EFFICACY OF MEMANTINE IN THE TREATMENT OF FIBROMYALGIA: A DOUBLE-BLIND RANDOMISED CONTROLLED TRIAL WITH 6-MONTH FOLLOW-UP.

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BACKGROUND

Fibromyalgia (FM) is a chronic rheumatic disease characterised by the presence of diffuse musculoskeletal pain, painful sensitivity to touch in at least 11 of 18 defined trigger points, and a constellation of symptoms including fatigue, disturbed sleep, cognitive problems and distress [42]. The prevalence of this syndrome in Europe is approximately 2.9% [2], and the prevalence in rheumatology consultations in Spain was found to be 12% [9]. A meta-analysis found statistically significant advantages of pharmacological interventions (SNRIs and pregabalin) over placebo on pain and quality of life in FM patients, but these effects were of questionable clinical relevance [29]. Overall, FM treatments are believed to have limited efficacy, with an effect size of approximately 0.5, regardless of whether they are administered in primary care or in specialised settings [10].

Pain is the most common and disabling symptom of FM. It is suspected that this pain is caused by the altered function of structures in the central nervous system, including the primary and secondary sensory and motor cortices, insula, anterior cingulate cortex, thalamus, dorsolateral prefrontal cortex and basal ganglia. These regions have been named the “pain matrix” because they are activated in response to a painful stimulus. A growing body of evidence suggests that glutamate (Glu), an excitatory neurotransmitter in the central nervous system, may play a part in the pathophysiology of FM, given that its concentration is elevated in the insula [16], hippocampus [40] and posterior cingulate cortex [8].

As a consequence, some authors have suggested that glutamate blocking drugs such as memantine may be useful in the treatment of FM [15], by reducing the harmful effects that result from excessively high levels of brain glutamate found in this condition [6]. Memantine is not believed to act by reducing levels of glutamate or preventing its release; rather, it is believed to reduce glutamate’s neurotoxic effect by blocking the N-methyl-D-aspartate (NMDA) receptor, thereby preventing the entry of excess calcium [17].

The NMDA receptor antagonist memantine has been used to treat Parkinson’s disease, spasticity, convulsions, vascular dementia and Alzheimer's disease and has an excellent clinical safety record spanning more than 20 years. It is a non-competitive

open-channel blocker that dissociates from the channel, which allows it to limit the pathological activity of the NMDA receptor without affecting normal synaptic activity [17]. Memantine has shown a very low incidence of side effects in clinical trials on humans [33], even with prolonged use [34]. Recent research has highlighted the efficacy of memantine for the treatment of complex regional pain syndrome [36] and phantom limb pain [24, 28], which suggests that the extent of analgesia depends on the type of pain being treated.

The aim of the present study is to evaluate the efficacy of memantine to increase pain threshold and to decrease pain perception in patients with fibromyalgia. The secondary objectives are to evaluate the efficacy of memantine in the treatment of other symptoms of fibromyalgia, such as cognitive function, health status, clinical global impression, anxiety, depression, and quality of life.

METHODS

Design: Double-blind, multi-centre, parallel randomised clinical trial with six-month follow-up.

The patients were randomised into two parallel groups: a treatment group, which was given 20 mg of memantine daily after a titration period of one month, and a control group, which received a placebo. There was a six-month follow-up period (including the dose adjustment period of one month).

This study is a randomised clinical trial with no commercial interest. It has been conducted in accordance with the standards of good clinical practice. It was performed according to the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT) [7], which recommends the inclusion of a set of core outcome domains in clinical trials of pain treatments. It also followed the recommendations established by the Consolidated Standards of Reporting Trials (CONSORT) statement [4, 25] for randomised controlled trials. The protocol of this study has previously been published [30].

Setting and Study Sample.

Patients diagnosed with FM were recruited for inclusion in the study from primary health care centres in Zaragoza, Spain, upon fulfilment of the following selection criteria: a) Age between 18-65 years; b) Ability to understand Spanish; c) Diagnosis of FM from a rheumatology specialist according to the American College of Rheumatology (ACR 1990) diagnostic criteria (1); d) Signing of an informed consent form; and e) Use of birth control during the study in the case of fertile women.

