

Efficacy of Memantine in Treating Patients with Dementia and Fibromyalgia

Abstract

Objective: To evaluate the efficacy of Memantine as a therapeutic intervention for dementia and fibromyalgia.

Methods: This clinical trial was conducted between October 2014 and December 2014. A total of 60 subjects, with diagnosed dementia or fibromyalgia, presenting to a private neurology clinic in Karachi, Pakistan were selected through purposive sampling technique. Adult patients belonging to both genders were included in the study. Patients were treated with incremental doses of Memantine. Data was analyzed using SPSS version 20 and associations were made using the Chi square test with p-value of less than 0.05 taken as significant.

Results: Out of 30 patients with dementia, 12 (40%) were males and 18 (60%) were females. The mean age of the subjects with dementia was found to be 70 years while that of with fibromyalgia was 38 years. Out of 30 patients with fibromyalgia, 2 (6.7%) were males and 28 (93.3%) were females, which shows a very high occurrence of fibromyalgia in females. The efficacy of the drug in patients with dementia was observed to be 96.7%, whereas in patients with fibromyalgia it was found to be 93.3%, both of which are significantly high. The baseline MMSE score when compared with the score at 3-month follow-up by applying Wilcoxon signed rank test showed mean±SD (17.93±4.69 vs. 23.27±4.69) where p=0.000. The baseline FIQ score when compared with the 3-month follow-up score showed mean ± S.D (67.18±13.23 vs. 34.17±15.18) where p=0.000. Both of these show a highly significant result (≤ 0.05). Results showed that cognitive functions, improved significantly by the end of the 3rd month of treatment in patients with dementia. All of the patients with fibromyalgia reported improvement in their physical functioning and majority of the patients felt less anxious and less depressed on their final follow-up visit. By the end of the 3rd month, the level of stiffness and intensity of the pain decreased significantly and patients reported less difficulty in performing work.

Conclusion: Memantine has shown significant beneficial effects in improving cognitive functions in patients with dementia and in reducing the intensity of pain and disability in patients with fibromyalgia.

Keywords: Memantine; Dementia; Fibromyalgia; Efficacy

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Introduction

The memantine has been in use in the US and Europe for neurocognitive disorders for quite some time. The three most common forms of dementia affecting old-aged people are Alzheimer's disease, vascular dementia and mixed dementia [1]. Excitatory neurotransmitters, like L-glutamate and its receptor subtypes, have been shown to play a role in pathogenesis of Alzheimer's disease as well as in promoting pain mechanisms.

Memantine works as a low-affinity, voltage-dependent, uncompetitive antagonist at N-methyl-D-aspartate (NMDA) glutamate receptors [2-4]. By binding to the NMDA receptor with a higher affinity than Mg^{2+} ions, Memantine inhibits the prolonged influx of Ca^{2+} ions which forms the basis of neuronal excitotoxicity. The low affinity, uncompetitive nature, and rapid dissociation rate of Memantine allows it not to accumulate substantially in the synaptic channels, hence, it does not interfere

with the normal synaptic transmission [5-7]. This preserves the function of the receptor at synapses, allowing it to be activated by physiological release of glutamate following depolarization of the presynaptic neuron [2,8-10]. Hence, Memantine has the potential to block excessive NMDA glutamate receptor activity and thus prevents excitatory amino acid neurotoxicity, without disrupting the intellectual capacity regulated by the physiological actions of glutamate.

Memantine, a low-affinity antagonist to NMDA glutamate receptors that are thought to be intrinsic to pain transmission, has also been shown to be effective in the treatment of migraine and tension-type headache [11-14]. The excitatory neurotransmitters, like glutamate, have been suggested to play an important role in potentiation and augmentation of the pain transmission cascade in chronic headache states in the same way these neurotransmitters are involved in signal transmission to spinal cord or brainstem in chronic pain conditions [11]. Memantine

has also shown potential in addressing the issues of complex regional pain syndrome and phantom limb pain, which suggests that its effectiveness in relieving pain depends on the kind of pain under consideration [15]. Cognitive problems have often been reported by patients with chronic pain disorders. Memantine, being a glutamate receptor antagonist, has the capacity to tackle both of these problems [13]. Furthermore, in several clinical trials, Memantine has shown very low incidents of adverse effects [16-17].

