2013

Pain Management and Menopausal Health Outcomes in Multiple Sclerosis

Rachel Jawahar
Virginia Commonwealth University

P**ain Management and Menopausal Health Outcomes in Multiple Sclerosis**

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

by

Rachel Hannah Jawahar

B.S. Engineering, Cornell University, 2007
M.P.H. Epidemiology, New York Medical College, 2010

Director:

Saba W. Masho, M.D. Dr.PH.

Associate Professor
Division of Epidemiology, Department of Family Medicine and Population Health

Virginia Commonwealth University
Richmond, Virginia
May, 2013

Acknowledgements

I thank the Women's Health Initiative for allowing their data to be used in this work. I also thank Kate L. Lapane, Ph.D. for her invaluable support and advice over the years as my faculty advisor and while on my dissertation committee.

Much thanks to my other dissertation committee members (Spencer Harpe, Pharm.D. Ph.D., Saba W. Masho, M.D. Dr.P.H., and Unsong Oh, M.D.) and Charles B. Eaton, M.D. for their patience and commentary throughout this work. Thanks to Shibing Yang, M.S. and Margaret L. Henderson, M.L.I.S. for their help with the systematic reviews.

This work is dedicated to my parents Jawahar Henry and Felsy M. Jawahar. Thank you for giving me the foundation to be the woman I am today. You both mean more to me than words can express.

Table of Contents

List of Tables and Figures

Abstract

PAIN MANAGEMENT AND MENOPAUSAL HEALTH OUTCOMES IN MULTIPLE SCLEROSIS

By Rachel Hannah Jawahar, MPH, PhD

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

Virginia Commonwealth University, 2013.

Major Director: Saba W. Masho, MD DrPH
Associate Professor,
Division of Epidemiology, Department of Family Medicine and Population Health

Background: Previous studies have addressed multiple sclerosis (MS) symptom management and improved health-related quality of life (HrQOL). Yet lowered estrogen levels in post-menopasual women with MS may further worsen physical function and symptomology and not all types of pain management have been examined.

Objectives: For post-menopausal women with MS, we evaluated the extent to which smoking is associated with worsened health outcomes and HrQOL, and the extent to which menopausal hormone treatment (MHT) improves health outcomes and HrQOL. For all adult men and women with clinically diagnosed MS, we systematically reviewed pharmacological and non-pharmacological strategies for the reduction of pain.

Methods: We identified 256 post-menopausal women with MS in the Women's Health Initiative Observational Study and examined changes from baseline to 3 years in activities of daily living, physical activity, SF-36 mental and physical component scales (MCS, PCS), and menopausal symptoms. In all adults, experimental studies published after 1965 were included if the sample was not restricted to participants with spasticity or trigeminal neuralgia and participant-reported pain was a primary or secondary outcome. Pain scores were reported as Cohen's d.

Results: Nine percent of post-menopausal women with MS were current smokers and 51% reported current MHT use. Smoking and MHT use had no effect on physical functioning, activities of daily living, or menopausal symptoms. Women with early age at smoking initiation experienced declines in MCS (adjusted β <20 vs. ≥ 25 years: -10.50, 95% Confidence Interval (CI) -2.1 to -18.1; adjusted β 20-24 vs. ≥ 25 years: -8.81, 95% CI: 0.6 to -17.4), but not in PCS. Relative to never MHT users, ever MHT users had higher MCS scores at year 3 compared to baseline (adjusted β: 3.0, 95% CI: 0.4 to 5.6), but no change in PCS. For all adults, transcutaneous electrical nerve stimulation (TENS; Cohen's d: -3.34), nabixomols (Cohen's d: -0.61), and dextromethorphan/quinidine (Cohen's d: -0.22) were reported effective in reducing pain.

Conclusions: Smoking prevention efforts should be increased for women with MS. Women with MS may also experience HrQOL gains with MHT, but contemporaneous data on MHT use is needed. TENS may be more effective than pharmacological methods in reducing MS pain.

