Fluoxetine in progressive multiple sclerosis

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Original Research Paper

Fluoxetine in progressive multiple sclerosis: The FLUOX-PMS trial

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Abstract

Background: Preclinical studies suggest that fluoxetine has neuroprotective properties that might reduce axonal degeneration in multiple sclerosis (MS).

Objective: To determine whether fluoxetine slows accumulation of disability in progressive MS.

Methods: In a double-blind multicenter phase 2 trial, patients with primary or secondary progressive MS were randomized to fluoxetine 40 mg/day or placebo for a period of 108 weeks. Clinical assessments were performed every 12 weeks by trained study nurses who visited the patients at their home. The primary outcome was the time to a 12-week confirmed 20% increase in the Timed 25 Foot Walk or 9-Hole Peg test. Secondary outcomes included the Hauser ambulation index, cognitive tests, fatigue, and brain magnetic resonance imaging (MRI).

Results: In the efficacy analysis, 69 patients received fluoxetine and 68 patients received placebo. Using the log-rank test ($p=0.258$) and Cox regression analysis ($p=0.253$), we found no significant difference in the primary outcome between the two groups. Due to an unexpected slow rate of progression in the placebo group, there was insufficient statistical power to detect a potential benefit of fluoxetine. We found no differences between the two groups for secondary outcomes.

Conclusion: The trial failed to demonstrate a neuroprotective effect of fluoxetine in patients with progressive MS.

Keywords: Multiple sclerosis, progressive multiple sclerosis, clinical trial, fluoxetine, outcome, neuroprotection

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Introduction

Multiple sclerosis (MS) is a disease of the central nervous system primarily characterized by inflammatory demyelinating lesions and a progressive degeneration of axons. A majority of patients start with inflammatory lesions resulting in relapses, several years later often followed by a secondary progressive deterioration (secondary progressive MS (SPMS)). Other patients develop a slowly progressive accumulation of neurological disability from the onset with little or no relapses (primary progressive MS (PPMS)). The inflammatory component of the disease can to a large extent be tackled by an increasing number of immunotherapies available for MS.[1] However, the neurodegenerative aspect responsible for the progressive phase of the disease remains poorly understood and largely untreatable.

Fluoxetine, well known as a selective serotonin-reuptake inhibitor used for depression and other psychiatric disorders, may reduce the inflammatory responses in MS as shown in experimental autoimmune encephalitis in rodents and in a small proof-of-concept study in patients with relapsing MS.[2–4] A number of preclinical studies suggest that fluoxetine may also have neuroprotective potential that could be beneficial in MS. Mechanisms include an increased release of brain-derived neurotrophic factor from astrocytes and stimulation of astrocytic glycogenolysis, which delivers lactate as energy supply to axons.[5,6]

A small single-center, randomized, double-blind, placebo-controlled trial investigated the effect of fluoxetine on progression in MS but failed to show any benefit.[7] However, inclusion rate was insufficient and

there was an unanticipated low rate of disability progression in the placebo group. The aim of this study was to further assess whether fluoxetine has a neuroprotective effect in progressive MS.

Methods

Patients

This was a multicenter, randomized, double-blind, placebo-controlled trial conducted in Belgium and The Netherlands between February 2012 and March 2016. The protocol of the study was described in TRIALS, to which we refer for further details.[8] The study was registered at the European Union Drug Regulating Authorities (EudraCT Number 2011-003775-11).

Patients with either SPMS or PPMS, aged 25–65 years with a score on the Expanded Disability Status Scale (EDSS)[9] of 3–6.5, and documented confirmed evidence of disease progression independent of relapse over the year prior to enrollment, defined as an increase of at least 0.5 point on the EDSS, were enrolled.

The main exclusion criteria were use of antidepressants, pregnancy or lactation, and other neurologic or psychiatric disorders (including major depression) or systemic disorders that could interfere with the assessments. For sexually active female patients with reproductive potential, use of reliable means of contraception was required. Concomitant medications that could lead to clinically significant interactions with fluoxetine (such as monoamine oxidase inhibitors) were not allowed. The use of interferon beta or glatiramer acetate was allowed, as these drugs are ineffective in slowing down disability accrual in progressive MS.[10,11] Patients using other immunosuppressive or immunomodulatory drugs could only be included if the drug was stopped at least for 2 months before randomization.