Exclusionary criteria at the time of study enrolment were as follows: a) Current drug treatment for fibromyalgia. In this case, patients had to discontinue treatment and go through a washout period of one week to minimise the influence of the medication on brain imaging measures. During this week, patients could take small doses of analgesics such as tramadol (100 mg) or paracetamol (325 mg) if needed, but only sporadically to minimise the influence of the medication on brain images; b) Current use of memantine or use of memantine during the 1 year prior to recruitment; c) Diagnosis of an Axis I psychiatric disorder, as assessed using the Structured Clinical Interview for DSM-IV (SCID-I), that might hinder adherence to the protocol (dementia, alcohol and/or substance abuse/dependence, or schizophrenia); d) Current pregnancy or breast-feeding; e) Hypersensitivity to the active ingredient, memantine, or to the excipients; f) Conditions that require special precautions when administering memantine, according to the summary of product characteristics (namely, epilepsy and circumstances that may cause high urine pH owing to Proteus urinary infection, renal tubular acidosis or a vegetarian diet, recent myocardial infarction, congestive heart disease and uncontrolled arterial hypertension); g) Clinically significant and active evidence of liver or kidney disease, haematological, respiratory, endocrine or cardiovascular disease or disorders. Patients with controlled diabetes, controlled hypertension and complete or incomplete right bundle branch block, however, could be included in the study; h) Use of drugs that may cause relevant interactions with memantine according to the summary of product characteristics, namely, NMDA receptor antagonists (e.g., amantadine, ketamine, or dextromethorphan), L-Dopa and dopamine agonists and cholinergic agonists; and i) Use of non-permitted concomitant medication during the week prior to the first evaluation visit, or expected treatment over the course of the study with at least one of the drugs not permitted, namely, antidepressants (e.g., duloxetine, venlafaxine, mirtazapine, bupropion, SSRIs, etc.), analgesics (e.g., pregabalin, gabapentin, opiates, etc.) or other drugs. During this week,

patients could take analgesics such as tramadol or paracetamol if needed, but only sporadically to minimise the influence of the medication on brain images.

There is currently no approved treatment for FM in Spain. In 2007, the FDA approved pregabalin as the first drug for the treatment of FM symptoms in the USA. The FDA has subsequently approved duloxetine and milnacipran for the same condition. Although these drugs are commercialised in Europe for other indications, European regulatory authorities have recently refused to widen their approval to include the treatment of FM [3].

A patient was considered to have withdrawn from the trial if he or she withdrew informed consent, if the researcher felt that he or she should withdraw from the study for reasons of safety/efficacy or if the researcher felt it to be in the best interest of the patient or if the patient did not comply with the treatment for more than 7 consecutive days.

Randomisation, allocation and masking of study groups

Each patient was assigned to one of the two groups using a computer-generated random number sequence without any restrictions. The random allocation sequence was implemented by a central telephone. The patients were enrolled by general practitioners working at the primary care centres involved. The assignment was carried out by an independent researcher belonging to REDIAPP (Research Network on Preventative Activities and Health Promotion) who was not involved in the study.

Patients agreed to participate before the random allocation and without knowing which treatment they would be assigned. Pharmacological treatment was administered by two doctors (JGC, RM) in the Arrabal health centre. Study personnel conducting psychological assessments (BOB, MCPY, MP, PHM) was masked to the participants' treatment. They confirmed the fulfilment of inclusion/exclusion criteria and administered the questionnaires at the centres where the patients were recruited, after explaining the characteristics of the study and obtaining informed consent. Both the doctors administering the treatment (memantine or placebo) and the researchers administering the questionnaires were blinded to group assignment. The success of blindness was assessed by an independent researcher not related to the study and not

belonging to the research group, who verified the double-blind study and that none of the patients, doctors or researchers administering the questionnaires had any knowledge of the allocated treatment.

Intervention

Treatment group

The treatment group received the study drug, memantine, in a dose of 20 mg daily for 6 months, including a 1-month titration period.

Control group

The control group received a daily dose of placebo (coated pills with the same external appearance as the active drug) and took the same number of pills as the treatment group. Pills were administered orally.

Because this was a double-blind study, the patients were randomised, and neither the patient nor the doctor nor the researcher administering questionnaires or spectrometry knew to which group the patient had been assigned. The recommended dose of memantine in adults is 20 mg daily. To minimise adverse effects, 20-mg doses were reached by the following titration schema: 1st week, 5 mg daily; 2nd week, 10 mg daily; 3rd week, 15 mg daily; 4th week, 20 mg daily.

The number of tablets in each dispensed container was monitored at each evaluation, and researchers kept track of the number of pills the patient should have taken and how many should have been remaining upon completion of the treatment. The route of administration was oral, in the form of film-coated tablets. The drugs used in the study (memantine pills and placebo) were prepared, conditioned and released by one qualified person according to the principles of Good Manufacturing Practice, under the responsibility of H. Lundbeck A/S. Upon completion of the trial, patients continued with standard FM treatment according to clinical practice guidelines.

Outcomes and Measurements

Main outcome variables

The main efficacy variable was improvement in the treatment of pain, specifically pain threshold and pain perception.

