Fluoxetine for the symptomatic treatment of Multiple System Atrophy: the MSA-FLUO trial

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Abstract:

Background: There are no effective treatments for multiple system atrophy (MSA).

Objective: To assess the efficacy and safety of the serotonin reuptake inhibitor fluoxetine (40 mg/day) for the symptomatic treatment of ~~multiple system atrophy (~~MSA~~)~~.

Methods: This was a double-blind, parallel-group, placebo-controlled, randomized (1:1) trial conducted in patients with "probable" MSA. The primary outcome was the change from baseline (Δ) to week-12 in the mean total score of the Unified MSA Rating Scale (UMSARS) Part I (historical review) + II (motor examination). Secondary outcomes included Δ-to-week-6 in total UMSARS, and Δ-to-week-12 in the Scales for Outcomes in Parkinson Disease-Autonomic Dysfunction, the Beck Depression Inventory, and the different domains of the MSA-Quality of Life questionnaire. Exploratory outcomes included Δ-to-week-12 in UMSARS Part I and II separately, and Δ-to-week-24 in total UMSARS.

Results: Eighty-one patients were randomized (40 to fluoxetine and 41 to placebo; mean age = 63 years; mean disease duration = 5 years). There was no significant difference in the primary outcome (treatment effect [95%CI], -2.13 units [-4.55;0.29],~~-~~p=0.08). There was a greater reduction on fluoxetine in Δ-to-12-week in UMSARS Part II (exploratory outcome: -1.41 units [-2.84;0.03], p=0.05) and in MSA-QoL emotional/social dimension (secondary outcome: -6.99 units [-13.40;-0.56], p<0.03). Five deaths were reported (2 on fluoxetine and 3 on placebo). No unexpected adverse events were observed. Those

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leading to treatment interruption or down titration were more frequent on fluoxetine.

Conclusion: The MSA-FLUO failed to demonstrate fluoxetine superiority over placebo on the total UMSARS score, but trends in motor and emotional secondary/exploratory outcomes deserve further investigation.

Introduction

Multiple system atrophy (MSA) is an orphan, sporadic, devastating neurodegenerative disorder characterized by alpha-synuclein positive glial cytoplasmic inclusions and selective neurodegeneration in multiple brain areas.[1,2] The clinical phenotype of MSA encompasses a heterogeneous combination of symptoms related to autonomic dysfunction, poorly levodopa-responsive parkinsonism and cerebellar ataxia, leading to major disability and fatal outcome within few years.[1,2] The current treatments for MSA are extremely limited and disappointing,[3] with a major need for better interventions.[4,5]

The serotonin systems degenerate in MSA, along with other neurotransmitters systems. A loss of serotonin neurons has been documented post-mortem in the brainstem of MSA patients.[6,7] Alterations of serotonin biomarkers have been reported in vivo in the CSF of patients with MSA[8] or using functional neuro-imaging.[9,10] The contribution of serotonin mechanisms in the genesis of the motor and non-motor symptoms of MSA remains unclear. In animal models of parkinsonism, serotonin modulates the mesolimbic dopaminergic pathway and increases locomotor activity.[11] Serotonergic dysfunction has been involved in the pathophysiology of autonomic dysfunction, respiratory disturbances, apathy, pain and fatigue in MSA patients.[12-14] Paroxetine, a selective serotonin reuptake inhibitor (SSRI), has been reported to improve glottic stenosis in 3 patients with MSA.[15] Fluoxetine, another SSRI, may improve orthostatic hypotension in patients with Parkinson's disease (PD), although this has not been tested in MSA.[16] SSRIs are first line treatments for major depression in the general population[17] and depression is a common symptom in MSA.[18] SSRIs ameliorate

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depressive symptoms in PD,[19] but this has never been assessed in MSA patients.

Serotonin can therefore be considered as a suitable therapeutic target for MSA, and medications like SSRIs, that have therapeutic value in relation to augmenting serotonergic neurotransmission, are available candidates. Such an approach has been rarely addressed in the past, with only one published randomized double-blind placebo-controlled study evaluating the effects of paroxetine.[20] The results of this pilot trial suggested that paroxetine may provide symptomatic benefit in MSA patients, although the small size of the sample (19 subjects) precluded definite conclusions. Therefore, the French Reference Center for MSA[21] and the French NS-Park/FCRIN network[22] set-up the MSA-FLUO trial to assess the symptomatic efficacy and safety of fluoxetine in patients with MSA.

