheptadine are appetite improvement and weight gain [41]. It seems that cyproheptadine can be useful in the treatment of neuropsychiatric disorders that are related to HIV/ART and improve HIV-positive patients' appetite and weight gain. In this review, potential benefits of cyproheptadine in prevention and treatment of ART-associated neuropsychiatric problems will be evaluated based on the available evidences.

2. Methods

The available evidences were collected by searching Scopus, PubMed, Medline, Cochrane central register of controlled trials, and Cochrane database systematic reviews. Cyproheptadine, depression, psychosis, hallucination, delusion, headache, nightmare, anxiety, sleep, insomnia, appetite, weight, HIV, HAART, and ART were used as keywords to search. We selected the evidences that supported the possible benefits of cyproheptadine in HIV/ART complications. No time limit was applied for selecting articles.

The numbers of retrieved articles were 75. The irrelevant articles (animal and basic experimental studies, *in vitro* studies, non-English language reports) have been excluded. Finally, we have included 27 relevant human studies up-to-date of publication. The important studies are organized in **Table 1**.

3. Cyproheptadine and neuropsychiatric adverse reactions

3.1 Cyproheptadine and insomnia/nightmare

Cyproheptadine seems to be effective in treatment of recurrent and posttraumatic nightmares. Two cases of recurrent nightmares that were treated with 4 – 8 mg cyproheptadine at bedtime have been reported. These patients did not experience nightmares following cyproheptadine addition, but the dreams recurred after discontinuation of cyproheptadine. One of the patients continued cyproheptadine electively during his stress periods. The second case discontinued cyproheptadine after 1 week due to his daytime sedation [35]. In a retrospective review, the efficacy of cyproheptadine (4 – 12 mg at bedtime) was evaluated in treatment of nightmares associated with posttraumatic stress disorders in nine patients. Full remission or reduction in the intensity and recurrence of nightmares was detected following cyproheptadine therapy in these patients. In this study, the cyproheptadine effects initiated after few days of treatment and its optimum effects were observed within 3 – 4 weeks. Cyproheptadine also improved the patients' sleep quality. In two patients, the nightmares relapsed after cyproheptadine discontinuation and disappeared after restarting cyproheptadine. Most of the patients reported improvement in their nightmares in follow-up periods at Month 9 or later. It was suggested that anticholinergic and antiserotonergic properties of cyproheptadine are responsible for reduction of rapid eye movement (REM) sleep and also reduction or remission of nightmares [42]. Rijnders *et al.* reported a case of posttraumatic nightmares (up to five nights a week) following her rape. Up to 12 mg cyproheptadine was prescribed for the patient and her severity and frequency of nightmares diminished to one per week. They used electroencephalogram (EEG), polysomnography data, and serum levels of cyproheptadine for evaluation of the patient's clinical status. Nearly normal sleep's pattern was reported in the polysomnography following cyproheptadine administration. Serum level of cyproheptadine was 6 µg/L after administration of 12 mg of cyproheptadine in this patient [37].

Tokunaga *et al.* have evaluated the effects of some H_1-receptot antagonists including oral cyproheptadine (at doses of 5 and 10 mg/kg) on the sleep–wake cycle in sleep-disturbed rats in comparison with oral nitrazepam (at doses of 0.5 and 1.0 mg/kg) in an experimental study. The EEG and electromyogram (EMG) were recorded by implanting electrodes into the frontal cortex and the dorsal neck muscle of rats, respectively. They used an electroencephalograph for recording EEG and EMG and Sleep Sign ver. 2.0 for analyzing EEG and EMG. EEG and EMG were recorded for 6 h after oral administration of drugs. In this study, cyproheptadine decreased the total waking time. It also increased the total non-REM sleep time, slow wave sleep, and delta activity [40].

Although most available evidences regarding beneficial effects of cyproheptadine in treatment of nightmare and sleep quality are based on the case reports or series, but due to the comprehensive clinical, EEG, EMG, and polysomnography evaluations in these reports, it can be concluded that cyproheptadine is an attractive agent for relieving nightmares and improvement of sleep quality and quantity in HIV/ART cases.