Chapter 1: Background

Multiple sclerosis (MS) is a chronic disease that affects nearly 2.5 million people worldwide.[1] The pathophysiology of the disease is still relatively unknown, but MS is physically characterized by the presence of lesions (sites of demyelinated axonal sheaths) in the CNS followed by partial or complete remyelination.[2] Lesions have been linked to 'attacks,' or episodes of neurological symptoms which persist for at least 24 hours.[3] While the human body naturally regenerates myelin, this process may require months[1] and subsequent attacks during the healing period may impair recovery, leading to more severe symptoms and functional disabilities.[2]

Using magnetic resonance imaging (MRI) evidence, MS is typically diagnosed by the dissemination of lesions or attacks over time (at least 30 days between each onset) and space (multiple lesions at once throughout the CNS).[3] The three major types of MS in order of frequency are relapsing-remitting (RRMS), primary progressive (PPMS), secondary progressive (SPMS).[4] RRMS is characterized by clearly defined relapses (lesions or attacks) with full or partial recovery and a lack of disease progression. Similarly, PPMS consists of alternating periods of relapses and partial recovery, but relapses are accompanied by disease progression; this leads to steadily worsened

disability over the lifespan. SPMS consists of an initial RRMS phase which later worsens into steadily-increased disability with few to no relapses.

The lesions which characterize MS may present at any time in the lifespan, with pediatric-onset (≤ 18 years of age)[2] and late-onset MS (diagnosed at age ≥ 50 years)[5] less common than adult-onset MS (diagnosed from 25 to 35 years of age).[6] Similarly, risk factors for MS can begin as early as birth, and behaviors throughout the lifespan may increase future risk of MS diagnosis. Like other autoimmune diseases, the strongest known risk factor for MS is family history; siblings of MS patients have 30 times greater risk of MS than others in the general population.[6] Females are also at greater risk for MS, as nearly two-thirds of all MS patients are women[6] and women have an earlier age of onset than men.[2, 7]

Risk factors which occur later in life are most likely to be modifiable. These include environmental factors such as the latitude of residence and behavioral factors such as vitamin D intake and smoking. Smoking has strong ties to MS incidence; studies have linked past and current smoking to earlier age of MS onset[8] and increased pack-years to greater risk of MS.[9, 10] Vitamin D insufficiency has been linked to greater risk of MS;[11] additionally, a higher incidence of MS at higher latitudes is thought to be related to decreased sun exposure and decreased serum levels of vitamin D.[12] In fact, many of the modifiable risk factors mentioned above are also related to worsened disease progression. MS patients who continue to smoke after diagnosis have been shown to have faster rates of disability,[13] while vitamin D insufficiency has been tied to more frequent relapses in RRMS.[14]

Because MS is a disease which originates in the central nervous system, the health-related quality of life for MS patients is strongly influenced by symptomology. Common symptoms include incontinence, pain, speech impairment, blurred vision, poor sleep quality, and loss of mobility.[15-18] Women with MS also experience hot flashes,[19, 20] sexual dysfunction,[21, 22] and vaginal dryness.[23, 24] Most MS-specific therapies focus on slowing disease progression, but few treatments are meant for MS-specific symptomatic management. Thus, it is necessary to find new ways to manage symptoms and improve health-related quality of life in MS patients over the lifespan.

This dissertation assesses pain management strategies for both men and women with MS and symptomology and quality of life in post-menopausal women by: evaluating the extent to which health outcomes are worsened for post-menopausal MS patients who have ever smoked in comparison to MS patients who have never smoked; estimating the extent to which ever menopausal hormone therapy use benefits the health outcomes of post-menopausal women with MS in comparison to MS patients who have never used hormone therapy; and systematically reviewing pain management strategies for the reduction of non-spastic and non-trigeminal neuralgic pain in MS patients;

By evaluating these outcomes in these particular subgroups, we seek to increase understanding of previously-published literature on pain management strategies in MS patients, while providing impetus for more randomized controlled trials and prospective longitudinal studies in the future. Additionally, the questions answered in post-menopausal women with MS are the first in this important subpopulation; women in the menopausal transition experience many of the symptoms listed above,[25] indicating

worsened health-related quality of life for those women with MS who are also experiencing menopause. Because the U.S. population is aging at an accelerated rate, [26] this research is intended to benefit future physician decisions regarding care for aging patients with MS.