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Methods

Study design and patients

This was a 24-week multicenter, randomized, double-blind, placebo-controlled, parallel-group, 2-arm clinical trial conducted by the French MSA national network of reference and competence centers across France (Aix-en-Provence, Bordeaux, Clermont-Ferrand, Dijon, Lille, Limoges, Marseille, Montpellier, Nantes, Paris-Henri Mondor, Paris-Pitié Salpêtrière, Poitiers, Rennes, Strasbourg, Toulouse), with the support of the French NS-PARK/FCRIN network. Patients were assessed at six consecutive visits: screening visit (within 4 weeks before baseline visit), week 0 (baseline), 6, 12, 24 and 28 (safety visit).

Patients were enrolled if they were aged between 30 and 80 years and if they were diagnosed with “probable” MSA according to international consensus diagnosis criteria.[23] Both parkinsonian (MSA-P) or cerebellar (MSA-C) phenotypes were eligible. Exclusion criteria were cognitive impairment precluding study evaluations, severe dysphagia making pill swallowing difficult, major depression disorder requiring specific treatment or having required any antidepressant agent during the 3 months preceding recruitment. Patients suffering from dementia (MMSE score < 24), wheel-chair bound or suffering from severe hyponatremia were also not included.

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Active treatment consisted of fluoxetine 20 mg/day for the first 6 weeks and then 40 mg/day until the end of the 24th week. Treatment could be tapered off to the initial 20 mg/day dose if patients experienced unacceptable side effects. Treatment was tapered off during 1 week after week 24 and then interrupted, and a final safety visit was held at week 28.

Symptomatic treatments for autonomic or parkinsonian symptoms were allowed, providing that their dose had been stable for 2 months before entering into the study and was anticipated to remain unchanged during the study.

The study was registered in the ClinicalTrials.gov database (NCT number: NCT01146548). All patients signed informed consent before participating into the trial after ethical approval by the “Comité de Protection des Personnes Sud-Ouest et Outre-Mer II” and the French Drug Agency (AFSSAPS). The study was sponsored by the Toulouse University Hospital and funded by the “Programme Hospitalier de Recherche Clinique” of the French Ministry of Health and Social Affairs (PHRC 2007 07-2001-01).

Randomization, treatments and masking

Balanced randomization in blocks of 4 was used, in a 1:1 ratio. The Pharmacy of the Toulouse University Hospital provided the computer randomization list. Subjects were randomized at baseline (week 0), after an eligibility assessment had been completed at a screening visit.

Fluoxetine hydrochloride was introduced at a dose of 20 mg/day (Prozac®, Eli Lilly) and then increased to 40 mg/day (2 x 20 mg pills) at the end of the 6th week. Matching placebo consisted in lactose pills with same color, odor and flavor as compared to fluoxetine. The investigators and personnel involved in patients' assessment, monitoring, analysis, and data management were masked to group assignment. Compliance was assessed by counting the difference in the number of pills delivered at a visit and brought back by the patients at the next visit. The proportion of patients with ≥ 80% compliance was assessed.

Outcomes

The primary outcome was the mean change from baseline (Δ) to week-12 (month 3) in the total Unified MSA Rating Scale (UMSARS) Part I (historical review) + Part II (motor examination) score.[24] The same investigator of each MSA reference/competence center performed the UMSARS evaluation for a given patient. The choice of week-12 (month-3) to assess the primary outcome was made in order to reduce the risk of changes in concomitant symptomatic medications on longer follow-up (24 weeks).

Secondary outcomes included Δ-to-week-6 in the mean scores of the total UMSARS, Δ-to-week-12 in the Scales for Outcomes in Parkinson's Disease -

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Autonomic Dysfunction (SCOPA-Aut) total score to assess autonomic disturbances,[25] in the Beck Depression inventory (BDI) to assess depressive symptoms,[26] and in the different dimensions of the MSA Health-Related Quality of Life (MSA-QoL) questionnaire (motor, non-motor, emotional/social scores & Health VAS).[27] Secondary outcomes, except UMSARS, were assessed at weeks 0 and 12 only.

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Exploratory variables included Δ-to-week-12 in the mean scores of UMSARS Part I and II assessed separately, and Δ-to-week-24 in total UMSARS.

Survival, adverse events (AEs) and vital signs were recorded at each visit.