Treatment for fibromyalgia has limited efficacy, with an effect size of about 0.5. Several studies conducted on patients with fibromyalgia have demonstrated increased concentration of glutamate in the insula, hippocampus and posterior cingulate cortex regions of the brain of these patients. This has led a number of authors to suggest the efficacy of glutamate antagonists such as Memantine in the treatment of fibromyalgia [18].

The aforementioned wide variety of uses of Memantine in the field of medicine, has greatly increased the interest of researchers in this revolutionary drug. Our area of interest is to find out the efficacy of Memantine in the treatment of dementia and fibromyalgia. To the best of our knowledge, no study has been conducted in our part of the world about the use of NMDA antagonists that could be of major interest in regards to the pathophysiology and future treatment of dementia and fibromyalgia.

Operational Definitions

Dementia: Dementia refers to loss of memory with impairment of any other cognitive function sufficient to interfere with social or occupational functioning. It is caused by a multitude of illnesses, including Alzheimer's disease (the most common cause), vascular disease and Lewy Body disease. Most of these illnesses are currently incurable, and cause progressive, irreversible brain damage. Symptoms of dementia include:

- Disturbances in executive functioning (planning, organizing, sequencing, abstracting).
- Balance problems.
- Difficulties with language, judgment and insight.
- Delusions and hallucinations.
- Memory impairment.
- Agnosia and apraxia [19].

Fibromyalgia: A chronic musculoskeletal pain syndrome in which the patient complains of muscle aches and stiffness with trigger points on palpation and non-refreshing sleep. Depression and anxiety are common associated features.

Materials and Methods

Study design: Clinical trial.

Setting: Neuro Clinic and Care, Karachi, Pakistan.

Duration: 3 months.

Data collection start date: October 2014.

Data collection completion date: December 2014.

Sample size: 60 patients.

Inclusion criteria

- a. Adult patients of both genders.
- b. Diagnosis of Dementia using DSM IV Criteria for Diagnosis of Dementia [20].
- c. Diagnosis of Fibromyalgia using American College of Rheumatology Criteria for Diagnosis of Fibromyalgia [21].
- d. Signature of Informed Consent Form
- e. In case of females of childbearing age, a commitment not to become pregnant during the entire duration of the study

Exclusion criteria

- a. Patients below the age of 18 years.
- b. Patients undergoing drug treatment for fibromyalgia or dementia. Patients already receiving treatment will stop treatment and a washout period of one week will be performed. During the washout period the patient may take, if necessary, analgesics such as Tramadol or Acetaminophen
- c. Patients already taking Memantine
- d. Another Axis I psychiatric disorder using Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) that may interfere with adherence to the study protocol (e.g. alcohol and/or substance abuse/dependence, schizophrenia, chronic delirium, acute depression etc.)
- e. Pregnancy or breast-feeding
- f. Hypersensitivity to the active ingredient, Memantine.
- g. Evidence of clinically significant liver or kidney disease, hematological, respiratory, endocrine or cardiovascular disorders.
- h. Use of NMDA receptor antagonists (amantadine, ketamine, dextromethorphan), L-Dopa, dopamine agonists, cholinergic agonists and other prescription drugs that may cause drug interactions with Memantine.
- i. Use of antidepressants (duloxetine, venlafaxine, mirtazapine, bupropion, SSRI, etc.), analgesics (pregabalin, gabapentin, opiates, etc.) or other non-permitted concomitant medications.

Data collection

Each patient diagnosed to have fibromyalgia or dementia coming to the outpatient department was explained about the purpose of the study, including the risks and benefits of participation in the study. After obtaining signed consent, intervention was started.

Intervention: A total of 60 subjects, with 30 patients in each group of diagnosed dementia and fibromyalgia, were selected through purposive sampling technique. Patients allocated to each group received 20mg of Memantine (2 tablets of 10mg each).

The dose of 20mg was reached following this schema:

1st week: 5mg daily.

2nd week: 10mg daily.

3rd week: 15mg daily.

From the 4th week up to the 12th week: 20mg daily.