- Pain threshold was measured by means of a sphygmomanometer, a widely used clinical test that has been demonstrated to be useful for identifying FM patients [41]. It is recommended that the blood pressure cuff should be inflated in increments of approximately 10 mm Hg up to 180 mm Hg or to the point that pain appears. Healthy persons tend to feel pain when the pressure cuff is inflated to 160 mm Hg or more, while FM patients generally present pain at pressures between 100 and 110 mm Hg or lower. Blood pressure should be recorded to adjust for the effect of hypertension on pain threshold.

- Pain visual analogue scale (PVAS): The PVAS was designed to allow for a thorough and understandable subjective assessment of pain. A visual analogue scale is usually a 10-cm horizontal line, with perpendicular lines on the edges, defined as the extreme limits of pain experience. Anchor points at each edge are characterised by verbal expressions, such as ‘‘no pain’’ (accompanied by the number 0) at one end and ‘‘maximum pain ever experienced’’ (accompanied by the number 100) at the other end. Higher scores indicate greater pain. The PVAS has demonstrated good psychometric properties in previous studies using anchors of 0 and 100. The psychometric usefulness of VAS in pain measurement has been widely demonstrated [37].

Although the Fibromyalgia Impact Questionnaire (FIQ) is the most common principal outcome in intervention studies with FM, previous research on memantine has suggested that pain could be a most appropriate target for this drug.

Secondary variables

Secondary efficacy variables were cognitive state, health status, state of anxiety and depression, clinical improvement impression and quality of life. They were measured using the following questionnaires:

- The Cognition Mini-Exam (MEC): This is a structured scale that consists of 35 points grouped into seven categories: orientation to place, orientation to time, recall, attention and concentration, memory, language and visual

construction. In non-geriatric populations (under the age of 65), such as the sample in this study, the threshold that suggests a "likely case" of a cognitive disorder is 27 points and lower. This test is the validated Spanish-language version of the Mini-Mental State Examination (MMSE) [23].

- The Fibromyalgia Impact Questionnaire (FIQ): This is a 10-item self-assessment questionnaire that measures the health status of FM patients. The first item focuses on the patient's ability to carry out physical activities. In the next two items, patients are asked to circle the number of days in the past week during which they felt good and how often they missed work. Each of the last seven questions (job ability, pain, fatigue, morning tiredness, stiffness, anxiety and depression) is measured on a VAS. The validated Spanish-language version of this questionnaire was used [35].

- The Hospital Anxiety Depression Scale (HADS): This is a self-report scale that was developed to detect the presence of depression and anxiety disorders in medical patients in primary care settings. It contains 14 items scored on a 4-point Likert-type scale. This scale is comprised of two subscales that separately assess depression (HADS-dep) and anxiety (HADS-anx). The validated Spanish-language version of this scale was used [39].

- The EuroQol 5D (EQ5D) questionnaire: This questionnaire is a standardised instrument used as a measure of health outcomes. It is applied to a wide range of health conditions and treatments and provides a simple descriptive profile and a single index value for health status. The Spanish-language version of this questionnaire was used [1]. This instrument has 2 parts. Part 1 records the self-reported problems of the patient in each of 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each domain is divided into 3 levels of severity corresponding to no problems, some problems, and extreme problems. Part 2 records the subject’s self-assessed health on a visual analogue scale, a 10-cm vertical line on which the best and worst imaginable health states are scored 100 and 0, respectively. In the present study, we only administered part 2.

- The Clinical Global Impression scale (CGI): This scale is commonly used as a measure of symptom severity, treatment response and the efficacy of treatments in studies of patients with mental disorders. The Clinical Global Impression - Severity scale (CGI-S) is a 7-point scale that requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis. Considering total clinical experience, a patient is assessed on severity of mental illness using the following ratings: 1, normal, not at all ill; 2, borderline mentally ill; 3, mildly ill; 4, moderately ill; 5, markedly ill; 6, severely ill; or 7, extremely ill [14].

- The UKU side effect rating scale: This is a clinician-rated scale with well-defined and operationalised items that comprehensively assesses the side effects of psychopharmacological medications. It includes 48 items [22].

Measurements

Patients were assessed at 4 time points: baseline, post-treatment (including one month of titration), and 3- and 6-months post-treatment. Researchers administering the questionnaires received a 4-hour training course on the assessment of the questionnaires used in the study to improve inter-rater reliability.

Statistical methods

Sample size

Using the results of the pilot study and taking reduction of pain (as determined using the Pain VAS and sphygmomanometry) as the primary variables, a pre-intervention mean score of 56 (SD=14.9) was obtained with the VAS, and 104 (SD=30.8) with sphygmomanometry. After treatment, means decreased to 44 (SD=16.9) and 85 (SD=20.6), respectively. Therefore, assuming a 95% confidence interval and a power of 80%, a sample size of 28 individuals was required for each group for the VAS finding and 30 individuals in each group for the reduction measured by sphygmomanometry. The resulting sample size that would enable us to analyse the final variable was 60 individuals, with 30 being assigned to each of the two groups. Smaller

sample sizes have been used in the identification of significant differences in glutamate levels in different brain regions between FM patients and controls. Based on previous studies (personal communication), an attrition rate of 5% can be expected. Therefore, the final expected number of patients for recruitment was 63 patients. The protocol did not include any interim analyses or stopping rules.