3.2 Cyproheptadine effects on anxiety, depression, and schizophrenia

It has been reported that 5-HT_2 receptor antagonists (such as cyproheptadine, ritanserin, and mianserin) have potential beneficial effects in ameliorating of schizophrenia, anxiety, and depression symptoms [30,31].

3.2.1 Cyproheptadine and anxiety

Cyproheptadine with its sedative effects can be a suitable agent in ameliorating of the anxiety symptoms in different

Table 1. Summary of the studies that have been evaluated neuropsychiatric effects of cyproheptadine in different populations.

Type of study (Number of subjects)	Intervention	Outcome (Ref.)
Cyproheptadine and Insomnia/nightmare		
Case report, patients with recurrent nightmares (n = 2)	4 – 8 mg of oral cyproheptadine at bedtime	Nightmares did not occur after initial dose of cyproheptadine, but the dreams relapsed after discontinuation of cyproheptadine [35]
Retrospective review, patients with nightmares associated with posttraumatic stress disorder (n = 9)	4 – 12 mg of oral cyproheptadine at bedtime	Cyproheptadine was effective in the reduction of nightmares associated with PTSD and also improved sleep quality [42]
Case report, Patient with posttraumatic nightmares (n = 1)	Up to 12 mg of oral cyproheptadine	The severity of nightmares diminished and nearly normal sleep was reported [37]
Cyproheptadine and anxiety		
Randomized, double-blind, comparative trial, patients with anxiety disorders (n = 67)	Mianserin as 10 mg three times a day or diazepam as 5 mg three times a day for 4 weeks in a double-blind condition, followed by crossing over all patients to placebo for further 3 weeks in a single-blind condition.	Both of treatment groups had similar improvement in scores (Hamilton Anxiety Rating Scale, Physician's Global Rating, Patient's Global Assessment and Treatment Emergent Symptoms Scale) during first 4 weeks. No change was detected in scores in both groups during subsequent 3 weeks of placebo therapy [43]
Randomized, double-blind, placebo-controlled clinical trial, patients with generalized anxiety disorder (n = 48)	Ritanserin 5 mg twice daily (n = 22) or placebo (n = 26)	The ritanserin-treated patients had significant improvement in Hamilton Anxiety Rating Scale scores, especially in the insomnia items, tension and depressed mood and also they became more energetic and more relaxed according to the Mood Rating Scale [44]
Cyproheptadine and depression		
Randomized, double- blind, comparative multicenter trial, patients with depression (n = 109)	Mianserin 20 mg three times daily or imipramine 50 mg three times daily for 4 weeks	No significant difference in antidepressant effect was seen between two groups [43]
Randomized, double-blind, placebo-controlled crossover trial, patients with major depression (n = 6)	Cyproheptadine or placebo 4 mg four times per day for 4 weeks, then 8 mg four times per day for another 4 weeks and then crossed- over to cyproheptadine HCl or placebo	Depression was improved in four patients based on Hamilton Depression Rating Scale scores [45]
Cyproheptadine and schizophrenia		
Open study, patients with chronic schizophrenia (n = 10)	Patients were stabilized on lowest effective dose of haloperidol for 4 weeks. Cyproheptadine was started with 4 mg daily and was titrated up to 32 mg daily over 2 weeks and this dose was maintained for another 4 weeks.	The clinical response in four patients was categorized as moderate to good. Negative symptoms improved significantly in these patients [46]

Table 1. Summary of the studies that have been evaluated neuropsychiatric effects of cyproheptadine in different populations (continued).