Patients were followed up initially at 1st week, 2nd week, then every month for a total of three months. On each follow-up visit, Mini-Mental State Examination (MMSE) was done on patients with dementia and the Fibromyalgia Impact Questionnaire (FIQ) was filled for patients with fibromyalgia and patients were observed for the efficacy of the drug.

Outcome measures: Improvement in clinical variables

Dementia

To assess improvement in cognitive functions from the baseline and relatively from each previous visit at 1st week, 2nd week, 1st month, 2nd month, and 3rd month. It will be measured by the MMSE [22], which is a widely used 30-point questionnaire to grade the cognitive state. It tests a broad range of cognitive functions including orientation, recall, attention, calculation, language manipulation and constructional praxis.

Interpretation: Scores ≥ 26 out of 30 - Normal cognition

20-25 – Mild impairment

10-19 – Moderate impairment

0-9 – Severe impairment [23]

Fibromyalgia

To assess improvement in health status of patients with fibromyalgia from the baseline and relatively from each previous visit at 1st week, 2nd week, 1st month, 2nd month, and 3rd month using FIQ [24]. FIQ is a 10-item questionnaire to measure the health status in patients with fibromyalgia.

Interpretation: 0 to <39 - Mild effect

≥ 39 to <59 - Moderate effect

≥ 59 to 100 - Severe effect [25]

Data analysis

SPSS version 20 was used for statistical analysis. Separate frequencies and percentages were calculated for categorical variables. The association was assessed through Chi square test and p-value ≤ 0.05 was taken as significant.

Results

Sample size for this study is 60, with 30 patients in each group of diagnosed dementia and fibromyalgia. Out of 30 patients with dementia, 40% (12) were males and 60% (18) were females. The mean age of the subjects was 70.2 \approx 70 years. The baseline MMSE score was classified on the basis of severity [23]. Out of 30 patients, 13 (43.3%) patients had mild dementia, 15 (50%) had moderate dementia and 2 (6.7%) had severe dementia.

Patients were given 5mg of Memantine daily for 1 week. Follow-up at the end of the 1st week revealed improvement in only 6.7% (2) of the patients according to their MMSE score. The dose of Memantine was increased to 10mg daily and the patients were called for follow-up at the end of the 2nd week at which 26.7% (8) of the patients showed improvement from the previous visit. Of these 8 patients, 2 had mild and 6 had moderate cognitive dysfunction at the beginning of the study. Subsequently, a weekly dose increase of 5mg up to a maximum dose of 20mg per day, as tolerated, was implemented. At the end of the 1st month, 66.7% (20) of the patients (comprising of 8 mild, 10 moderate and 2 severe cases of cognitive dysfunction at the baseline) reported improvement in their cognitive function from the previous visit, which was demonstrated by their MMSE score as well. At the end of the 2nd month, 53.3% (16) of the patients (consisting of 6 mild, 9 moderate and 1 severe case of cognitive impairment at the baseline) had further improvement in their score as compared to the score at the 1-month follow-up visit, while at the end of the 3rd month 26.7% (8) of the patients demonstrated further improvement in their MMSE score relative to the score at the previous visit at two months. Of these patients, 2 suffered from mild and 6 from moderate cognitive impairment.

As shown in Table 1, out of 30 patients, 2 (6.7%) patients had improvement in their MMSE score at 1-week follow-up, both of whom were males and had mild cognitive dysfunction at the baseline. At 2-week follow-up, 10 (33.3%) patients demonstrated improvement in the MMSE score from the baseline. 25 (83.3%) patients had improvement in their MMSE score at the end of one month as compared to the baseline score, while 29 (96.7%) patients had better MMSE score than the baseline score at the end of two months and 1 (3.3%) patient had a worse MMSE score relative to the baseline score. The rest of the patients had the same MMSE score as their baseline score. At the final visit at three months, 29 (96.7%) patients had improvement in their MMSE score from the baseline, 11 of whom were males and 18 were females. 1 patient had the same MMSE score as his baseline score. None of the patients had a worsening of the MMSE score (Figure 1 & 2). Out of the patients who had improvement in their MMSE score relative to the baseline at the final follow-up visit at three months, 13 patients had mild, 14 had moderate and 2 suffered from severe cognitive dysfunction at the initial visit.