Analysis strategy

Clinical efficacy was assessed using intention-to-treat analysis. The last observation carried forward (LOCF) method was used to handle missing data. An initial comparison was made between both groups, examining key variables to establish the groups' baseline comparability after randomisation. To describe quantitative variables, means and standard deviations were calculated when they fulfilled normality criteria. Chi-squared tests were used for qualitative variables, such as some socio-demographic measures. The differences between clinical variables at baseline, one month, three months and six months was calculated using analysis of covariance (ANCOVA) adjusted by baseline data.

To study the main variable, repeated-measures analysis of variance (ANOVA) was performed on all evaluations using time as a repeated-measure. The main variable (pain perception) was considered as a continuous variable for this purpose. The models included adjustments for baseline pain values and for any other variables that showed differences at baseline. Possible Group x Time interactions were studied using mixed-factor ANOVAs. Additionally, linear regression models were used to compare the differences between the two groups for each of the evaluations over time compared to baseline. Similar analyses were performed on the secondary clinical variables.

Calculations of between-groups effect sizes using Cohen's d with a 95% confidence interval [5] were based on the pooled standard deviation at baseline. The rule of thumb for Cohen's d is that 0.20 is small, 0.50 is medium, and 0.80 is large.

To make the findings from the RCT more meaningful to scientists and practitioners, the number needed to treat (NNT) [21] was also reported. For this purpose, following IMMPACT recommendations [7] we dichotomised participants into those who attained a decrease in patients' pain intensity P50%, as this is considered to

be a ‘‘substantial’’ improvement. Statistical analyses were performed with the SPSS 19.0 statistical software package, with *p* values below 0.05 considered to be significant.

Safety and monitoring.

Any adverse events and serious adverse events were recorded and a determination was made as to whether any medical action was related to the administered drug. Any adverse event related to the study drug was recorded and monitored until its resolution or stabilisation, and the regulatory notification process was followed in accordance with the pertinent legislation in force (time frames, unmasking, etc.). Study participants were requested to report to the researchers any adverse effect (serious or otherwise) that arose in the period between visits or any other circumstances that led to their withdrawal from the study.

Ethical aspects

Informed consent was obtained from participants before they were aware of their group assignment and before any assessment. Before they gave their consent, patients were provided with a general overview of the aims and characteristics of the study and the psychological and pharmacological intervention. They were informed that they would be participating voluntarily and that they could choose to withdraw at any time with the guarantee that they would continue to receive the treatment considered most appropriate by their doctor. With regard to the potential risks of the study, data gathering involved no risks for the subjects participating in the study, and the neuroimaging studies performed were non-invasive techniques that did not place subjects in any danger.

The study followed Helsinki Convention norms and posterior modifications and the Declaration of Madrid of the World Psychiatric Association. The Study Protocol was approved by the Clinical Research Ethics Committee of Aragón (06/2012) and the Medicines and Health Products Agency of Spain (EUDRACT 2011-006244-73).

Results

Participant flow and compliance

Figure 1 illustrates the flow of participants during the trial. Of the 71 patients diagnosed with fibromyalgia and recruited in primary care settings initially screened, 8 were excluded. Of these individuals, 2 were excluded because they did not fulfil the study criteria and 6 because they declined to participate. Of the 63 patients enrolled, 31 were randomly assigned to the memantine group and 32 were randomly assigned to the placebo group. All patients received the allocated intervention. All of the patients were analysed using intention-to-treat (ITT) analyses. There were not protocol deviations from the study as planned. The investigation was carried out in the period from September to November 2012 for recruitment and the follow-up finished in May 2013.

The attrition rate was low: 26 of 31 (83.87%) patients in the memantine group and 26 of 32 (81.25%) patients in the placebo group completed the post-treatment and the 1-, 3- and 6-month follow-up assessments. A total of 11 participants (17.46%), 5 (16.12%) in the memantine group and 6 (18.75%) in the placebo group, dropped out of the study. The reasons for dropping out were as follows: adverse events (2, 6.45%, in the memantine group and 1, 3.12%, in the placebo group) and patient decision (3, 9.67%, in the memantine group and 5, 15.62%, in the placebo group). As a result of the low rate of dropouts, predictors of dropout were not subjected to further analysis.

