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Is aquatic therapy an effective treatment for reducing fatigue in adult females living with MS?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

Objective: The objective of this selective EBM review is to determine, "Is aquatic therapy an effective treatment for reducing fatigue in adult females living with MS?"

Study Design: A systematic review of three randomized controlled trials (RCTs) published between 2015 and 2018.

Data Sources: All three RCTs were published in English peer reviewed journals and were discovered on PubMed using selective search criteria. Studies were chosen based on their relevance and competency to answer the clinical question proposed.

Outcome Measured: The main outcome of focus in each of the articles selected for this review was fatigue reduction. Outcomes were measured using the Modified Fatigue Impact Scale (MFIS) and/or the Fatigue Severity Scale (FSS) at baseline and at eight weeks following study completion. The RCT conducted by Kargarfar et al. utilized the MFIS and the RCT by Razazian et al. measured outcomes using the FSS. Both the MFIS and FSS were used for measurement in the RCT by Kooshiear et al.

Results: In the study conducted by Kargarfard et al., aquatic therapy led to a significant reduction in fatigue severity compared with control ($P<0.01$), supported by a mean change from baseline of 10.3 in the study group versus -16.5 in control . In the RCT by Kooshiar et al., aquatic therapy resulted in a statistically significant reduction in fatigue compared to control ($P=0.000$), demonstrated by a mean change from baseline of 23.44 versus -1.66. Lastly, Razazian et al. found a statistically significant reduction in fatigue severity with aquatic exercise compared to control ($P<0.001$) using both the MFIS and FSS, as supported by mean change from baseline values of 11.25 versus -0.71 and 6.69 versus -0.81.

Conclusion: Each of the three studies analyzed in this review determined aquatic therapy to have a large treatment effect in terms of reducing fatigue experienced by adult females living with MS, as evidenced by means and p-values. The results suggest that aquatic therapy would be a beneficial adjunct to pharmacological treatment. Further studies should explore additional population cohorts with more patients to determine generalizability, treatment duration and potential adverse effects.

Key Words: multiple sclerosis, aquatic, women

INTRODUCTION

Multiple sclerosis (MS) is a disabling, chronic inflammatory disease of the central nervous system in which the immune system attacks myelinated axons, resulting in both central and peripheral nerve damage. Nerve demyelination leads to delayed signaling between the brain and the rest of the body. Classic MS symptoms include: fatigue, vision loss, impaired coordination, weakness, pain and sensory deficits. Optic neuritis is one of the most common presentations. Signs and symptoms are dependent on the amount and type of nerve damage. Onset of MS is most common between the ages of 20 and 50 years old, however it can present in the young and elderly as well. Diagnosis is based on a thorough medical history and neurologic evaluation. Classic MRI findings demonstrate lesions in the white matter of the brain. There are four MS classifications that are based on patient presentation and symptoms, which are listed in terms of increasing disability: relapsing-remitting, primary progressive, secondary progressive and progressive relapsing. At the time of diagnosis, 85% of cases are relapsing-remitting MS (RRMS), which is characterized by attacks followed by periods of complete remission.[1]

Multiple sclerosis is a global health problem impacting an estimated 2.8 million people worldwide.[2] In 2012, the estimated prevalence of MS in the United States alone was 149.2 per 100,000 individuals, equating to over 400,000 people affected.[3] Women are more commonly affected than men at a ratio of approximately 3:1.[4] Both incidence and prevalence of MS in developed and developing countries have been on the rise. In terms of annual healthcare utilization, there is not an exact estimate of healthcare visits related to MS and related flare ups; however, patients with MS were found to use physician services at a rate ratio of 1.53 times higher than the general population, beginning as early as five years prior to the diagnosis and increasing visits with disease progression.[5] Due to the functional limitations linked with MS, it is associated with

a heavy disease burden and often patients require close follow-up care for exacerbations and management from a multifaceted healthcare approach to preserve quality of life. The increased need for care and increasing disease prevalence of MS places a heavy resource and economic burden on healthcare systems. In 2013 alone, approximately $28 billion was spent in the United States on medical costs related to multiple sclerosis.[6]

The etiology of multiple sclerosis and the underlying mechanisms behind the disease are not fully understood or known; however, may gene-environment interactions have been found to play a substantial role in disease progression and development. Environmental factors found to play a role include: low vitamin D levels, infection (Epstein Barr virus), obesity and smoking.[4]