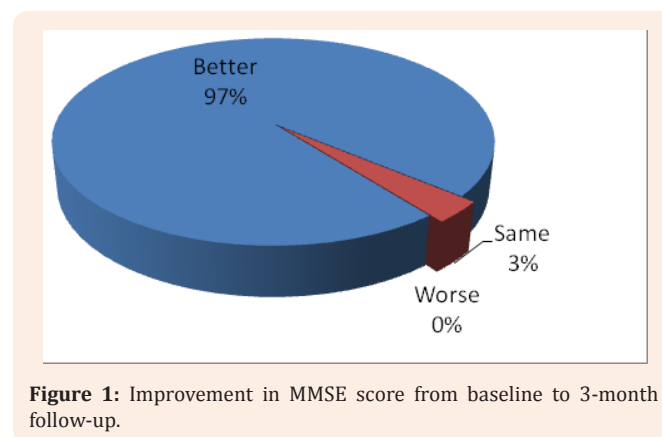


Figure 1: Improvement in MMSE score from baseline to 3-month follow-up.

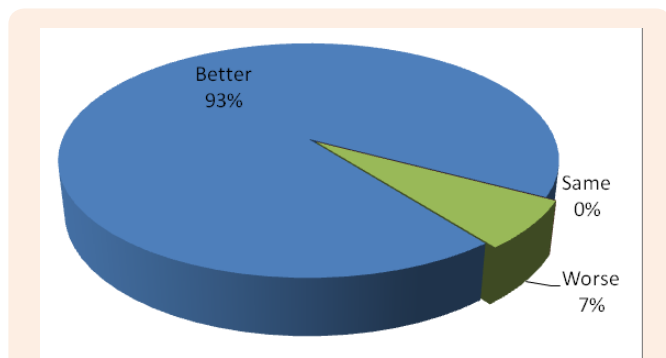


Figure 2: Improvement in FIQ score from baseline to 3-month follow-up.

The efficacy of the drug in patients with dementia was observed to be 96.7%, which is significantly high. The baseline MMSE score when compared with the score at 3-month follow-up by applying Wilcoxon signed rank test showed mean±SD (17.93±4.69 vs. 23.27±4.69) where $p=0.000$ (<0.05) which shows a highly significant result.

There were 6.7% (2) of males and 93.3% (28) of females which shows a very high occurrence of fibromyalgia in females. Average age of the subjects was 37.6±38 years. The baseline FIQ score was classified on the basis of severity [25]. Out of 30 subjects, 1 (3.3%) patient had mild, 5 (16.7%) patients had moderate and 24 (80%) patients had severe disease.

Follow-up at the end of the 1st week showed improvement in only 13.3% (4) of the patients according to the FIQ score. All of these patients had severe disease. 60% (18) of the patients revealed improvement in their FIQ scores compared to the previous visit at the end of the 2nd week. Of these 18 patients, 1 had moderate and 17 had severe disease. At the end of the 1st month, 86.7% (26) of the patients reported improvement in their health status and quality of life from the previous visit, which was also demonstrated by the improvement in their FIQ score. At the end of the 2nd month, 83.3% (25) of the patients had further improvement in their FIQ score as compared to the score at the 1-month follow-up visit and the same percentage of patients had improvement in their FIQ score at the final follow-up visit at three months compared to their score at 2-month follow-up. Out of these 25 patients, 3 had moderate and 21 had severe disease.

As depicted in Table 2, out of 30 patients, 5 (16.7%) patients showed improvement in their FIQ score at 1-week follow-up. All of these patients were females and suffered from severe disease. At 2-week follow-up, 18 (60%) patients had improvement in the FIQ score from the baseline. 28 (93.3%) patients demonstrated improvement in their FIQ score at the end of one month as compared to the baseline and the same percentage of patients had a better FIQ score than the baseline score at the end of two months. At the final follow-up visit at three months, 28 (93.3%) patients had improvement in their FIQ score from the baseline, of which 2 were males and 26 were females. 2 patients who had severe disease had worsening of FIQ score at the final visit relative to the initial visit. Out of 28 patients who showed improvement, 1 had mild, 5 had moderate and 22 had severe disease.