Characteristics of the sample

The sociodemographic profile of a typical participant, as expected in fibromyalgia, was a woman, approximately 47 years of age, married, with primary studies, employed with frequent sick leaves or unemployed, and diagnosed with FM for approximately 13 years at the time of study enrolment. Comorbidity with anxiety and depressive disorders and tobacco abuse were frequent. Regarding clinical symptoms, the whole sample showed impaired functionality, moderate quality of life, moderate-to-severe pain, comorbidity of anxiety and depressive symptoms and more cognitive impairment than expected based on their age.

Group baseline characteristics

Table 1 displays the baseline characteristics of the two groups. There were no statistically significant differences between groups in any sociodemographic or clinical variable, indicating that the two groups were equivalent on the variables measured. No

differences were found between the groups in blood pressure. Consequently, it was not necessary to adjust statistical analyses for any baseline variable.

Main and secondary outcomes

Table 2 displays descriptive statistics (means and standard deviations), significance and size effects (Cohen's *d*) according to post-treatment, 3- and 6-month post-treatment assessments. FM patients treated with memantine showed significant improvements, compared with placebo group, in the primary outcomes. Effect sizes at 6 months were large for both outcomes.

Regarding secondary outcomes, the memantine group also showed significant improvements in global function (assessed by FIQ), clinical global impression (measured by CGI), quality of life (assessed by the visual analogue scale of the EQ5D), depression (evaluated by HADS-dep) and cognitive function (evaluated by MMSE). At six months, the effect size for each of these measurements was large except for depression, which was moderate. Anxiety (measured by HADS-anx) did not show significant differences between the memantine and placebo groups at any of the follow-up assessments.

Number needed to treat (NNT)

We calculated the NNT following IMMPACT recommendations [28], which consider decreases in patients' pain intensity P50% as ''substantial'' improvements. According to that criterion, 16.13% (5 out of 31) of the participants in the memantine group and 0 percent (0 out of 32) in the placebo group reached the IMMPACT responder criterion after treatment. Compared to placebo, the absolute risk reduction obtained with memantine was 16.13% (95% CI: 2.0-32.6%), and the NNT was 6.2 (95% CI: 3-47).

Adverse effects (AEs)

Finally, no severe AEs or side effects were reported in the study. As Table 3 shows, the most frequent AEs in the memantine group were dizziness (8 patients, 25.8%), followed by headache (4 patients, 12.9%). In the placebo group, the most frequent AE was headache (5 patients, 15.6%), followed by dizziness and nausea (4 patients each, 12.5%). No significant differences were found in the prevalence of AEs

when comparing the two groups. As summarised in Fig. 1, only 2 patients out of 31 (6.45%) in the memantine group abandoned the study because of AEs compared with 1 out of 32 (3.12%) in the placebo group.

Discussion

This is the first randomised, controlled study of memantine for the treatment of fibromyalgia. Consistent with our hypothesis, memantine was significantly effective in the treatment of pain in patients with fibromyalgia relative to placebo, as it was shown to increase pain threshold and decrease pain perception in this disorder. Memantine was expected to be useful for the treatment of pain in FM based on previous studies on efficacy for different types of pain [24, 28, 36] and laboratory studies in rats [26]. In addition, spectrometric studies in fibromyalgia have identified a strong correlation between high levels of glutamate and pain [8], such that the use of a NMDA receptor blocking drug aimed to decrease brain glutamate levels could also be expected to improve pain. In fact, some authors have previously suggested the use of memantine in FM [32]. The benefits of memantine in FM treatment are thus expected to be threefold: 1) neuroprotection via antagonism of NMDARs, 2) analgesia through the normalisation of dysregulated pro- and antinociceptive pathways, and 3) enhanced analgesia and prevention of opioid tolerance in a combinatorial analgesic approach [17].

The efficacy of memantine in cognitive improvements is the most foreseeable effect because this drug is one of the recommended treatments for cognitive disorders such as dementias [27], and it also has been successfully used in other psychiatric disorders with cognitive dysfunction such as schizophrenia [19]. Cognitive impairment in fibromyalgia seems to be strongly related to depression and pain [38], and the improvement that memantine produces in these two variables could also partially explain its efficacy on cognition.

The effects of memantine on some secondary outcomes were also not surprising. Depression, another frequent symptom in fibromyalgia, was expected to improve with memantine. Due to its pharmacological effect [31], memantine has been considered to have a sustained mood-stabilising effect, and it has been used in bipolar disorders [20]. Spectrometric studies in fibromyalgia have also identified a strong correlation between high levels of glutamate and depression and global function [8], such that both

symptoms could be expected to improve with a drug with actions at the NMDA receptor, such as memantine. In fact, memantine has also been used in other psychiatric disorders related to depression, such as obsessive-compulsive disorder [12] and kleptomania [13].

Adverse events were mild and infrequent, as has been confirmed in the long-term treatment of other disorders such as dementia. Memantine is considered one of the safest and most well-tolerated drugs for the elderly [18]. This quality is especially relevant for the long-term management of FM, a chronic condition that is frequently associated with other medical disorders that are treated with many drugs, leading to a high risk of pharmacological interactions.