Currently there is no cure that exists for multiple sclerosis. Medical treatment is aimed at targeting symptom relief, preventing exacerbations, and slowing disease progression and course. Medications used for attacks and disease modification include plasmapheresis, immunomodulators such as interferon beta and peginterferon, and immunosuppressants such as methylprednisolone and dexamethasone. Adjunct treatments include physical therapy to preserve strength and muscle flexibility and psychotherapy to provide emotional support to those suffering from depression associated with the disease. These treatment options play an effective role in managing MS; however, treatment plans often take much trial and error, may only last short term and can be associated with many risks and side effects. Immunosuppressants and corticosteroids lower resistance to infection and immunomodulators can cause drowsiness, fatigue and neuropathy. Pharmacologic therapy alone serves to manage the disease and symptoms but is limited in terms of treating the whole person. Aquatic therapy may be used as an adjunct nonpharmacological treatment option to reduce the fatigue associated with MS, therefore serving to increase quality of life. Exercise therapy has been demonstrated to be

beneficial in treating those with MS by improving walking performance, cognitive skills, exhaustion and depression.[7] Women are underrepresented in many published exercise studies and evaluation of both physical and functional capacity, including fatigue, is limited. Exercise does come with limitations in those suffering with MS, so appropriate selection of therapy is extremely important. For example, 60-80% of MS patients report increased fatigue and neurological symptoms with an increase in basal body temperature, often provoked by intense activity.[8] Aquatic therapy allows for better temperature regulation and also offers greater support for exercises that otherwise may be difficult for patients to complete on ground. Despite the possibility of greater benefits with aquatic therapy, it is often underused by physical therapists, especially in MS patients. This paper evaluates three randomized controlled trials (RCTs), evaluating the efficacy of aquatic therapy as an adjunct treatment to reduce MS related fatigue, specifically focusing on the female patient population.

OBJECTIVE

The objective of this selective EBM review is to determine, "Is aquatic therapy an effective treatment for reducing fatigue in adult females living with MS?"

METHODS

The selection of the three randomized controlled trials evaluated in this systematic review was based on fulfillment of certain criteria, including: patient-oriented outcomes, population, intervention, reliability, clinical application and ability to answer the proposed clinical question. All three articles referenced in this review were published in English and were discovered on PubMed using the keywords "multiple sclerosis," "women," and "aquatic." Further inclusion criteria necessary for selection consisted of additional requirements. Studies had to be randomized controlled trials published in a peer reviewed journal after 2010 including human,

female participants. Studies published after 2010, secondary designs, those focusing on other CNS disorders, or studies with populations including children or males were excluded.

The articles selected focused specifically on the population of adult females living with a confirmed clinical diagnosis of MS. Each article investigates the effectiveness of aquatic therapy as an intervention and determining its effectiveness in reducing MS related fatigue. A non-intervention control group was used for comparison in each of the studies. Table 1 highlights the demographics and characteristics of each of the included studies. A summary of statistical analyses utilized for comparison between exercise and control groups in measuring fatigue reduction consist of p-values, mean changes from baseline, standard deviation and F-score.

OUTCOMES MEASURED

Fatigue reduction was the patient-oriented outcome assessed in each of the three articles utilized in this EBM review, which was measured using the Modified Fatigue Impact Scale (MFIS) and/or the Fatigue Severity Scale (FSS). The Kargarfard et al. study addressed perception of fatigue using the MFIS at baseline and after eight weeks of intervention or control. The MFIS is a 21 item self-reported questionnaire evaluating fatigue in terms of physical, cognitive and psychosocial function using a five-point scale, ranging from zero to four. An item scored as zero represents no problems, while a score of five represents extreme problems. This review focuses on the total MFIS score calculated, consisting of physical, psychosocial and cognitive components of fatigue perception.[7] The RCT conducted by Razazian et al. measured fatigue severity with the FSS at baseline and eight weeks later. The FSS is composed of nine statements in which a seven-point rating scale is utilized for each item to calculate fatigue severity. A score of one represents strongly disagreeing with the statement, while a score of seven represents strongly agreeing. The Kooshiar et al. study measured fatigue severity and

perception using both the MFIS and FSS before and after the eight-week long study. Higher scores on both scales are correlated with greater fatigue severity.