Chapter 2: Association between Smoking and Health Outcomes in Postmenopausal Women Living with Multiple Sclerosis

Abstract

Background: Previous studies have addressed multiple sclerosis (MS) symptom management and improved health-related quality of life (HrQOL) through modifiable risk factors such as smoking.

Objective: Evaluate the extent to which smoking is associated with worsened health outcomes and HrQOL for postmenopausal women with MS.

Methods: We identified 251 participants with MS in the Women's Health Initiative Observational Study. Outcomes included changes from baseline to 3 years in in self-reported activities of daily living, physical activity, HrQOL mental and physical component scales (MCS, PCS) of the SF-36, and menopausal symptoms.

Results: Nine percent of women were current and 50% past smokers. While never smokers experienced declines in physical activity, current and past smokers maintained their activity. Women with early age at smoking initiation experienced declines in MCS (adjusted MCS β <20 vs. ≥ 25 years: -10.50, 95% Confidence Interval (CI) -2.1 to -18.1; adjusted MCS β 20-24 vs. ≥ 25 years: -8.81, 95% CI: 0.6 to -17.4), but not in PCS. No changes in menopausal symptoms were associated with smoking status.

Conclusion: No effects of smoking status were observed on changes in menopausal symptoms. Regardless, women with MS should be encouraged to quit smoking because young age at smoking initiation was associated with declining mental HrQOL during menopause.

Introduction

Multiple sclerosis (MS) is a chronic disease of the central nervous system whose symptoms impact health-related quality of life (HrQOL) across the lifespan.[15, 27] MS disproportionately affects more women than men.[6] Yet, the extent to which the menopausal transition in women worsens MS symptoms remains largely unexplored. Previous studies have addressed symptom management in MS through modifiable risk factors such as smoking.[28] It is known that 40%[10, 13] of women with MS are current smokers, yet it is unknown how smoking affects MS outcomes post-menopause.

In both menopausal and post-menopausal women, current smokers report increased odds of vasomotor symptoms, hot flashes, forgetfulness,[29] and worsened HrQOL.[30] In MS, smoking has been linked to increased incidence[10] and faster MS progression[8, 13] leading to worse health outcomes.[31] More than 37 million women are approaching or experiencing menopause[32] in a quickly aging U.S. population,[26] indicating the need for greater focus on symptom management for women with MS during the menopausal transition and beyond. Using a multi-center prospective study of U.S. postmenopausal women, we aimed to evaluate the extent to which health outcomes and HrQOL are worsened for MS patients who currently smoke or previously smoked relative to never-smoking MS patients.

Methods

Participants

The Women's Health Initiative Observation Study (WHI-OS), sponsored by the National Institutes of Health and the National Heart, Lung, and Blood Institute, followed 93,676 racially diverse women ages 50 to 79 years who were recruited from 40 clinical centers throughout the U.S.[33] Women were eligible for participation in the WHI-OS if they were post-menopausal, not enrolled in other WHI clinical trials, and unlikely to relocate or die within 3 years. Protocols for WHI-OS were reviewed and approved by human subjects review committees at each participating institution.[34] Analyses included 251 WHI-OS participants with MS who completed baseline to year three assessments and had complete exposure information by January 2013. Participants were considered diagnosed with MS if they reported 'yes' when answering the question, "Has a doctor ever told you you had MS?"

