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Sameen Khalid
Neuro Clinic and Care, Karachi, Pakistan

Bashir A. Soomro
Neuro Clinic and Care, Karachi, Pakistan

Zahida Mahmood
Neuro Clinic and Care, Karachi, Pakistan

EFFICACY OF MEMANTINE IN TREATING PATIENTS WITH FIBROMYALGIA

Sameen Khalid[1], Bashir A. Soomro[1], Zahida Mahmood[1]
[1] Neuro Clinic and Care, Karachi, Pakistan

Correspondence to: *Sameen Khalid, 43/ II Zulfiqar Street No: 03, Phase VIII DHA, Karachi. Postal Code: 75500. Email: sameen_khalid18@yahoo.com*
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ABSTRACT

Objective: To evaluate the efficacy of Memantine as a therapeutic intervention for fibromyalgia. **Methods:** This clinical trial was conducted between October 2014 and December 2014. A total of 30 subjects with diagnosed 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 Chi square test with p-value of less than 0.05 taken as significant. **Results:** Out of 30 patients, 2 (6.7%) were males and 28 (93.3%) were females which shows a very high occurrence of fibromyalgia in females. The mean age of the subjects was found to be 38 years. Efficacy of the drug in patients with fibromyalgia was observed 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 ± S.D (67.18±13.23 vs. 34.17±15.18) where p=0.000. This shows a highly significant result (≤0.05). 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 pain decreased significantly and patients reported less difficulty in performing work. **Conclusion:** Memantine has shown significant beneficial effects in reducing the intensity of pain and disability in patients with fibromyalgia.

KEY WORDS: Memantine, Fibromyalgia, Efficacy.

INTRODUCTION

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.[2,3,4] By binding to the NMDA receptor with a higher affinity than Mg2+ ions, Memantine inhibits the prolonged influx of Ca2+ 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.[5,6,7] This preserves the function of the receptor at synapses, allowing it to be activated by physiological releaseof glutamate following depolarization of the presynaptic neuron.[2,8,9,10] 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.[11,12,13,14] 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]

Further more, 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 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 fibromyalgia.

OPERATIONAL DEFINITION

Fibromyalgia:

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

MATERIALS AND METHODS

A total of 30 subjects with diagnosed fibromyalgia presenting to Neuro Clinic and Care, a private neurology clinic in Karachi, Pakistan were selected through purposive sampling technique. Data was collected over a period of three months between October 2014 and December 2014.

Inclusion criteria included:

Adult patients of both genders. Diagnosis of Fibromyalgia using American College of Rheumatology Criteria for Diagnosis of Fibromyalgia[19]. Signature of Informed Consent Form. In case of females of childbearing age, commitment not to become pregnant during the entire duration of the study.

Exclusion criteria included:

Patients below the age of 18 years. Patients undergoing drug treatment for fibromyalgia. Patients already receiving treatment will stop treatment and a washout period of one week will be performed. During the wash out period the patient may take, if necessary, analgesics such as Tramadol or Acetaminophen. Patients already taking Memantine, Another Axis I psychiatric disorder using Structured Clinical Interview for DSM-IVAxis I Disorders (SCID-I) that mayinterfere with adherence to the study protocol (e.g. alcohol and/or substance abuse/dependence, schizophrenia, chronic delirium, acute depression etc.) Pregnancy or breast-feeding. Hypersensitivity to the active ingredient, Memantine. Evidence of clinically significant liver or kidney disease, hematological, respiratory, endocrine or cardiovascular disorders. 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. Use of antidepressants (duloxetine, venlafaxine, mirtazapine, bupropion, SSRI, etc.), analgesics (pregabalin, gabapentin, opiates, etc.) or other non-permitted concomitant medications.

Each patient diagnosed to have fibromyalgia 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. Patients received 20mg of Memantine (2 tablets of 10 mg each). The dose of 20 mg was reached following this schema:

1st week: 5 mg daily
2nd week: 10 mg daily
3rd week: 15 mg daily

From the 4th week up to the 12th week: 20 mg daily Patients were followed upinitially at 1stweek, 2ndweek, then every month for a total of three months. On each follow-up visit, 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. 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 FIQ20. FIQ is a 10-item questionnaire to measure the health status in patients with fibromyalgia.

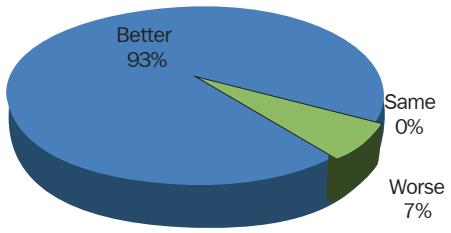
Interpretation:

0 to < 39 – Mild effect
≥ 39 to < 59 – Moderate effect
≥ 59 to 100 – Severe effect[21]

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

RESULT

FIGURE 1: IMPROVEMENT IN FIQ SCORE FROM BASELINE TO 3-MONTH FOLLOW-UP



Out of 30 patients, 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.21Out 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 1, 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 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. 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 ± S.D (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. 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 fibromyalgia. 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.[22] 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 20 mg/day of Memantine after 1 month of titration, significant improvement in pain, quality of life, global functioning and depression was noted.[23] 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

Table 1: 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 1st week %	Improvement at 2nd week %	Improvement at 1st month %	Improvement at 2nd month %	Improvement at 3rd 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

baseline. 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 house work, because of fibromyalgia symptoms after taking the drug. Another double-blind, randomized, controlled clinical trial conducted byOlivan-Blazquezto evaluate the efficacy of Memantine in the treatment of pain in patients with fibromyalgia showed that after 3 months of treatment with 20 mg/day of Memantine after titration for 1 month, patients exhibited significant improvement in cognitive decline, symptoms of depression and global functioning. [18] 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 ± S.D (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.[24] Several studies have shown the efficacy of Memantine in improving symptoms of depression in fibromyalgia patients.[18, 23] 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, 23] 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 fibromyalgia.