Type of study (Number of subjects)	Intervention	Outcome (Ref.)
Randomized, double-blind, placebo-controlled study, patients with chronic schizophrenia (n = 20)	Patients received placebo or oral cyproheptadine, 4 mg daily and then titrated up to 32 mg over 2 weeks. Patients maintained on this dose for 4 weeks.	All scales (Brief Psychiatric Rang Scale, Negative Symptom Rating Scale, and schedule for assessment negative symptoms) except Simpson Angus scale did not significantly differ between two groups during this study. Cyproheptadine did not have any effect on the negative symptoms of schizophrenia, but it caused fewer extrapyramidal side effects in comparison with placebo [47]
Randomized, double-blind, placebo-controlled clinical trial, patients with chronic schizophrenia (n = 46)	Patients received up to 12 mg haloperidol for 2 weeks, and then they received placebo or oral cyproheptadine (8 mg for first 3 days and then tapered up to 24 mg on Day 7) for 6 weeks.	Combined cyproheptadine and haloperidol did not have any further benefits over haloperidol alone in chronic schizophrenia except fewer extrapyramidal side effects [33]
Randomized, double blind, placebo-controlled crossover study, patients with chronic schizophrenia (n = 18)	Single dose of 20 mg oral cyproheptadine	Cyproheptadine did not have any effect on the patients' frontal lobe function [48]
Randomized, double-blind, placebo-controlled clinical trial, patients with chronic schizophrenia (n = 30)	Patients were treated with 30 mg haloperidol and 24 mg cyproheptadine per day or 30 mg haloperidol and placebo per day for 8 weeks	A significant difference in positive and negative syndrome scale scores was detected between two groups. Cyproheptadine showed beneficial effects in treating negative symptom of schizophrenia [34]
Randomized, double-blind placebo-controlled cross-over study, patients with schizophrenia (n = 18)	Oral cyproheptadine 8 mg twice per day or placebo was prescribed for 4 weeks, then after 6 – 8 weeks washout period, patients in each group were crossed-over	There was not any significant difference between placebo or treatment group in all psychopathological rating scales. Significant statistically improvement was reported in neurological tests. Cyproheptadine can modulate the frontal lobe function, but it did not change negative symptoms of schizophrenia [49]
Cyproheptadine and headache		
Randomized, double-blind, comparative trial, patients with depression and chronic headache (n = 38)	oral ritanserin 10 mg daily or amitriptyline 50 mg daily during treatment period	Anti-headache activity of ritanserin is similar to amitriptyline in this study [50]
Randomized, double-blind, placebo-controlled clinical trial, patients with migraine (n = 259)	Four groups of patient received either placebo, 2 mg cyproheptadine twice a day, 40 mg propranolol twice a day, and combination of 2 mg cyproheptadine twice a day and 40 mg propranolol twice a day.	Cyproheptadine decreased frequency, duration, and severity of migraine attacks. The most statistically significant pain relief was seen in propranolol- and cyproheptadine-treated group [51]
Cyproheptadine and appetite/weight		
Randomized, double-blind, placebo-controlled, healthy adult (n = 12)	Placebo was administered to all subjects during first, second, fifth, and sixth weeks. During the third and fourth weeks, placebo or cyproheptadine 2 mg three times daily for the first 4 days and 4 mg three times per day for other days was administered.	Cyproheptadine caused significant weight gain in the subjects [53]

Table 1. Summary of the studies that have been evaluated neuropsychiatric effects of cyproheptadine in different populations (continued).

Type of study (Number of subjects)	Intervention	Outcome (Ref.)
Residential study, healthy volunteers (n = 7)	Patients received placebo on days 1, 2, 3, and 6, and cyproheptadine, 4 mg on days 4 and 5 with either regular diet, low carbohydrate diet, and high carbohydrate diet	The total caloric intake was increased by cyproheptadine only in the regular diet condition. Cyproheptadine improved caloric intake by increasing the number of eating occasions but not the eating occasion size [54]
Retrospective chart review, ADHD patients (n = 20)	Cyproheptadine 4 – 8 mg every night for at least 14 days	Cyproheptadine caused significant weight gain and improved sleep in the most subjects [41]
Randomized, double-blind, placebo-controlled; clinical trial, patients with CF (n = 18)	Patients received placebo or cyproheptadine 2 mg four times daily for 1 week and then increased to 4 mg four times daily for 11 weeks	Weight, height, BMI percentiles, ideal body weight/height, weight for age z-scores, and fat and fat-free mass were significantly increased in cyproheptadine group [55]
Randomized, double-blind, placebo-controlled; clinical trial, patients with CF (n = 16)	Patients received placebo or cyproheptadine, 4 mg four times daily for 9 months	Cyproheptadine's appetite stimulant effect maintained over the time in CF patients [56]
Randomized, double-blind, placebo-controlled; clinical trial, patients with CF (n = 28)	Patients received placebo or cyproheptadine, 4 mg three times daily for 12 weeks	The patients' body mass index and weight were significantly increased in cyproheptadine group [57]
Randomized, double-blind, placebo-controlled; clinical trial, malnourish children (n = 70)	Children received placebo or cyproheptadine, 0.1 mg/kg/dose three times daily for 8 weeks	Cyproheptadine group showed significantly higher absolute weight gain than placebo group at the end of this trial [58]