Table 1. Demographics & Characteristics of Included Studies

Study	Type	# Patients	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Intervention
Kargarfard (2018)[7]	RCT	40	36.4+/- 8.2	Female, relapsing-remitting MS dx of at least 2 years, able to exercise regularly EDSS score ≤ 3.5	Relapse in the past month	8	Aquatic training program vs. non-exercise control
Razazian (2016)[9]	RCT	54	25-50	Female, dx of MS of primary or secondary-progressive, relapsing-remitting or progressive-relapsing type, age 25-50, EDSS ≤ 6, stable, regular and monitored pharmacological treatment of MS (immune modulatory treatments)	Unable or unwilling to complete questionnaires or follow intervention, psychiatric disorder, pregnant/ breastfeeding, current tx with psychopharmaca, relapse attack w/in 2 months, yoga tx, somatic issues – CVD, arthritis, diabetes	0	Aquatic therapy vs. non-exercise control
Kooshiar (2015)[8]	RCT	40	19-45	Female, documented MS dx, cognitive competency for consent, citizen of Iran living in Mashhad, age 19-45, Expanded Disability Status Scale (EDSS) of 1-5.5.	Pregnancy, primary progressive MS, severe stress or relapse within 4 weeks, Immune modulator drugs other than Avonex, Hgb <10, hx of routine exercise, physical or psych disorders, comorbidities – CVD, MSK disease, CA.	3	Aquatic therapy vs. non-exercise control

RESULTS

Kargarfard et al. conducted an RCT with female participants (mean age of 36.4 +/- 8.2 years SD) who were diagnosed with relapsing-remitting MS for a minimum of two years by the Isfahan Multiple Sclerosis Society.[7] The study was performed over an eight-week period and

compared the effects of an aquatic training program to a control group without exercise intervention.[7] The main outcome evaluated and focused on, for the purposed of this review, was perception of fatigue. The authors enrolled 40 participants who were randomly assigned, via a computer-generated list, to the exercise aquatic therapy intervention or control group.[7] A staff member, independent of the study, maintained randomization by distributing sealed envelopes containing group allocations evenly dividing the participants into two even groups of 20.[7] Due to the nature of the study, participants and therapists were not blinded and were aware of treatment assignment; however, research assistants independent of randomization were responsible for outcome measurement testing.[7] Both groups met two to three times per week throughout the course of the eight-week study and received educational sessions.[7] Those in the experimental group additionally partook in aquatic training three times per week for eight weeks, while the control group was instructed to continue on with their usual activities.[7] Three individuals dropped out of the experimental group and five were excluded from the control group for nonmedical reasons, thus a total of 32 women completed the study; intention-to-treat analysis was performed to account for missing data.[7]

Perception of fatigue was clinically determined at baseline prior to treatment and again after the eight-week intervention. The Modified Fatigue Impact Scale (MFIS) was outcome of measurement utilized by the authors to determine the efficacy of intervention to control. Table 2 demonstrates the changes in the mean of total MFIS and standard deviation (+/- SD) before and after treatment and summarizes results for each group. Both the exercise group ($P < .01$) and control group ($P < .001$) were found to have statistically significant results.[7] The aquatic therapy group showed an improvement in MFIS score with a pretreatment value of 43.1 +/- 14.6 and posttest score of 32.8 +/- 5.9, resulting in a mean change from baseline of 10.3.[7] In contrast, the

MFIS score was worsened in the control group, evidenced by a pretest score of 44.5 +/- 9.3 and a posttest score of 61.0 +/- 8.23, resulting in a mean change from baseline of -16.5.[7] Aquatic therapy was demonstrated to be superior as reflected by a 26.8 point group difference. The group by time interaction F-score was calculated to be 63.461, demonstrating a large treatment effect.[7]

Table 2. MFIS Change in Fatigue Severity from Baseline to Week 8 Follow-up[7]

	Before Treatment (Mean +/-SD)	**Week 8** (Mean +/- SD)	**Mean Change from Baseline**	**P-value**
Aquatic group	43.1 +/- 14.6	32.8 +/- 5.9	10.3	<.01
Control group	44.5 +/- 9.3	61.00 +/- 8.23	-16.5	<.001