CONCLUSION

Memantine is an effective drug for the treatment of fibromyalgia in terms of improving cognitive functions as demonstrated by the drastic improvement in 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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REFERENCES

1. Areosa SA, Sherriff F. Memantine for dementia. Cochrane Database Syst Rev. 2003;(3):CD003154.
2. Chen HSV, Pellegrini JW, Aggarwal SK et al. Open-channel block of N-methyl-D-aspartate (NMDA) responses by memantine: therapeutic advantage against NMDA receptor-mediated neuro -toxicity. J. Neurosci. 1992;12(11): 4427–36.
3. Rogawski, MA, Wenk GL. The neuropharmacological basis for the use of memantine in the treatment of Alzheimer's disease. CNS Drug Rev. 2003;9(3): 275–308.
4. Robinson, DM, Keating GM. Memantine: a review of its use in Alzheimer's disease. Drugs. 2006;66 (11): 1515–34.
5. Wood PL. The NMDA receptor complex: a long and winding road to therapeutics. Drugs. 2005;8(3): 229-35.
6. Hewitt DJ. The use of NMDA-receptor antagonists in the treatment of chronic pain. Clin J Pain. 2000; 16(2 Suppl):S73-9.
7. Block F, Habermeyer B. Glutamate antagonists for treatment of neuropathic pain. Schmerz. 2003; 17(4): 261-7.
8. Xia P, Chen HSV, Zhang D, Lipton SA. Memantine preferentially blocks extrasynaptic over synaptic NMDA receptor currents in hippocampal autapses. J. Neurosci. 2010;30 (33): 11246–11250.
9. Rogawski, MA. Low affinity channel blocking (uncompetitive) NMDA receptor antagonists as therapeutic agents—toward an understanding of their favorable tolerability. Amino Acids. 2000;19 (1): 133–49.
10. Parsons CG, Stöffler A, Danysz W. Memantine: a NMDA receptor antagonist that improves memory by restoration of homeostasis in the glutamatergic system — too little activation is bad, too much is even worse. Neuropharmacology. 2007; 53 (6):6 99–723.
11. Krusz, JC, Cammarata D. Memantine for Chronic Migraine Prophylaxis. Poster presentation to the annual conference of the American Headache Society, Philadelphia, June, 2005; and the European Federation of Neurologic Societies conference, Athens, Greece, September, 2005.http://www.help -forh-eadaches.com/articles/memantine8x11.pdf (Date accessed: February 2015)
12. Henry KA. Memantine for the prophylaxis of chronic tension-type headache.Curr Pain Headache Rep. 2009; 13(6): 423-4.
13. Bigal M, Rapoport A, Shefrell F, et al. Memantine in the preventive treatment of refractory migraine. Headache. 2008; 48(9): 1337-42.
14. Lindelof K, Bendtsen L. Memantine for prophylaxis of chronic tension-type headache - a double-blind, randomized, crossover clinical trial.Cephalalgia. 2009; 29(3): 314-21.
15. Recla JM, Sarantopoulos CD.Combined use of Pregabalin and Memantine in Fibromyalgia Syndrome Treatment: A Novel Analgesic and Neuroprotective Strategy? Med Hypotheses. 2009 ;73(2):177-183.
16. Reisberg B, Doody R, Stöffler A, et al. Memantine in moderate-to-severe Alzheimer's disease. N Engl J Med. 2003;348:1333–1341.
17. Tariot PN, Farlow MR, Grossberg GT, et al. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. JAMA. 2004;291:317–324.
18. Olivan-Blazquez B, Puebla M, Masluk B. Evaluation of the efficacy of memantine in the treatment of fibromyalgia: study protocol for a doubled-blind randomized controlled trial with six-month

follow-up. Published online 2013. PMCID: PMC 3598995. (Date accessed: February 2015)
19. American College of Rheumatology, 2010 Fibromyalgia Diagnostic Criteria – Excerpt.https://www.rheumatology.org/practice/-clinical/classification/fibromyalgia/fibro_2010.asp (Date accessed: March 2015)
20. Fibromyalgia Impact Questionairre. www.cebp.nl-/vault_public/filesystem/?ID=1323 (Date accessed: March 2015)
21. American College of Rheumatology Fibromyalgia Impact Questionnaire. https://www.rheumatology.org /Practice/Clinical/Clinicianresearchers/Outcomes_In strumentation/Fibromyalgia_Impact_Questionnaire_(FIQ)/ (Date accessed: March 2015)
22. Fayed N, Olivan-Blazquez B, Herrera-MercadalP et al. Changes in metabolites after treatment with memantine in fibromyalgia. A double-blind randomized controlled trial with magnetic resonance spectroscopy with a 6-month follow-up. CNS NeurosciTher. 2014; 20(11): 999-1007.
23. Olivan-Blazquez B, Herrera-Mercadal P, Puebla-Guedea M et al. Efficacy of memantine in the treatment of fibromyalgia: A double-blind, randomised, controlled trial with 6-month follow-up. Pain. 2014; 155(12): 2517-25.
24. Aguglia A, Salvi V, Maina G, Rossetto I, Aguglia E. Fibromyalgia syndrome and depressive symptoms: comorbidity and clinical correlates. J Affect Disord. 2011;128:262–266.

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Dr. Sameen Khalid: Study concept and design, protocol writing, data collection, data analysis, manuscript writing, manuscript review

Dr. Bashir Soomro: Data collection, data analysis, manuscript writing, manuscript review

Dr. Zahida Mahmood: Data collection, data analysis, manuscript writing, manuscript review