populations. Results of a double-blind comparative trial of mianserin and diazepam in 67 patients with anxiety disorders have been reported. Patients randomly received mianserin (10 mg three times a day) or diazepam (5 mg three times a day) orally for 4 weeks in a double-blind condition followed by crossing-over all patients to placebo for further 3 weeks in a single-blind condition. Hamilton Anxiety Rating Scale (HARS), Physician's Global Rating, Patient's Global Assessment, and Treatment Emergent Symptoms Scale were completed at base line and at weekly intervals. Patients in both the groups had similar improvement in different scores during first 4 weeks of treatment. No significant change was observed in the scores in both groups during subsequent 3 weeks of placebo therapy. In this study mianserin showed anxiolytic and side effects similar to diazepam [43].

The efficacy of a selective 5-HT_2 antagonist, that is, ritanserin was investigated in 48 patients with generalized anxiety disorder for 4 weeks in a double-blind trial. Ritanserin 5 mg twice daily was administered for 22 patients, and 26 patients were included in the placebo group. The HARS and the Visual Analog Mood Rating Scale were used for assessing symptoms. The ritanserin-treated patients had significant improvement in HARS scores, especially in the insomnia items, tension, and depressed mood, and they became more energetic and relaxed according to the Mood Rating Scale. The statistically significant differences between two groups were detected after 2 weeks [44].

Although a few studies have evaluated the antianxiety effects of 5-HT_2 antagonists, but as these studies were well designed and double blinded with control groups, it can be concluded that these agents may be considered for symptomatic treatment of anxiety disorders in different populations.

3.2.2 Cyproheptadine and depression

There are limited studies that have evaluated the role of cyproheptadine monotherapy or as adjunct therapy with other antidepressants in management of depression. Murphy *et al.* also reported that mianserin is effective as imipramine in the management of depression in a double-blind, comparative multicenter trial. Mianserin 20 mg three times daily or imipramines 50 mg three times daily for 4 weeks were randomly administered to 109 male and female depressive individuals. Severity of depression was assessed by a 17-items physician rating scale and a 10-items visual analogue self-rating scale before treatment and on days 7, 14, and 28 of treatment. No significant differences in antidepressant effects were seen between two groups [43]. Greenway *et al.* also reported antidepressant effects of cyproheptadine in six patients with major depression in a double-blind, crossover trial. Cyproheptadine or placebo was randomly prescribed as 4 mg, four times per day for 4 weeks, then 8 mg four times per day for another 4 weeks, and then crossed-over the patients to cyproheptadine or placebo. Hamilton Depression Rating Scale and 1-mg dexamethasone suppression test were applied immediately before stating cyproheptadine and at 4 weeks intervals during this study period. Two patients with non-suppressible dexamethasone suppression tests could not tolerate cyproheptadine due to their anxiety and irritability. Hamilton Depression Rating Scale scores decreased significantly in four patients with suppressible dexamethasone suppression tests during the study [45].

Based on the results of these few studies with small sample size, the judgment about positive effects of cyproheptadine as monotherapy or adjunct therapy in treatment of depression is difficult. Well-designed, randomized clinical trials are needed to confirm the role of cyproheptadine in the treatment of depression.