The RCT conducted by Razazian was similar in design compared to the previous study mentioned; however, fatigue severity and perception were measured using the FSS. This study included women, recruited from the MS center of the Imam Reza Hospital in Iran, between the ages of 25 and 50 years old with a confirmed diagnosis of MS.[8] Participants were assigned to one of three conditions: yoga, aquatic exercise or a non-exercise control group.[8] The study was piloted over a period of eight weeks and focused on primary outcomes of fatigue, depression and paresthesias.[8] Aquatic exercise and control group outcomes of fatigue severity were analyzed for the purpose of this review. There were 54 patients recruited for this study who were randomized into three groups of 18 via selection of colored chips from an opaque box.[8] Due to the nature of this study, it was impossible for patients to be blinded. A psychologist who was otherwise not involved in the study and blind to patient assignments was responsible for chip selection and group allocation in order to reduce bias.[8] The color selected, red, green or blue, corresponded to the group assigned.[8] This review focuses on a total of 36 patients, 18 of which were assigned to aquatic and 18 assigned to control.[8] Those in the aquatic exercise group met at a hospital rehabilitation center for one-hour sessions, carried out by certified trainers independent of the study, three times per week for a duration of eight weeks total.[8] The control group participants met two to three times per week for 60-90-minute sessions where they were free to socialize and

to interact with physicians, staff and occupational therapists.[8] No participants were lost to follow up during the course of the study; all 36 subjects were included in data analysis.[8]

Evaluation for efficacy and improvement in fatigue severity using the FSS were observed at baseline and after study completion at week eight.[8] Outcomes were measured using comparison of mean values. The results were statistically significant as demonstrated by a time-group interaction p-value of 0.000. [8] The aquatic group revealed a decrease in mean values with a FSS score of 48.72 prior to treatment and a score of 25.28 after exercise therapy completion, resulting in a mean change from baseline of 23.44.[8] Contrariwise, fatigue severity was worsened in the control group with a FSS mean value of 39.56 at baseline and 41.22 at the end of eight weeks, resulting in a mean change from baseline of -1.66.[8] The treatment effect revealed by this study was large based on an η^2p value of .69.[8] The results are summarized below in Table 3.

Table 3. FSS Change in Fatigue Severity from Baseline to Week 8 Follow-up[8]

	Before Treatment (Mean (SD))	**Week 8** (Mean (SD))	**Mean Change from Baseline**	**Time-Group Interaction**
Aquatic group	48.72 (11.46)	25.28 (11.71)	23.44	P = 0.000
Control group	39.56 (14.68)	41.22 (13.52)	-1.66	

Kooshiar et al. also led an eight-week long randomized controlled trial to determine the effects of aquatic therapy on fatigue in women diagnosed with MS living in Iran.[9] The RCT included 40 women, ranging from 19 to 45 years of age, who were divided equally into two groups: aquatic exercise (N=20) and control (N=20).[2] Patients were randomly assigned to groups by name drawing from a hat.[9] Double blinding was not possible due to study design. To minimize bias, researchers involved in group assignment were not involved in data collection.[9] Those in the aquatic exercise group met three times each week at an outpatient clinic in Iran and participated in 45-minute training sessions.[9] Women assigned to the control group did not receive any exercise intervention and were asked to continue on with their normal treatments. Two patients from the control group were excluded from the study due to relapse or withdrawal.[9]

One patient was lost to follow up from the control group due to a change in residence.[9] Intention to treat analysis was not performed; data analysis includes 37 subjects.[9]

Mean values were also used in this RCT to determine the efficacy of aquatic therapy in reducing fatigue after eight weeks of intervention.[9] Measurements using the MFIS and FSS were collected prior to and after treatment in exercise and control groups, and the results were found to be statistically significant ($P < 0.001$).[9] The aquatic group showed a decrease in mean values with a large treatment effect using both measures. The MFIS mean decreased from 43.81 to 32.56, resulting in a mean change from baseline of 11.25.[9] The FSS mean decreased from 41.75 to 35.06, resulting in a mean change from baseline of 6.69.[9] The control group exhibited an increase in mean values, signifying worsening fatigue, which was consistent with the two studies previously discussed. The MFIS mean increased from 41.29 to 42.00, resulting in a mean change from baseline of -0.71, and the FSS mean increased from 38.33 to 39.41, resulting in a mean change from baseline of -0.81.[9] The results are summarized in Table 4 and 5 below.