The study was approved by the Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten (FAGG, Belgium), Centrale Commissie Mensgebonden Onderzoek (CCMO, Netherlands), as well as by the ethics committees of the participating hospitals. All patients gave written informed consent.

Procedures

Eligibility was determined at the screening visit (week 4). After randomization (1:1 using a block size of 10) at week 0, study medication was started with one daily tablet of 20 mg fluoxetine or placebo (both supplied by Eurogenerics, Brussels, Belgium) for the first 4 weeks, followed by a daily single intake of two tablets of 20 mg fluoxetine or placebo until week 108.

Study visits were carried out by trained study nurses visiting the patients at their home, where they performed all clinical assessments at weeks 0, 12, 24, 36, 48, 60, 72, 84, 96, and 108. An optional follow-up visit was planned at week 120 to confirm sustained progression appearing at week 108. The study nurses were the primary contact persons for the patient and sent their data to the principal investigator's team at UZ Brussel. They provided the study medication, planned magnetic resonance imaging (MRI) of the brain, evaluated medication adherence and changes in medications, and recorded adverse events. If necessary, additional unscheduled visits were performed.

The treating neurologist continued the routine follow-up of their patient but was not involved in any of the study assessments. If there was a change in immunomodulatory treatment (other than interferon beta or glatiramer acetate) or antidepressants had to be started, the treating neurologist was asked to notify the principal investigator's team who then decided whether the patient could remain in the study. Medication changes were also recorded at each study visit. In case of a suspected relapse, patients were referred to their treating neurologist.

At each visit, the study nurses measured the Timed 25 Foot Walk (T25-FW; assessment of lower limb function) and the 9-Hole Peg test (9-HPT; assessment of upper limb function) and recorded the Hauser Ambulation Index. At weeks 0, 60, and 108, the patients underwent a cognitive test battery consisting of the Symbol Digit Modalities Test (SDMT), California Verbal Learning Test-II (CVLT-II), and Controlled Oral Word Association Test (COWAT), and both the Beck Depression Inventory-II (BDI-II) and Modified Fatigue Impact Scale (MFIS) were recorded.

Outcomes

The primary outcome was the time between weeks 12 and 108 to confirmed disease progression, defined as either at least a 20% increase in performance on the T25-FW or at least a 20% increase in the 9-HPT, unrelated to relapse and sustained for at least 12 weeks up to the end of the trial or drop-out. Secondary clinical endpoints were the proportion of patients without sustained 20% increase in the T25-FW and the 9-HPT between weeks 12 and 108; the proportion of patients

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with a stable Hauser ambulation index; cognitive changes measured through the cognitive test battery; and the BDI-II and MFIS.

Secondary surrogate endpoints, which were not compulsory, were brain MRI and optical coherence tomography (OCT). Technical details are provided in the TRIALS paper.[8] Brain MRI was performed in six hospitals on a 3-T scanner (Philips or Siemens). All MRI data were automatically processed by Icometrix (Leuven, Belgium) using MSMetrix software to extract volumetric measurements for whole brain, gray matter, cortical gray matter, white matter, and the T2 lesion load.[12] Diffusion tensor imaging (DTI) quantified by fractional anisotropy and mean diffusivity was used to assess white matter tissue integrity. The DTI analysis (32 diffusion directions, b, 800 s/mm^2; TE, 85 ms; TR, 8500 ms; voxel size, $2 \times 2 \times 2$ mm^3; acquisition time, 9.48 minutes) was a voxel-based analysis and the diffusion values were evaluated across the whole cerebral white matter using a population-specific template. OCT to measure retinal nerve fiber layer (RNFL) thickness and macular volume was performed only in patients recruited at the University Hospitals of Brussel and Gent.

Statistical analysis

A previous observational study in untreated patients with PPMS found a 20% sustained worsening on either the T25-FW or 9-HPT over a period of 2 years in 55%.[13] Our sample size was based on an estimated rate of confirmed disability progression of 0.55 for the control group and 0.30 for the fluoxetine group. Using sample size calculation for two survival curves (Statemate™; GraphPad Software, San Diego, CA, USA), a sample of 60 patients per group have 80% power to detect a decrease in confirmed disability progression of 0.25 with a significance level (alpha) of 0.05 (two-tailed). For every patient who dropped out within the first 12 weeks, a new patient was included. In anticipation of further drop-outs between weeks 12 and 108, 10 extra patients per group were added. No power estimates were made for the secondary outcomes.