3.2.3 Cyproheptadine and schizophrenia

Several studies have evaluated the potential benefits of cyproheptadine as augmentation therapy with a typical antipsychotic (such as haloperidol) in the management of negative and positive symptoms of schizophrenia. Silver *et al.* evaluated the effects of cyproheptadine in 10 patients with chronic schizophrenia. Prior to cyproheptadine administration, patients were stabilized on lowest effective dose of haloperidol for 4 weeks. Cyproheptadine was started with a dose of 4 mg per day and was titrated up to 32 mg per day over 2 weeks. This dose was continued for another 4 weeks and then was tapered down within 1 week. Clinical response was assessed at baseline and at weekly intervals during the study period and after 2 weeks of cyproheptadine withdrawal. The Brief Psychiatric Rating Scale (BPRS), the Clinical Global Inventory (CGI), and the Krawiecka-Goldberg Scale (KGS) were used for the patients' overall clinical state assessment. In addition, Simpson Angus (SA) scale and Negative Symptom Rating Scale (NSRS) were, respectively, applied for the patients' extra-pyramidal (EPS) and negative symptoms evaluation in this study. The clinical response to cyproheptadine in four patients was categorized as moderate to good (20 – 43% improvement in the total BFRS scores). The most significant effect of cyproheptadine was reported in the improvement of negative symptoms of the patients. The authors concluded that cyproheptadine can ameliorate both positive and negative symptoms in chronic schizophrenic patients, and the most significant improvement was seen in negative symptoms [46].

Effects of cyproheptadine in the treatment of chronic schizophrenia were evaluated in a randomized, double-blind study. Haloperidol 10 – 60 mg daily was prescribed for 20 patients for at least 4 weeks prior to the trial. Patients received placebo or oral cyproheptadine 4 mg daily and then titrated up to 32 mg over 2 weeks. Patients were undertreated with this dose for 4 weeks. BPRS and NSRS were used for assessment of patients' negative symptoms and SA scale for extrapyramidal side effects in this study. The scales were completed at baseline, 4 and 6 weeks after treatment. All scales except SA showed no significant differences between two groups during the study. The results of this study showed that cyproheptadine did not have any effects on the negative symptoms of schizophrenia, but it caused fewer EPS in

comparison with placebo [47]. Lee *et al.* investigated the anti-schizophrenic effects of cyproheptadine in 46 chronic schizophrenic patients in a randomized, double-blind clinical trial. Patients received up to 12 mg haloperidol for 2 weeks, and then received placebo or oral cyproheptadine (8 mg daily for first 3 days and then tapered up to 24 mg daily on Day 7) for 6 weeks. BPRS, CGI, and SA were, respectively, used for the assessment of negative, positive, and EPS symptoms of the patients at baseline and biweekly until end of the study. They did not find any significant differences between two groups for any scales during the study period except SA. They concluded that concomitant administration of cyproheptadine and haloperidol did not have any further beneficial effects over haloperidol in chronic schizophrenia except fewer extrapyramidal side effects [33]. In another study, cyproheptadine with dose of 20 mg as a single dose was prescribed for 18 patients with chronic schizophrenia in a double-blind placebo-controlled crossover study. Cyproheptadine did not have any effect on neuropsychological tests such as stroop, verbal fluency, Wisconsin card sort, trail making, and memory. They concluded that single dose of cyproheptadine did not have pronounced effect on the frontal lobe function [48].

Akhondzadeh *et al.* 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. Positive and negative syndrome scale (PANSS) was used to measure patients' outcome at baseline and after 2, 4, 6, and 8 weeks after initiation of the treatment. PANSS scores were higher in placebo group in comparison with cyproheptadine group at weeks 4, 6, and 8. A significant difference in PANSS scores was detected from Week 6 between two groups. They concluded that cyproheptadine may be useful in ameliorating of negative symptoms of schizophrenia [34]. In another study, Chaudhry *et al.* evaluated effects of cyproheptadine on the frontal lobe function and also the negative symptoms in 18 patients with schizophrenia that were stabilized on a depot neuroleptics in a randomized, double-blind, crossover study. Oral cyproheptadine 8 mg twice per day or placebo was administered for 4 weeks and subsequently after 6 – 8 weeks washout period, patients in each group were crossed-over. They used neuropsychological tests (verbal fluency, stroop color word task, and trial making) and rating scales (Manchester scale, SA, and PANSS) for assessment of patients on days 7 and 28. They reported that there were not any differences between placebo or treatment group in all psychopathological rating scales during the study period, but significant improvement was reported in neurological tests in patients in the treatment group. They suggested that 5-HT_2 antagonists such as cyproheptadine can modulate the frontal lobe function, but they did not change negative symptoms of schizophrenia [49].