The efficacy of the drug was found to be 93.3%, which is significantly high. The baseline FIQ score when compared with the score at 3-month follow-up by applying Wilcoxon signed rank test showed mean±SD (67.18±13.23 vs. 34.17±15.18) where $p=0.000$ (<0.05) which shows a highly significant result.

All of the 30 patients reported improvement in their physical functioning at the final follow-up visit three months. 26 (86.7%) out of 30 patients stated that they felt better relative to their emotional status at the initial visit. 24 (80%) patients said that they missed less number of days at work, including housework, because of fibromyalgia symptoms after taking the drug. 28 (93.3%) patients reported less difficulty performing work and less interference of fibromyalgia symptoms with their ability to do work as compared to the baseline. The same percentage of the patients said that the level of stiffness had decreased after taking Memantine. Almost all (29, 96.7%) patients reported improvement in pain and waking up well rested in the morning after taking Memantine. 27 (90%) patients reported improvement in fatigue and anxiety at the final follow-up visit at three months. Improvement in symptoms of depression was noted by 26 (86.7%) patients.

Discussion

The present study sought to demonstrate the efficacy of Memantine in the treatment of dementia and fibromyalgia. Several studies have demonstrated the potential role of Memantine as a safe and effective treatment in dementing disorders [1-4]. In a systematic review of randomized controlled trials conducted by the Areosa & Sherriff [1] to determine the efficacy of Memantine in patients with dementia, statistically significant improvement in cognitive functions and activities of daily living was noted at 28 weeks compared to the baseline. The dose of Memantine given to the patients was 20mg/day. The results are comparable to those of our study. In our study, more than half of the patients (83.3%) had improvement in their cognitive impairment and activities of daily living at one month. Almost all of the patients (96.7%) had an improvement in cognitive functions and routine activities by the end of three months. The baseline MMSE score when compared with the score at 3-month follow-up by applying Wilcoxon signed rank test showed mean±SD (17.93±4.69 vs. 23.27±4.69) where $p=0.000$ (<0.05) which shows a highly significant result.

Several researches have been performed to highlight the potential role of glutamate antagonists in the treatment of fibromyalgia [18,26-28]. According to a randomized controlled clinical trial conducted on 25 patients with fibromyalgia to evaluate the efficacy of Memantine on metabolite levels in the brain, patients treated with Memantine exhibited an increase in cerebral metabolism of glutamate and other metabolites, which suggests its potential role in the treatment of fibromyalgia [26].

A number of studies have been conducted to evaluate the potential role of NMDA glutamate receptor antagonists like Memantine, Ketamine, Amantadine and Dextromethorphan in the treatment of neuropathic pain and other kinds of chronic pain [6,7]. In a six-month long randomized controlled trial carried out in Spain on 63 patients with fibromyalgia who were administered 20mg/day of Memantine after 1 month of titration, significant improvement in pain, quality of life, global functioning and depression was noted [27]. In the present study, all of our

patients reported improvement in their physical functioning at the final follow-up visit at 3 months and almost all (96.7%) patients reported improvement in pain and waking up well rested in the morning after taking Memantine. 28 (93.3%) patients reported less difficulty performing work and less interference of fibromyalgia symptoms with their ability to do work as compared to the baseline. The same percentage of the patients said that the

level of stiffness had decreased after taking Memantine. 90% of the patients reported less fatigue and anxiety at the final follow-up visit at 3 months. Improvement in symptoms of depression was noted by 86.7% of the patients. Some of the patients (80%) said that they missed less number of days at work, including housework, because of fibromyalgia symptoms after taking the drug.

Table 1: Improvement in MMSE score from baseline to follow-up at 1 week, 2 weeks, 1 month, 2 months and 3 months.