Statistical analysis

Quantitative variables were described by means and standard deviations, while number of cases and percentages were used for qualitative variables. Differences across treatment groups were analysed by bivariate and multivariate techniques. Bivariate analysis included Chi-square or Fisher exact test for qualitative outcomes and T-test or Mann-Whitney test for the quantitative ones. Multivariate analyses were performed by linear regression, using treatment as an independent variable and including the following covariates recorded at baseline: age, UMSARS total (I+II) score, BDI score, disease duration and any other variable for which a significant between-group difference was found at baseline. Interaction between center and treatment was also studied and was not significant for any outcome.

Efficacy analysis was conducted in the intention to treat (ITT) population, defined as all randomized subjects. Imputation of missing data was performed by the Last Observation Carried Forward method (LOCF). Sensitivity analyses

included imputation by multiple regression and no imputation and analyses in the Full Analysis Set (FAS) defined as patients having received at least one dose of treatment and having at least one evaluation post-randomization. Safety data were evaluated for all randomized participants who took at least one dose of study drug.

Powering of the study estimated that a sample size of 33 subjects per group would provide a 90% power at a 5% difference level to detect a difference in the Δ at week-12 in the UMSARS total score between fluoxetine and placebo, with an assumed difference of 4 UMSARS points and a standard deviation of 4 UMSARS points. A 25% drop-out rate was expected, and recruitment of 50 patients per group was therefore previewed.

Results

Eighty-seven patients were screened, out of whom 81 were randomized, 40 to fluoxetine and 41 to placebo (ITT population) between June/2008 and October/2010. Two patients (both randomized to placebo) had no evaluation post-baseline (one patient died from suicide at week 4 and a second refused to come back after the baseline visit). The FAS population included therefore 79 patients, 40 on fluoxetine and 39 on placebo. Thirteen patients on fluoxetine and 10 on placebo dropped-out prematurely from the trial (Figure 1). The proportion of patients with compliance greater than 80% was similar among the placebo and fluoxetine groups (82% in both groups). A larger proportion of subjects in the placebo group (80%) reached and was maintained on the target dose (40 mg/d) as compared to the fluoxetine group (62%).

At baseline, there were no differences between the placebo and fluoxetine groups regarding demographics and outcomes data, except for a higher non-motor MSA-QoL sub-score and a shorter disease duration in the fluoxetine group (Table 1).

No significant between-group difference was observed in the primary outcome measure (Δ-to-week-12 in total UMSARS score), although UMSARS total scores were numerically lower on fluoxetine than placebo at all visits, except baseline (Figure 2), and there was a trend in favor of a greater treatment-effect on fluoxetine (treatment effect [95%CI], -2.13 units [-4.55;0.29], p=0.08). Adjusted analyses are reported in Table 2. The treatment-effect was greater on fluoxetine at week-12 for the UMSARS Part II sub-score (exploratory outcome, p=0.05) and for the emotional/social functioning sub-score of the MSA-QoL scale (secondary outcome, p=0.03). No other differences were observed. Sensitivity analyses provided similar results (data not shown).

Five patients died during the trial: 3 in the fluoxetine group (one sudden death and two respiratory distress) and 2 in the placebo group (one suicide and one respiratory distress). None were considered to be related to treatment. Ninety-seven percent of patients on fluoxetine and 92% on placebo reported at least one Adverse Event (AE). Serious AEs were more frequently observed in patients randomized to fluoxetine than placebo (28% versus 17% respectively). Twenty-eight percent of patients on fluoxetine had an AE leading to treatment

premature interruption or down titration, as compared to 11% on placebo. The most relevant AEs are listed in Table 3.

Discussion

The MSA-FLUO placebo-controlled randomized trial failed to demonstrate the superiority of fluoxetine on its primary outcome and must therefore be considered as a “negative” study. However, several trends in favor of fluoxetine were observed, including Δ-to-week-12 changes in UMSARS total score (primary endpoint, p=0.08), UMSARS motor examination sub-score (exploratory outcome, p=0.05) and emotional/social functioning sub-score of the MSA-QoL scale (secondary outcome, p=0.03). Trends supporting a potential short-term positive symptomatic effect of fluoxetine in MSA deserve discussion, as the treatment of this severe orphan disorder is limited to disappointing interventions supported by a low level of evidence.