Although available evidences support the beneficial effects of cyproheptadine as adjunct therapy in management of negative symptoms of schizophrenia and ameliorating of EPS effects of typical antipsychotics, its beneficial effects on positive symptoms is questionable. Different doses of cyproheptadine were used in the available studies. Also, small sample size and application of different neuropsychiatric scales for evaluation of cyproheptadine effects are other limitations of these studies. It must be emphasized that all available evidences about positive effects of cyproheptadine in schizophrenic patients are based on adjunct therapy with an effective antipsychotic. More studies with sufficient sample size are required to clarify the role of cyproheptadine in treatment of schizophrenia in HIV/AIDS patients.

3.3 Cyproheptadine and headache

Cyproheptadine with dose of 4 – 12 mg per day is commonly used as migraine headache prophylaxis [36,37]. Analgesic and antidepressant properties of ritanserin (a 5-HT_2 antagonist such as cyproheptadine) were evaluated in 38 patients with depression and chronic headache in a double-blind trial. This study was divided in to three periods; 1 month run in period, 3 months treatment period, and 1 month washout period. The patients randomly received oral ritanserin, 10 mg daily or amitriptyline, and 50 mg daily during the treatment period. Patients recorded their headache episodes, duration, severity, and analgesics requirement. The investigators also calculated pain total index (PTI) and completed Hamilton Depression Rating Scale and Hamilton anxiety Rating Scale in monthly interval until end of the washout period. Ritanserin reduced Hamilton Depression Rating Scale and Hamilton Anxiety Rating Scale scores significantly during both the treatment and washout periods. Reduction in PTI and analgesic consumption were similar between ritanserin- and amitriptyline-treated groups. Results of the study showed that the anti-headache activity and antidepressive properties of ritanserin is similar to amitriptyline [50]. Rao *et al.* evaluated role of propranolol and cyproheptadine in the migraine prophylaxis in a controlled double-blind trial. They compared the efficacy of propranolol, cyproheptadine, combination of them, and placebo in 259 patients with migraine headache. The patients were classified into four groups: placebo, 2 mg cyproheptadine twice a day, 40 mg propranolol twice a day, and a combination of 2 mg cyproheptadine and 40 mg propranolol twice a day for 3 months. Amelioration in frequency, duration, and severity of the patients' headache were recorded as 100 (complete relief), 75, 50, 25, and 0% (no relief) during the study period. In this study cyproheptadine significantly decreased the frequency, duration, and severity of the patients' migraine attacks. The most statistically significant relief in the patients' headache attacks was detected in the combination treatment of propranolol and cyproheptadine [51].

There are enough evidences to support the role of cyproheptadine in prevention of migraine-type headaches in different populations, and it can be an effective alternative for prevention of migraine-type headache in HIV/AIDS patients.