The main strength of this study is that this is the first randomised, controlled trial of memantine for the treatment of FM and that a subsample has been studied with neuroimaging techniques to assess changes in brain glutamate (these data will be described in an independent manuscript). In addition, the external validity of this study is high, despite being a RCT, because the inclusion/exclusion criteria were not overly stringent and the sample is representative of patients with FM treated at primary care settings.

This study does have several main limitations. This is not a multicentre study because all the patients were recruited from the same city. Although we identified significant differences and even large effect sizes, the sample size is small. More studies with larger samples that allow for meta-analysis are necessary to reach definitive conclusions. Finally, the follow-up period could be considered rather short. Previous studies in chronic pain disorders have shown that pharmacological treatments have a decay effect, with decreasing efficacy at 6-12 months follow-up [11]. Longer follow-ups are necessary to confirm the long-term stability of improvements resulting from memantine.

In conclusion, although additional studies with larger samples and longer follow-ups are needed to confirm these results, this study provides preliminary evidence of the utility of memantine for the treatment of many clinical domains in FM.

Abbreviations:

ACR: American College of Rheumatology; ANOVA: Analysis of variance; CGI: Clinical Global Impression; Cr: Creatine; EQ5D: EuroQol 5D; ET: Echo delay time; FIQ: Fibromyalgia Impact Questionnaire; FM: Fibromyalgia; fMRI: functional magnetic resonance imaging; FOV: Field of view; Glu: Glutamate; GPC: Glycerophosphorylcholine; HADS: Hospital Anxiety Depression Scale; MEC: Cognition Mini-Exam; LOCF: Last-Observation-Carried-Forward; mI: myo-inositol; MMSE: Mini-Mental State Examination; MRS: Magnetic resonance spectroscopy; NAA: N-acetylaspartate; NAAG: N-acetyl-aspartyl-glutamate; NMDA: N-methyl-D-aspartate; PCh: Phosphocholine; PET: Positron emission tomography; PROBE/PRESS: Proton brain spectroscopy/point-resolved spatially localised spectroscopy; REDIAPP: Research Network on Preventative Activities and Health Promotion; SD: Standard Deviation; SCID-I: Structured Clinical Interview for DSM-IV axis-I; SPECT: Single photon emission computed tomography; TR: Repetition time; VAS: Visual analogue scale; VOIs: Volumes of interest.

Competing interests

The authors declare that they have no conflicts of interest. The research group that designed and developed this study is financed by the Department of Science, Technology and University of the Government of Aragon and by the Carlos III Institute of Health, which is attached to the Spanish Ministry of Science and Innovation.

Authors' contributions

JGC, RM, BO, MR, YLdH and NF are the principal researchers and developed the original idea for the study. The study design was further developed by MCPY, MPG and PHM. EA developed the statistical methods. All authors have read and corrected draft versions and approved the final version.

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Figure 1: Flow chart of participants during the trial.