Methodological issues must be discussed before considering any putative fluoxetine effects in MSA patients based on the present results. The dose of fluoxetine tested in the MSA-FLUO trial (40 mg/day) might not have been optimal to demonstrate full efficacy. Higher doses are known to be slightly more effective to treat major depressive disorders, but this benefit appears to plateau at 50 mg/day and is offset by decreased tolerability.[28] Twenty-eight percent of the MSA-FLUO patients did not tolerate the 40 mg/day dose, making the practical interest of higher doses unlikely in this population. Three months of follow-up are long enough to document the benefit of SSRIs in depressed

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patients, and this may also apply to capture a symptomatic effect in MSA.[29] Conversely, it is possible that the MSA-FLUO study was underpowered to document a benefit, as the observed treatment effect (-2.13 UMSARS points) was smaller than the estimate for the sample size calculation (-4 UMSARS units), at threshold that reflects a clinically meaningful difference.[30] The trial also included patients with both MSA-P and MSA-C. This may have induced a greater variance than in trials focusing on MSA-P only,[31] further reducing the power of the study. The risk of having included some patients suffering from other disorders than MSA cannot be excluded in the absence of post-mortem neuro-pathological confirmation. However, all patients of the MSA-FLUO had a "probable" diagnosis of MSA[23], established by experts from MSA reference/competence centers, in order to reduce the risk of false diagnosis. Finally, the MSA-FLUO population had a more advanced disorder at baseline (~5 years from diagnosis) than that of other trials which allowed including patients with "possible" MSA,[31] and one may speculate that the effect of fluoxetine could be greater at an earlier stage.

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A first important practical conclusion of the MSA-FLUO study is that fluoxetine did not worsen patients' disability, as monitored with the UMSARS in double-blind placebo-controlled conditions. Indeed, patients randomized to fluoxetine had consistently lower mean scores at each visit, except at baseline. SSRIs, including fluoxetine, are listed among the medications that can induce drug-induced parkinsonism.[32] Thus, the MSA-FLUO data provides evidence that using fluoxetine in MSA patients should not expose them to the risk of significant deterioration on the short-term.

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At week-12, there was a trend in favor of fluoxetine in the UMSARS Part II (motor examination) sub-score (p=0.05). This sub-score captures motor performance, as assessed by the investigator, as opposed to UMSARS Part I, which is a more global historical patient-reported review on oropharyngeal symptoms, difficulties in activities of daily living and dysautonomic symptoms.[24] UMSARS Part II is more sensitive than Part I to change over time in MSA prospective cohorts.[33] It is therefore conceivable that fluoxetine might have a greater impact on motor function than on other features of MSA, including autonomic ones. This assumption is consistent with the lack of effect observed on the SCOPA-Aut outcome in the same patients. The mechanisms underlying this potential motor effect remains speculative. Both MSA-P and MSA-C patients were included in the trial, and such an effect could then be equally driven by an effect of serotonin within the basal ganglia loops,[34] or within the cerebellar circuitry.[35] It is also possible that some positive effect on emotional features (see below) may have indirectly improved the motor behavior of the patients. Regardless of its underlying mechanisms, the amplitude of this putative motor effect is not expected to be dramatic (~1.5 units of the UMSARS motor score according to the present findings), although such an effect is still considered as clinically relevant.[30] Moreover, any symptomatic effect of fluoxetine in MSA is important to identify for research purposes, as this drug is listed among candidates for neuroprotective strategies in models of parkinsonism and MSA.[36-38] If fluoxetine is to be tested in the future using a disease-modifying trial design based on UMSARS outcomes, this effect might induce a significant confounding bias.[39]

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A second signal detected in the MSA-FLUO trial was that patients randomized to fluoxetine had greater improvement in the emotional/social functioning sub-score of the MSA-QoL scale (p=0.03). Depression is a common and disabling symptom of MSA,[40,41] and correlates with poor QoL.[42] It is conceivable that the central serotonin deficiency observed in patients with MSA may participate into the genesis of depressive symptoms.[6] It is common practice to use SSRIs to treat depression in MSA,[43] in spite of the fact that their efficacy and safety have never been tested in this population. The emotional/social functioning dimension of the MSA-QoL scale includes ratings of fatigue, cognitive ability, depression and apathy.[27] It is unclear which of these domains could be influenced by fluoxetine. The lack of effect observed in the BDI score does not support a direct antidepressant effect, although this scale might not be the most appropriate one to detect an antidepressant effect in MSA, and the study was not powered for this outcome. It is interesting to note that worsening of depression or suicide ideation was reported as an adverse event in 11% of the patients randomized to placebo while none of the patients on fluoxetine reported such events (see Table 3). It is also possible that fluoxetine may act on other emotional features than depression, as correlations between fatigue scores and 5HT1A binding have been recently reported in vivo in MSA patients.[14] The level of evidence currently supporting the use of any intervention to manage emotional features in patients with MSA is based on empirical and anecdotal observations only. The MSA-FLUO findings support further assessment of the use of fluoxetine to manage such disabling symptoms in this severe orphan disorder.