All other statistical analyses were performed using Statistical Package for Social Sciences version 25 (SPSS, Chicago, IL, USA). We performed Kaplan–Meier survival curves with the log-rank test to compare differences in time to confirmed disease progression between the two treatment groups. Cox regression was used to estimate the reduction in hazard associated with fluoxetine treatment compared with placebo.

Differences in proportions were compared between arms with the chi-square test and differences in means with the Mann–Whitney U test. To analyze changes from baseline in cognitive testing, BDI-II, MFIS, and brain MRI measurements and to evaluate whether there were differences between the two treatment arms, linear mixed models analysis was used. A p value <0.05 was considered to indicate statistical significance.

Results

Patients

A total of 151 patients were randomly assigned to fluoxetine ($n=74$) or placebo ($n=77$); 69 patients in the fluoxetine group and 68 patients in the placebo group entered the efficacy period starting at week 12 (Figure 1). Both groups were similar for baseline characteristics except for age and BDI-II score (Table 1).

Clinical endpoints

With regard to time to progression, both the log-rank test ($p=0.258$) and Cox regression analysis ($p=0.253$) failed to show a significant difference between the two treatment arms. The Cox regression analysis showed an unadjusted hazard ratio (reduction in hazard by fluoxetine compared to placebo) of 1.253 (95% confidence interval (CI): 0.787–2.487). Figure 2 shows the Kaplan–Meier curve. The hazard ratio adjusted for age and BDI-II score was 1.182 (95% CI: 0.634–2.205; $p=0.598$). A not-preplanned analysis found no significant difference between the two treatment groups when analyzing PPMS and SPMS patients separately. We also performed the analysis using only the 9-HPT to determine whether patients were less likely to have upper limb function progression, which might be a potentially more sensitive marker in progressive MS studies,[14] but this did not show a significant difference between the two treatment arms either.

Of the 69 patients, 48 (69.6%) in the fluoxetine group and 42 of the 68 (61.8%) in the placebo group remained stable during the study period ($p=0.336$). The proportion of patients with a stable Hauser ambulation index was also not significantly different between the two treatment arms ($p=0.411$). We did not find any difference between the two treatment groups for the cognitive tests (SDMT, CVLT-II, and COWAT), BDI-II, and MFIS. Table 2 shows the mean values of the different tests over time.