S.No.	Baseline MMSE Score	Improvement at 1 st week	Improvement at 2 nd week	Improvement at 1 st month	Improvement at 2 nd month	Improvement at 3 rd month
		%	%	%	%	%
1	20	0	0	20	40	40
2	18	0	11	56	56	61
3	11	0	0	0	54	54
4	15	0	0	20	33	60
5	18	0	0	11	33	33
6	11	0	0	45 (deterioration)	9 (deterioration)	0
7	23	0	0	0	4	4
8	23	0	0	9	4	4
9	20	0	15	15	25	25
10	19	0	0	16	16	16
11	24	4	4	4	17	17
12	24	0	0	4	4	4
13	17	0	6	18	41	41
14	20	0	0	40	40	45
15	18	0	6	11	33	39
16	12	0	33	33	67	67
17	9	0	0	33	67	67
18	24	13	13	21	21	21
19	12	0	33	33	33	33
20	16	0	0	13	25	50
21	20	0	0	15	15	15
22	19	0	0	0	5	5
23	24	0	4	4	4	4
24	24	0	0	4	17	17
25	18	0	11	33	33	33
26	20	0	0	0	40	40
27	18	0	0	11	11	33
28	12	0	0	67	67	67
29	9	0	0	67	67	67
30	20	0	0	20	20	40

Table 2: Improvement in FIQ score from baseline to follow-up at 1 week, 2 weeks, 1 month, 2 months and 3 months.

S. No.	Baseline FIQ Score	Improvement at 1 st week	Improvement at 2 nd week	Improvement at 1 st month	Improvement at 2 nd month	Improvement at 3 rd month
		%	%	%	%	%
1	80	0	0	48	61	73
2	42	0	0	18	31	54
3	76.3	0	17	23	31	36
4	81.4	0	7	12	18	40
5	32	3 (deterioration)	3 (deterioration)	3	18	32
6	77.5	0	0	13	25	30
7	69.4	0	0	16	20	29
8	67.8	0	0	24	31	43
9	71.4	0	10	10	31	37
10	63.1	0	14	14	41	52
11	69	0	9	21	32	41
12	71.1	10	16	33	39	57
13	85.9	0	27	43	43	65
14	77.6	5	50	54	68	75
15	68.5	6	10	36	56	58
16	65.3	0	19	20	33	55
17	78.2	2	56	61	73	73
18	76.9	0	20	31	51	57
19	85.1	0	54	57	64	69
20	65	0	27	34	51	70
21	52	4	22	37	43	62
22	68.6	0	0	0	2	2
23	41.8	0	0	49	49	49
24	57.6	0	0	22	28	46
25	59.3	0	35	43	64	73
26	75	0	4 (deterioration)	4 (deterioration)	4 (deterioration)	4 (deterioration)
27	70.3	0	15	25	36	50
28	75.2	0	0	24	26	41
29	65.3	0	19	20	33	55
30	46.8	0	0	49	49	49

Another double-blind, randomized, controlled clinical trial conducted by Olivan-Blazquez et al. [18] evaluate the efficacy of Memantine in the treatment of pain in patients with fibromyalgia showed that after 3 months of treatment with 20mg/day of Memantine after titration for 1 month, patients exhibited significant improvement in cognitive decline, symptoms of depression and global functioning. In our study, at 2-week follow-up, more than

half of the patients (60%) exhibited improvement in their FIQ score relative to the baseline. Almost all of the patients (93.3%) demonstrated improvement in their FIQ score as compared to the baseline at the end of 1 month. The baseline FIQ score when compared with score at 3-month follow-up by applying Wilcoxon signed rank test showed mean±SD (67.18±13.23 vs. 34.17±15.18) where p=0.000 (<0.05) which shows a highly significant result.

Depression is a common and quite disabling comorbidity in patients with fibromyalgia [29]. Several studies have shown the efficacy of Memantine in improving symptoms of depression in fibromyalgia patients [18,27]. 86.7% of the patients in our study reported less or none symptoms of depression at the final follow-up visit at three months.

A number of studies have demonstrated that the incidence of adverse effects related to the drug is low [1,8,16-17,27]. The fact that the drug is well-tolerated has been shown in our study as well. In our study, none of the patients developed significant adverse effects to warrant exclusion from the study. Although additional studies that are randomized, controlled, conducted on a larger sample size and with a longer follow-up time frame are needed, the present study provides preliminary evidence regarding efficacy of Memantine in the treatment of dementia and fibromyalgia.

Conclusion

Memantine is an effective drug for the treatment of dementia and fibromyalgia in terms of improving cognitive functions as evidenced by the drastic improvement in the MMSE score in patients with dementia and the overall health status and quality of life in patients with fibromyalgia as evidenced by the improvement in FIQ score. A randomized, placebo-controlled, double-blind clinical trial conducted on a larger sample size is needed to confirm our observations.

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