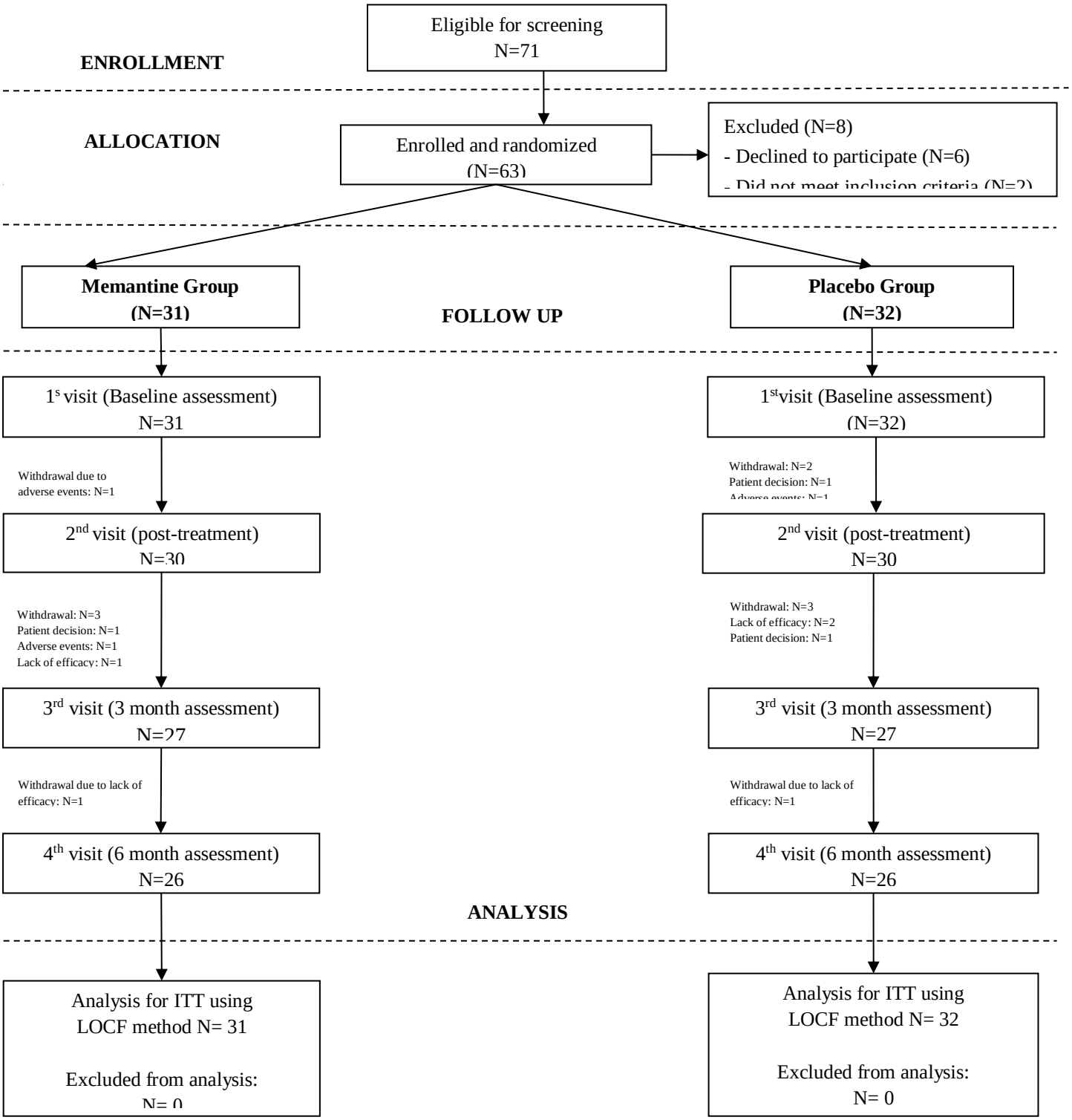

Table 1. Baseline sociodemographic and clinical characteristics of the sample (N= 63)

	Memantine group N=31	Placebo group N=32	Significance
Sociodemographic variables			
Gender: Female	30 (96.77%)	31 (96.88%)	*p*=0.982
Age (years)	48.09 (8.70)	47.62 (8.18)	*p*=0.814
Marital status			*p*=0.664
Married	24/31 (77.42%)	21/32 (65.63%)	
Single	4/31 (12.90%)	5/32 (15.63%)	
Divorced/separated	2/31 (6.45%)	5/32 (15.63%)	
Widowed	1/31 (3.23%)	1/32 (3.13%)	
Education			*p*=0.401
Illiterate	0 (0%)	0 (0%)	
Primary studies, incomplete	1 (3.13%)	1/32 (3.12%)	
Primary studies, complete	16/31 (51.61%)	14/32 (43.75%)	
Secondary studies	5/31 (16.13%)	10/32 (31.25%)	
University	9/31 (29.03%)	7/32 (21.87%)	
Labor status			*p*=0.361
Housewife	5/31 (16.13%)	1/32 (3.13%)	
Unemployed	6/31 (19.36%)	9/32 (28.14%)	
Employed	9/31 (29.03%)	12/32 (37.50%)	

Sick leave	4/31 (12.50%)	4/32 (12.5%)	
Retired	1/31 (3.23%)	1/32 (3.13%)	
Disabled	5/31 (16.13%)	5/32 (15.63%)	
Height (cms)	1.61 (0.05)	1.62 (0.05)	*p*=0.772
Weight (kgs)	68.67 (10.29)	69.46 (12.58)	*p*=0.978
Clinical variables			
FIQ	66.18 (15.18)	63.53 (16.03)	*p*=0.394
CGI	4.58 (0.88)	4.71 (0.92)	*p*=0.613
PVAS	6.56 (2.15)	6.48 (2.07)	*p*=0.851
Pain level (sphygmo)	88.54 (21.64)	91.56 (21.56)	*p*=0.554
HADS-Anx	12.29 (4.59)	11.56 (4.22)	*p*=0.581
HADS-Dep	9.12 (4.12)	8.93 (4.48)	p=0.751
MMSE	33.45 (1.80)	33.40 (2.18)	*p*=0.771
EQ5D	39.51 (21.03)	43.53 (20.77)	*p*=0.457

Table 2. Outcome variables at 6-month follow-up between memantine and placebo groups