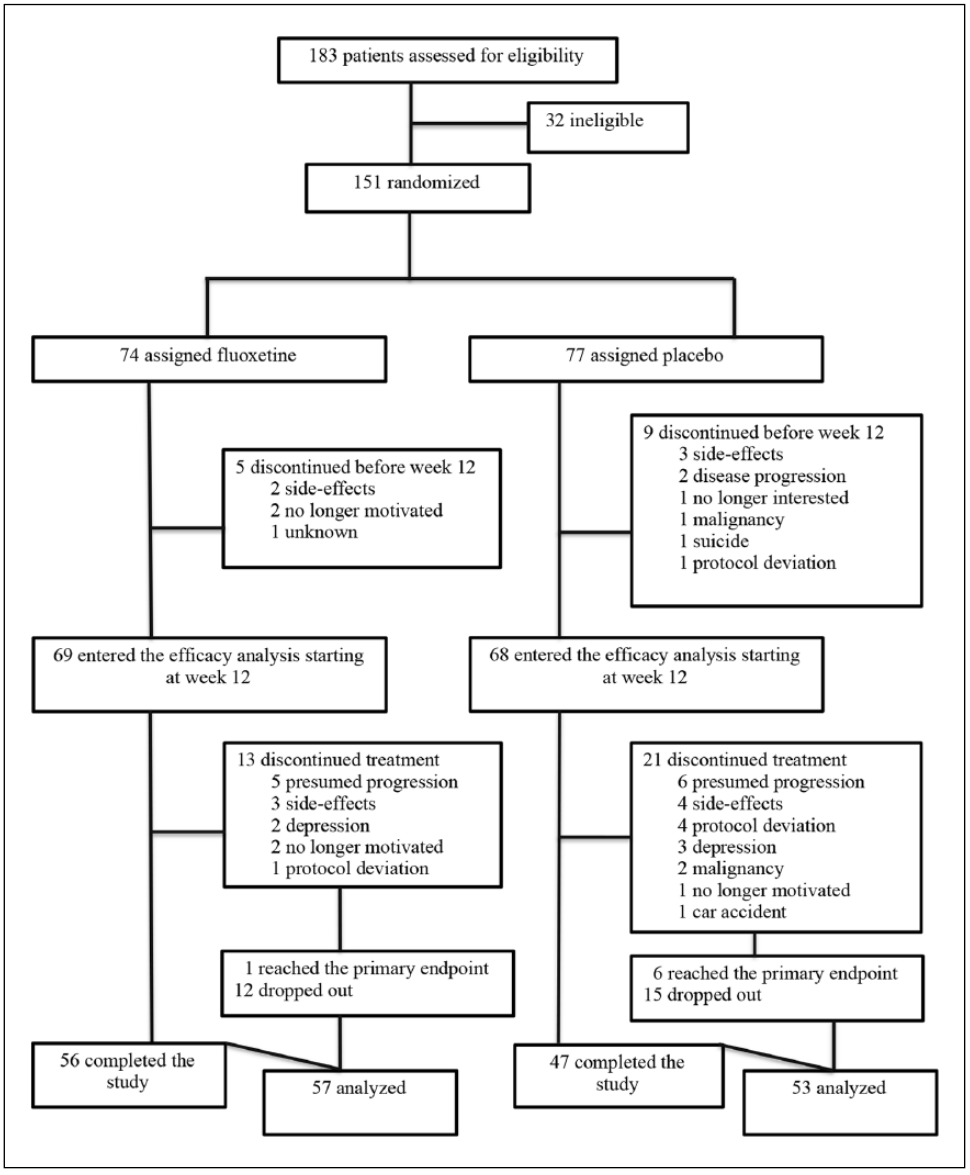

Figure 1. Trial profile.

Brain MRI

Of the patients, 68% in the fluoxetine group and 51% of patients in the placebo group underwent brain MRI at both weeks 12 and week 108. There was no difference between the two groups in loss of whole brain volume, gray matter volume, cortical gray mater volume, and white matter volume (Figure 3). There was also no difference in changes in T2 lesion load and in diffusion tensor MRI measurements of fractional anisotropy and mean diffusivity.

OCT

Only 10 placebo and 11 fluoxetine-treated patients underwent OCT at weeks 12 and 108. There was no difference in change of the RNFL thickness and macular volume between the two groups.

Adverse events

Adverse events are listed in Table 3. Fluoxetine is a drug discovered in 1970, and its potential side-effects are therefore well known. There were no unexpected side-effects during the trial.

Four patients treated with fluoxetine and two patients treated with placebo were reported to have had a relapse. During the trial, 14 patients (5 in the fluoxetine group) received corticosteroids prescribed by their treating neurologist.

Table 1. Baseline characteristics of patients included in primary efficacy analysis by study group.

	Fluoxetine ($n=69$)	Placebo ($n=68$)
Sex		
Female	31 (44.9%)	30 (44.1%)
MS type		
PPMS	40 (58.0%)	37 (54.4%)
SPMS	27 (39.1%)	28 (41.2%)
Age* (years)		
Mean (SD)	54.0 (6.11)	51.2 (7.64)
Median (range)	54.0 (37;66)	51.0 (33;63)
Disease duration (years)		
Mean (SD)	14.4 (8.79)	12.2 (7.87)
Median (range)	12.0 (3;40)	10.0 (3;41)
EDSS		
Mean (SD)	5.1 (1.25)	5.2 (1.36)
Median (range)	5.5 (3.0;6.5)	6.0 (2.5;6.5)
Disease-modifying treatment[a]		
Yes	18 (26.1%)	19 (27.9%)
MFIS		
Mean (SD)	40.3 (19.29)	40.1 (13.24)
Median (range)	42.0 (0;77)	42.5 (7;67)
BDI-II*		
Mean (SD)	14.7 (10.07)	11.3 (6.43)
Median (range)	13.5 (1;63)	10.0 (0;28)
SDMT		
Mean (SD)	36.2 (11.07)	37.6 (11.39)
Median (range)	34.5 (16;70)	39.0 (16;65)
CVLT-II		
Mean (SD)	128.8 (30.75)	131.7 (25.59)
Median (range)	134.5 (45;182)	133.0 (63;178)
COWAT semantic		
Mean (SD)	20.2 (5.95)	20.5 (6.44)
Median (range)	20.0 (7;35)	19.0 (9;42)
COWAT phonetic		
Mean (SD)	30.1 (13.60)	30.1 (16.87)
Median (range)	31.0 (7;66)	27.0 (9;125)