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No effects were observed on any other outcomes of the MSA-FLUO trial, including those addressing autonomic dysfunction, as measured by the SCOPA-Aut scale. Serotonergic systems are likely involved in the control of autonomic functions and their impairment in MSA could contribute to various aspects of autonomic dysfunction in this disorder.[16] It is possible that the SCOPA-Aut was not sensitive enough to detect changes induced by fluoxetine, while the study was not powered for that.

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No unexpected adverse events were reported in the MSA-FLUO trial, as compared with the known safety and tolerability profile of the drug in patients suffering from psychiatric disorders. More patients on fluoxetine than placebo reported anorexia, weight loss or nausea as an adverse event during the trial, all well-known adverse reactions of the drug.[44] Five patients died during the study, three on fluoxetine and two on placebo. None of these deaths were considered to be related to treatment. Such a rate of death in this population is in line with the natural history of a severe disease like MSA, as four years since the first visit has been recently reported as the patients' median survival in the large French MSA cohort.[45]

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In summary, the MSA-FLUO trial failed to demonstrate superiority of fluoxetine at the dose of 40 mg/day in the treatment of MSA. Several trends suggested however a possible partial improvement in motor and emotional/social functioning symptoms. Considering the paucity of efficacious treatments to manage such a severe disorder, and the existence of serotoninergic

abnormalities in MSA, the findings of the MSA-FLUO trial warrant further investigation.

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Figure 1. Study flow chart (ITT: intention-to-treat; FAS: full analysis set)

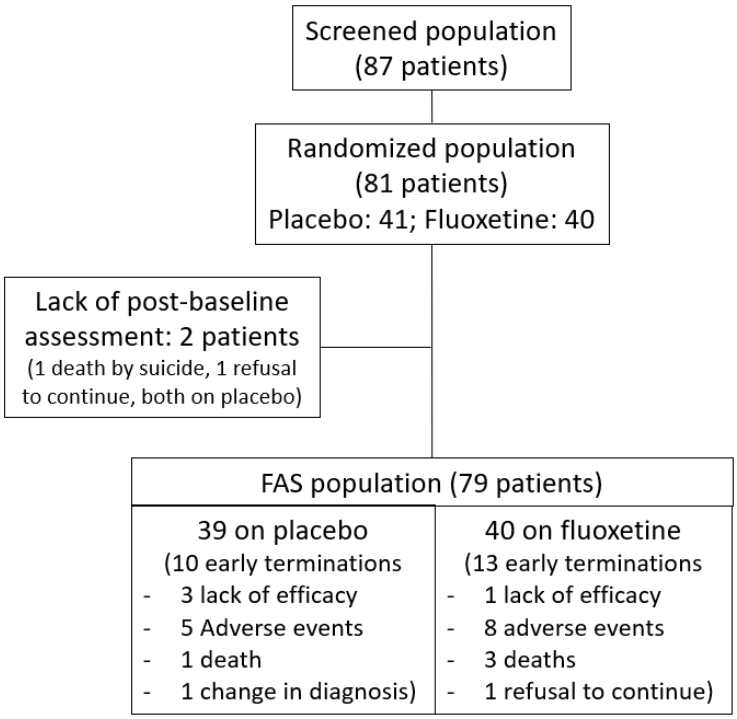

Figure 2. Changes from baseline to Week 24 in UMSARS I+II score in the ITT population (placebo =41; Fluoxetine = 40). No significant between-group differences were observed at any visit (primary study outcome measure: Week 12).