3.4 Cyproheptadine and appetite/weight gain

Cyproheptadine can stimulate appetite and cause moderate weight gain. Cyproheptadine as an appetite stimulant has been tried in patients with HIV infection with doses from 4 mg oral twice daily to four times daily [52]. Stiel *et al.* described the mechanisms of cyproheptadine induced weight gain through its effects on food intake and metabolism. Their study had two parts. In part A of the study, effects of cyproheptadine in 12 healthy adults on ad libitum diets were evaluated for 6 weeks in a double-blind method. Placebo was administered for all subjects during first, second, fifth, and sixth weeks. During the third and fourth weeks, placebo or cyproheptadine was randomly administered for the subjects. Due to drowsiness of cyproheptadine, placebo and cyproheptadine were administered in one-half tablet (2 mg) three times daily for the first 4 days and one tablet (4 mg) three times per day for other days. Subjects' weight, appetite, and side effects were recorded daily. In addition, urine samples were collected daily. All six subjects who received cyproheptadine, experienced weight gain with a mean of 2.2 kg (1.4 to 3.1 kg) during the third and fourth weeks. A mean of 0.45 kg weight gain during the first and second weeks and a mean of 0.64 kg weight loss during fifth and sixth weeks were detected in these subjects. Weight gain in the treatment period (weeks 3 and 4) was significantly higher than the first placebo period (weeks 1 and 2). Placebo subjects gained only 0.14, 0.18, and 0.36 kg weight during each 2 weeks of the study, respectively, and their weight gain was not statistically significant. Increase in appetite and food intake was reported by majority of the subjects during cyproheptadine therapy periods. Urinary nitrogen, potassium, or volume did not change significantly during each 2 weeks study period. Drowsiness was reported by three subjects in cyproheptadine group that decreased the patients' normal activity. In part B of the study, three patients in cyproheptadine group were randomly selected and maintained on a constant diet for another 3 weeks. They received placebo one tablet three times per day during the first and third weeks and cyproheptadine 4 mg three times daily during second week of the study. Fasting blood glucose, plasma insulin, plasma growth hormone (GH), and basal metabolic rates were measured on days 1, 5, 8, 12, 15, 19, and 21 of the study. In addition, the patients' weight, appetite, and side effects were recorded at those days. All patients experienced weight gain with a mean of 0.73 kg under constant diet, and their weight gain was statistically significant but was less than that of subjects who were under ad libitum diet. Fasting blood glucose, plasma insulin, GH, and basal metabolic rate did not change during cyproheptadine therapy. The investigators concluded that cyproheptadine can cause weight gain in both adult and children by two possible mechanisms. The major mechanism is an increase in appetite and subsequently food intake. Other mechanism that plays minor role is decrease in patient's activity because of its sedative effects [53].

Comer *et al.* reported the results of a residential study in seven healthy volunteers that received oral cyproheptadine or placebo for 18 days. Three types of diet were assessed in this study: regular, low carbohydrate, and high carbohydrate diet. Patients received placebo on days 1, 2, 3, and 6, and cyproheptadine with dose of 4 mg on days 4 and 5 of each diet. Total caloric intake was increased about 20% following cyproheptadine consumption only in the volunteers that were under the regular diet condition. Cyproheptadine caused improvement in caloric intake by increasing the numbers of eating occasions but not the eating occasion size [54].

In another study, Daviss *et al.* evaluated the benefits of cyproheptadine in a retrospective chart review of 28 young individuals with attention deficit hyperactivity disorder (ADHD) who were under treatment with stimulants. Cyproheptadine ordered for them due to weight loss or insomnia. Data from 21 patients who received cyproheptadine (4 – 8 mg every night) at least for 14 days were analyzed. The patients' weight changes were recorded during two time spans. First time span was between initiation of stimulant and the time when cyproheptadine was added (time 1). Second time span was between initiation of cyproheptadine and the last visit of the patients (time 2). In addition to sleep chart, Clinician's Global Impressions Improvement (CGI) scale was used for evaluation of the patient's insomnia during the two time spans. Weight loss was detected in most patients on stimulant alone. Weight gain was reported when cyproheptadine was added to stimulant. Weight gain was significantly faster in the second time span compared with the first time span. At first, 17 patients had sleep problems when they were under treatment with stimulant, and 11 out of them experienced significant improvement in their sleep after cyproheptadine was added to stimulant. The authors concluded that cyproheptadine had beneficial effects in ADHD patients who suffered from stimulants induced weight loss [41].

Homnick *et al.* evaluated short-term effects of cyproheptadine on appetite in 18 patients with cystic fibrosis (CF) in a randomized, double-blind clinical trial. Patients received placebo or cyproheptadine with dose of 2 mg four times daily for 1 week and then increased to 4 mg four times daily for 11 weeks. Shwachman score, anthropometrics (weight, height, body mass index, skin folds, and body composition by bioelectric impedance analysis), spirometry, calorie intake, days of oral (PO) and intravenous (IV) antibiotics, and patients' satisfaction were measured at baseline and every 4 weeks. Weight, height, BMI percentiles, ideal body weight/height, weight for age z-scores, and fat and fat-free mass were significantly increased in cyproheptadine group. No significant changes were detected in spirometry and duration of IV or PO antibiotic treatment. The only side effect was transient mild sedation. The authors concluded that cyproheptadine can be used as appetite stimulant in CF patients [55]. Homnick *et al.* also evaluated long-term effects of cyproheptadine in the previous study. The patients received

placebo or cyproheptadine, 4 mg four times daily for 9 months in a randomized, double-blind manner. Anthropometrics, spirometry, and duration of PO and IV antibiotics were measured at baseline (end of the pervious study), 3, 6, and 9 months during the recent study. Patients who changed their medication from placebo to cyproheptadine showed significant weight gain over 3 – 6 months, and those who continued their cyproheptadine from the previous study maintained weight gain during this period. No significant changes were detected in spirometry and IV or PO antibiotic treatment. They concluded that the cyproheptadine effect as appetite stimulant maintained over the time in CF patients [56].