EDSS: Expanded Disability Status Scale; MFIS: Modified Fatigue Impact Scale; BDI-II: Beck Depression Inventory-II; SDMT: Symbol Digit Modalities Test; CVLT-II: California Verbal Learning Test–II; COWAT: Controlled Oral Word Association Test.
[a]Only interferon beta or glatiramer acetate was allowed.
*$p < 0.05$.

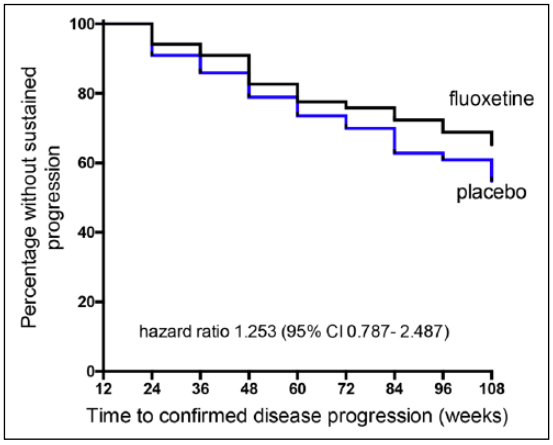

Figure 2. Survival curve of the time to progression for the fluoxetine (upper curve) and placebo groups.

Discussion

In this phase 2 trial, we could not demonstrate a neuroprotective effect of fluoxetine in patients with progressive MS for both clinical parameters of disease progression and brain MRI outcome measures. The primary endpoint in our trial was the time to confirmed disease progression defined as at least a 20% increase in either the T25-FW or the 9-HPT. Our sample size was based on the findings of Bosma et al.,[13] who found, using this composite endpoint, a 2-year disease progression rate of 55% in patients with PPMS. Interestingly, this corresponds, using the same combined endpoint, to the reported 2-year cumulative confirmed disease progression rate of 56.7% in the placebo cohort of the PPMS patients in the PROMiSe trial.[15] However, the confirmed disease progression rate in our trial for the placebo group was only 38.2%, which in our design approached the anticipated 30% progression rate for the fluoxetine group. Given the unexpected slow rate of progression in the placebo arm, there is insufficient statistical power to detect a potential treatment effect of fluoxetine. In addition, the drop-out rate after week 12 was 27 instead of the anticipated 20 (Figure 1). Assuming a progression rate of 40% in the placebo group and 30% in the fluoxetine group, we would need around 350 patients in each treatment arm to detect a statistically significant effect of fluoxetine.

Different to the Bosma and PROMiSe cohorts is that we included both SPMS and PPMS patients. However, the pathophysiological mechanisms leading to progressive axonal degeneration in SPMS and PPMS are likely the same as both proceed at remarkably similar rates.[16,17] We found no treatment effect on the primary endpoint by analyzing the SPMS and PPMS groups separately.

Adding the traditional EDSS to the composite endpoint might have led to the registration of more progression events.[15] However, we decided not to include the EDSS because clinical assessments were performed by study nurses visiting the patients at their home. The study nurses were well trained to assess

Table 2. Mean values (SD) for the cognitive tests, BDI-II, and MFIS over time.