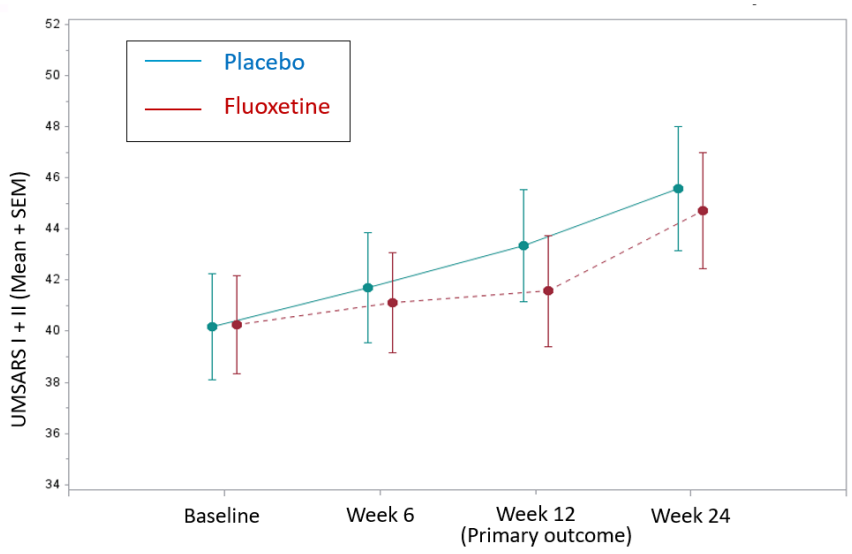

Table 1. Demographics and outcomes at baseline [ITT population; Means ± Standard deviations or n (%)] (LEDD: levodopa equivalent daily dose)

	Placebo (n=41)	Fluoxetine (n=40)	p-value
Age	63.5±8.1	63.1±7.8	0.82
Females	17 (41.5%)	14 (35.0%)	0.55
Weight	75.8±15.5	73.1±16.5	0.73
MSA “probable”	41 (100%)	40 (100%)	-
MSA type “P”	20 (48.8%)	24 (60.0%)	0.31
Disease duration	6.4±4.0	4.6±2.1	0.04
LEDD	458.6±496.5	487.5±517.4	0.75
UMSARS I+II	40.2±13.3	40.3±12.1	0.97
UMSARS I	18.7±6.9	19.2±6.5	0.95
UMSARS II	21.5±7.3	21.1±6.4	0.85
SCOPA-Aut	20.4±8.3	23.4±8.8	0.19
BDI	11.1±6.6	12.4±7.3	0.50
MSA-QoL scale			
Motor	44.4±19.5	46.8±20.3	0.72
Non-motor	34.3±17.3	42.6±18.3	0.04
Emotional/social functioning	31.8±20.5	38.1±22.1	0.27
Health VAS	49.0±17.8	46.2±22.0	0.66

Table 2. Study outcomes at Week 12 (ITT population, means ± Standard deviations)

	Score at Week 12			
	Placebo N=41	Fluoxetine N=40	Treatment effect (95% CI) Adjusted	p-value
UMSARS I+II	43.3±14.0	41.6±13.7	-2.13 (-4.55;0.29)	0.08
UMSARS I	20.3±6.9	20.2±6.6	-0.72 (-2.23;0.79)	0.34
UMSARS II	23.0±7.8	21.4±7.8	-1.41 (-2.84;0.03)	0.05
SCOPA-Aut total	20.3±8.9	23.2±8.4	0.05 (-2.93;3.03)	0.97
BDI	12.7±7.8	13.4±7.9	-0.47 (-3.31;2.38)	0.74
MSA-QoL scale				
Motor	47.3±22.4	45.4±18.8	-4.26 (-10.50;1.99)	0.18
Non-motor	33.4±18.2	39.1±19.1	-3.16 (-9.35;3.02)	0.31
Emotional/social	33.2±21.3	31.5±17.4	-6.99 (-13.40;-0.56)	0.03
Health VAS	50.3±20.9	47.6±20.2	-0.67 (-10.7;9.37)	0.89

Table 3. Most relevant Adverse Events (Number of cases and %).

	Placebo (n=39)	Fluoxetine (n=40)
Worsening of depression	3 (8%)	0
Suicidal ideation	1 (3%)	0
Anxiety	2 (5%)	1 (3%)
Agitation	1 (3%)	5 (13%)
Insomnia	1 (3%)	3 (8%)
Anorexia/Weight loss	7 (18%)	14 (35%)
Tremor	2 (5%)	5 (13%)
Nausea	3 (8%)	6 (15%)