Table 4. MFIS Change in Fatigue Severity from Baseline to Week 8 Follow-up[9]

	Before Treatment (Mean (SD))	**Week 8** (Mean (SD))	**Mean Change from Baseline**	**Time-Group Interaction**
Aquatic group	43.81 (14.87)	32.56 (16.07)	11.25 (5.33)	$P < 0.001$
Control group	41.29 (12.53)	42.00 (12.15)	-0.71	

Table 5. FSS Change in Fatigue Severity from Baseline to Week 8 Follow-up[9]

	Before Treatment (Mean (SD))	**Week 8** (Mean (SD))	**Mean Change from Baseline**	**Time-Group Interaction**
Aquatic group	41.75 (8.33)	35.06 (12.20)	6.69 (7.18)	$P < 0.001$
Control group	38.33 (9.01)	39.14 (8.10)	-0.81 (2.58)	

DISCUSSION

Multiple sclerosis is a devastating chronic disease that poses many physical and mental challenges to those who are affected. Unfortunately, there is no cure that currently exists; therefore, it is essential that treatment methods be further researched in order to lessen disease burden. The addition of nonpharmacological treatments to current pharmacological treatments is key to improving patient quality of life by bridging the gap of limitations using systemic therapy

alone. It is important to note that role of physical therapy in treating MS in past years was a controversial topic due to concerns of worsening fatigue and symptoms. Nevertheless, numerous recent studies have been performed and revealed exercise therapy to substantially reduce functional limitations and improve quality of life. Aquatic therapy studies in MS patients are limited, but it has been found to be beneficial in a wide variety of conditions ranging from post-surgical recovery to orthopedic issues and chronic pain. Contraindications include skin disease, infection, significant cardiac disease and aquaphobia. Unfortunately, therapy can be time-consuming and requires compliance, and it also brings additional cost which can be a significant barrier. Pharmacological treatment alone can cost patients anywhere from $3,000 to $50,000 per year depending on insurance status.[10] Lack of or limited insurance coverage and added travel costs may serve as an obstacle to accessing additional therapy in terms of affordability.

This review served to determine the efficacy of aquatic therapy as an adjunct treatment option to reduce fatigue severity in adult female patients living with MS. All three studies demonstrated statistically significant reduction in fatigue severity using the Modified Fatigue Impact Scale and/or the Fatigue Severity Scale after an eight-week long aquatic therapy intervention. Results were confirmed with an ample mean change from baseline values in aquatic therapy groups, statistically significant p-values and sizable treatment effects, suggesting aquatic therapy to be a superior treatment method compared to the non-exercise control.

The studies utilized in this review did not come without limitations. Due to the nature of the study designs, patients were unable to be kept blind to treatment, which introduces potential bias and the possibility of a false sense of improvement in the intervention group. Furthermore, fatigue score was worsened in the control groups. Since the control group did not perform any structured physical activity, worsened fatigue could be explained by disease progression and

deterioration due to the nature of the disease; however, this data could have also been influenced by lower motivation due to not receiving intervention, which further calls validity and reliability into question. Additionally, Kooshiar et al. did not perform an intention to treat analysis to account for missing data from subjects lost. A final notable limitation worth mentioning is the fact that patients' treatment plans prior to starting the study may not have been standard across participants, which could have influenced outcomes based on current medications, or lack thereof. Kargarfard et al. and Kooshiar et al. did not mention monitored, regular pharmacological treatment as a requirement of inclusion criteria as Razazian et. al did.

CONCLUSION

The results reported in this systematic review determine aquatic therapy to be an effective treatment in reducing fatigue in adult females living with MS compared to control. All three RCTs found a statistically significant mean decrease in fatigue severity after eight weeks of treatment. Although results were proven to be effective, the populations addressed in all three studies only included adult females living in Iran with mild cases of MS. The lack of patient ethnic variability calls data generalizability into question, as other extraneous factors may play a role in treatment effectiveness. Understanding potential candidates who would best benefit from aquatic therapy based on disease severity is something that would be necessary for practice implementation. Further research needs to be done with additional trials including larger sample sizes with a more diverse patient population. Additionally, it would be valuable to include males and children into future studies to determine if results would be similar. It would also be beneficial to further analyze treatment effects over a longer duration of time with varying numbers of weekly sessions to determine the minimum amount of aquatic therapy sessions required to see improvement in fatigue severity, and any possible drawbacks or adverse effects.

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