	Week 0	*N*	Week 60	*N*	Week 108	*N*	*p* value
SDMT							0.769
Placebo	37.6 (11.3)	66	37.0 (12.1)	54	37.0 (12.4)	46	
Fluoxetine	36.5 (11.0)	68	35.9 (11.4)	59	35.9 (10.6)	55	
CVLT-II							0.769
Placebo	131.7 (25.5)	63	137.0 (27.2)	52	137.7 (37.3)	45	
Fluoxetine	128.8 (30.7)	68	137.5 (28.8)	59	138.6 (32.6)	56	
COWAT semantic							0.313
Placebo	20.5 (6.4)	58	20.0 (6.1)	55	20.3 (6.4)	46	
Fluoxetine	20.2 (5.9)	66	20.4 (5.9)	59	19.6 (5.1)	56	
COWAT phonetic							0.051
Placebo	30.1 (16.8)	66	29.1 (10.5)	56	30.4 (9.7)	46	
Fluoxetine	30.1 (13.6)	68	34.6 (12.8)	59	33.5 (15.3)	56	
BDI-II							0.050
Placebo	11.3 (6.4)	66	11.3 (7.3)	55	8.9 (7.3)	44	
Fluoxetine	14.7 (10.0)	68	11.9 (8.6)	59	12.6 (8.2)	56	
MFIS							0.157
Placebo	40.1 (13.2)	66	35.0 (17.4)	55	36.4 (16.5)	44	
Fluoxetine	40.3 (19.2)	68	39.5 (16.1)	59	42.7 (16.2)	56	

SD: standard deviation; SDMT: Symbol Digit Modalities Test; CVLT-II: California Verbal Learning Test–II; COWAT: Controlled Oral Word Association Test; BDI-II: Beck Depression Inventory-II; MFIS: Modified Fatigue Impact Scale.

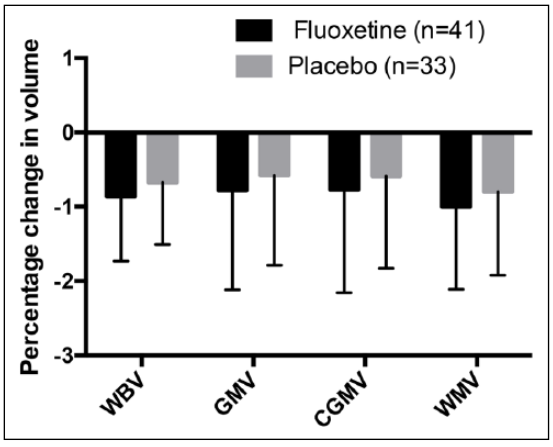

Figure 3. Percentage (±SD) in brain volumetric changes between week 108 and week 12.
WBV: whole brain volume; GMV: gray matter volume; CGWV: cortical gray matter volume; WMV: white matter volume.

the T25-FW and 9-HPT but not to perform and register the EDSS.

Concerns have been raised that upper instead of lower limb function may be needed to observe effects in progressive MS. In the ASCEND trial, natalizumab had no effect in lower limb function (EDSS and T25-FW), but a significant effect on arm function (9-HPT) at 96 weeks.[14] We did not observe a treatment effect of fluoxetine in our trial by only using the 9-HPT as progression criterion.

Our primary focus was clinical endpoints assessed in the natural environment of the patient. Not all patients were eager to undergo brain MRI, and therefore, this part of the study was not compulsory and must therefore be interpreted with caution. In the patients who participated, we found no significant changes in both anatomical MRI measurements of atrophy and structural DTI. The recently reported preliminary results of the Multiple Sclerosis-Secondary Progressive Multi-Arm Randomisation Trial (MS-SMART)[18] showed that fluoxetine 40 mg a day given for 96 weeks did not slow brain atrophy on brain MRI in patients with SPMS.[19]

We did not find any effect of fluoxetine on cognitive tests and fatigue. As no power estimates were made for the secondary outcomes, any conclusions should be regarded as tentative. Fluoxetine was in general well tolerated without unexpected side effects.

In conclusion, our trial found no evidence that a daily dose of 40 mg fluoxetine has a neuroprotective effect in patients with progressive MS. However, it should be emphasized that because the study was underpowered, our results do not allow to draw firm conclusions.

Table 3. Adverse events.

Adverse events	Fluoxetine ($n=69$)	Placebo ($n=68$)
Tiredness	4	1
Rash/itch	3	1
Restlessness	2	
Nausea	2	
Drowsiness	2	
Mood changes	2	3
Headache	2	1
Dizziness	1	1
Weight gain	1	
Insomnia	1	
Diarrhea	1	
Blurred vision	1	
Neoplasm		2

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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