Epifanio *et al.* investigated short-term effects of cyproheptadine on weight gain in 28 patients with CF in a randomized, double-blind, placebo-controlled trial for 12 weeks. Patients received placebo or cyproheptadine 4 mg three times daily. Weight, height, and spirometry were measured at baseline and at the end of 12 weeks trial. Body mass index and weight were significantly increased in cyproheptadine group. They found that cyproheptadine can be effective for inducing weight gain during short time period [57].

In non-CF population, Rerksuppaphol *et al.* reported results of a randomized, double-blind, placebo-controlled trial in 70 malnourished children. Children received placebo or cyproheptadine (0.1 mg/kg/dose) three times daily for 8 weeks. Anthropometrics parameters (weight, height, skinfold thickness, waist and hip circumferences, and fat composition by bioelectric impedance analysis) were measured at baseline and every 2 weeks during the study period. Cyproheptadine group showed significantly higher absolute weight gain than placebo at the end of the trial. They concluded that cyproheptadine can be effective in gaining weight in a short-term period [58].

In the available studies, different doses of cyproheptadine have been evaluated in different populations as appetite stimulant and promoter of weight gain. In addition, various assessment tools were applied for evaluation of the cyproheptadine effects on weight gain and appetite stimulation. Despite these limitations, cyproheptadines traditionally used as an appetite stimulant and besides its other beneficial effects, available evidences support cyproheptadine use in HIV-positive individuals that usually suffer from decreased appetite and weight loss.

3.5 Cyproheptadine and interactions with ART

The psychotropic medications that have been used for management of HIV/ART-associated neuropsychiatric complications include antidepressants (such as citalopram, sertraline, mirtazepine, reboxetine, venlaflaxine), antipsychotics (such as olanzapine, risperidone), mood stabilizers (such as valproate, lamotrigine), and anxiolytics (such as oxazepam, lorazepam, temazepam). The psychotropic drugs can interact with antiretroviral medications through cytochrome P450 pathways. These interactions can change the blood levels of both groups of drugs and may lead to toxicity [15,22]. Cyproheptadine does not have significant interactions with antiretroviral medications through cytochrome P450 [26-28]. It is a great benefit of cyproheptadine over psychotropic medications. With this favorable pharmacokinetic profile, cyproheptadine can be a safe option for treatment of some neuropsychiatric complications in HIV/AIDS patients.

4. Expert opinion

In this review, different beneficial effects of cyproheptadine for treatment of neuropsychiatric complications associated with HIV/ART have been evaluated. Antiretroviral medications and HIV infection have some neuropsychiatric adverse effects that may be improved with cyproheptadine. Different studies have reported the efficacy of cyproheptadine and other 5-HT_2 antagonists in the treatment of anxiety, depression, negative and positive symptoms of schizophrenia, nightmares, headache, and insomnia. These problems are the most common neuropsychiatric adverse effects that are associated with HIV/ART. Although cyproheptadine have not evaluated in the HIV-positive patients for these neuropsychiatric complications, based on the evidences from other populations, it seems that cyproheptadine has the potential to ameliorate HIV/ART-associated neuropsychiatric complications. Cyproheptadine also is an available, cheap, and relatively safe medication. It does not have significant interactions with antiretroviral drugs through cytochrome P450 pathways. Cyproheptadine-related common side effects including increasing appetite and weight gain can be useful in HIV-positive individuals with decreased appetite and weight loss. There are limited evidences about the efficacy of cyproheptadine in neuropsychiatric disorders. It is essential that the efficacy of cyproheptadine in the management of neuropsychiatric side effects associated with HIV/ART be evaluated in well-designed studies in the future.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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