Variable		Memantine group (n=31)		Placebo group (n=32)		significance	size effect
		mean	**SD**	**mean**	**SD**		
PRIMARY OUTCOMES							
PVAS							
	1 month	4.83	1.63	6.64	1.73	|t|=4.24; gl=61;p=0.001	d=-1.07
	3 months	5.06	1.21	6.85	1.58	|t|=5.04; gl=61;p=0.001	d=-1.27
	6 months	4.87	1.45	7.01	1.53	|t|=5.68; gl=61;p=0.001	d=-1.43
Pain level (sphygmo)							
	1 month	112.09	39.15	87.34	19.67	|t|=3.18; gl=61; p=0.002	d=-0.79
	3 months	121.93	14.92	81.25	21.84	|t|=8.61; gl=61; p=0.001	d=-2.17
	6 months	115.81	16.68	89.68	30.84	|t|=4.16; gl=61; p=0.001	d=-1.05
SECONDARY OUTCOMES							
HADS-Anxiety							
	1 month	12.32	4.53	11.37	4.35	|t|=0.84; gl=61; p=0.401	d=-0.21
	3 months	11.81	3.00	11.75	3.73	|t|=0.06; gl=61; p=0.947	d=-0.01
	6 months	11.51	4.88	11.84	4.02	|t|=0.29; df=61; p=0.772	d=0.07
HADS-Dep							
	1 month	7.81	2.97	10.75	3.41	|t|=3.65; gl=61; p=0.001	d=0.92
	3 month	7.32	3.17	10.56	4.83	|t|=3.13; gl=61; p=0.002	d=0.79
	6 month	7.87	3.06	10.46	3.52	|t|=3.11; df=61; p=0.002	d=0.78
MMSE							
	1 month	33.83	1.39	32.87	2.57	|t|=1.81; gl=61; p=0.071	d=-0.46
	3 months	34.48	0.92	33.53	1.66	|t|=2.79; gl=61; p=0.007	d=-0.71
	6 months	34.54	0.85	32.65	1.63	|t|=5.72; gl=61; p=0.001	d=-1.45

EQ5D							
	1 month	54.83	18.55	40.78	18.14	|t|=3.04; gl=61; p=0.035	d=-0.76
	3 months	58.06	19.73	43.43	18.29	|t|=3.05; gl=61; p=0.003	d=-0.77
	6 months	60.48	15.07	43.75	15.39	|t|=4.35; gl=61; p=0.001	d=-1.09
FIQ							
	1 month	47.23	9.01	62.93	16.29	|t|=4.31; gl=51; p=0.000	d= 1.19
	3 months	49.91	9.88	59.67	16.02	|t|=2.64; gl=51; p=0.011	d=-0.73
	6 months	50.02	11.03	69.57	12.20	|t|=6.05; gl=51; p=0.000	d=-1.68
CGI							
	1 month	3.76	0.51	7.33	0.91	|t|=2.74; gl=51; p=0.008	d=-0.77
	3 months	3.69	0.78	4.31	0.88	|t|=2.64; gl=51; p=0.011	d=-0.74
	6 months	3.66	0.56	4.96	0.61	|t|=7.68; gl=51; p=0.000	d= 2.22
Cohen’s d: 0.2=small; 0.5=moderate; 0.8=large							

Table 3. Adverse events during the study

	Number of cases		
	Memantine N=31(100%)	**Placebo N=32(100%)**	**Significance**
INFECTIONS AND INFESTATIONS			
Urinary tract infection	2(6.4%)	0	0.238
SKIN AND SUBCUTANEOUS SYSTEM DISORDERS			
Hyperhidrosis	0	1(3.1%)	0.999
NERVOUS SYSTEM DISORDERS			
Balance system alteration	2(6.4%)	0	0.238
Headache	4(12.9%)	5(15.6%)	0.999
Dizziness	8(25.8%)	4(12.5%)	0.213
Drowsiness	0	2(6.25%)	0.492
GASTROINTESTINAL DISORDERS			
Abdominal pain	1(3.2%)	0	0.492
Constipation	1(3.2%)	0	0.492
Nausea	0	4(12.5%)	0.113
Gastrointestinal disorders	0	1(3.1%)	0.999
Emesis	1(3.2%)	2(6.25%)	0.999
GENERAL DISORDERS			
Pain	1(3.2%)	1(3.1%)	0.999
Fatigue	0	2(6.2%)	0.492
Swelling	0	1(3.1%)	0.999
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
Arthralgia	2(6.4%)	0	0.238
Loss of muscle strength	1(3.2%)	0	0.492
Tendinitis	1(3.2%)	0	0.492
PSYCHIATRIC DISORDERS			
Insomnia	3(9.67%)	3(9.3%)	0.694
Anxiety	2(6.45%)	1(3.1%)	0.613
Night terror	0	1 (3.1%)	0.999
Panic disorder	1(3.2%)	0	0.492
TOTAL	**30(96.7%)**	**28(87.5%)**	**0.355**