Determination of smoking status

Smoking status was determined from baseline self-report and was separated into six cigarette smoking exposure variables. During the WHI data collection period, participants were asked, "During your entire life, have you smoked at least 100 cigarettes?" Those who responded 'yes' were then asked, "Do you smoke cigarettes now?" The responses to these questions were combined to indicate baseline smoking status as ever (with separate categories for current or past use) or never smoker. Current and past smokers were asked their ages at smoking initiation (<20 years, 20-24 years, 25 years and older), the number of cigarettes smoked per day (<15 cigarettes per day, ≥ 15 cigarettes per day), and the number of years they smoked regularly (<30 years, ≥30 years). Past smokers were also asked their age at cessation (<40 years, ≥40 years of age). All categorizations were provided by the WHI. The number of

smoking pack-years was calculated by multiplying the total years of smoking by the number of cigarettes smoked per day divided by 20,[35] and categorized as <10 pack-years, 10-29 pack-years, and ≥30 pack-years.

Outcome ascertainment

We evaluated changes in three types of measures: health-related quality of life, menopausal symptoms, and indicators of physical functioning and activity measures. HrQOL was measured using the RAND 36-Item Health Survey (SF-36)[36] which has been validated in MS patients;[37] for these analyses, we calculated the Mental Component Score (MCS) and the Physical Component Score (PCS) for each participant, each ranging from 0 to 100 points with 50 representing the mean score in the general population. Scores below 50 indicated worse mental or physical health relative to the general population.

A similar approach was used to evaluate changes in activities of daily living (ADL) and physical activity. ADLs (modified from the original Katz[38] index) consisted of four separate items regarding the participant's ability to eat, get in and out of bed, dress, and/or take a bath on her own, and each item had three possible values (1=without help, 2=some help, and 3=completely unable). For baseline and year 3, scores (ranging from 4 to 12) were summed to represent overall ADLs with a lower score indicating better health. Baseline ADL scores were subtracted from year 3 ADL scores so that a positive change score represented a decline in ADLs. Physical activity was computed from self-reported energy expenditures for recreational activities, including walking and other mild/moderate/strenuous activity. These responses were scored as total metabolic equivalent tasks (MET) hours per week. Previous studies in WHI

participants have shown calculated MET hours per week are comparable to physical activity diaries.[39] Baseline scores were subtracted from year 3 scores such that a positive change score indicated an increase in physical activity.

Based on menopause-specific symptoms adapted from the Postmenopausal Estrogen/Progestin Interventions symptom tool,[40] we considered the following to be menopausal symptoms: forgetfulness, difficulty concentrating, mood swings, joint pain or stiffness, headaches or migraines, breast tenderness, increased or decreased appetite, hot flashes, night sweats, vaginal/genital irritation, and vaginal/genital dryness. For each symptom, participants were asked how bothersome the symptom was in the past four weeks (0=did not occur, 1= mild, 2=moderate, 3=severe). Each response was collapsed into binary variables (0=did not occur, 1=symptom occurred (mild, moderate, severe)). At baseline and year 3, a summary measure was constructed by adding the number of symptoms reported (scores ranged from 0 to 11). We treated the outcome as a continuous variable by subtracting the baseline sum from the year 3 summary measure.

Potential Covariates

Potential confounders considered included years since menopause, alcohol use, body mass index (BMI), menopausal hormone therapy (MHT) use, and vitamin D intake. Years since menopause was calculated as the difference between youngest reported age when menses ceased (age when participant experienced last menstruation, oophorectomy, or initiated MHT) and reported age at baseline. Baseline alcohol use was assessed using self-reported use and beer, wine, and liquor servings in the Food Frequency Questionnaire (FFQ) and categorized as never, past, and current use.

Baseline BMI was calculated in kg/m^2 units from heights and weights measured with calibrated balances and stadiometers. For these analyses, BMI was categorized according to the 2012 World Health Organization guidelines: BMI <18.5 kg/m^2 as underweight, BMI between 18.5 kg/m^2 and less than 25 kg/m^2 as normal weight, 25 kg/m^2 to less than 30 kg/m^2 as overweight, and at least 30 kg/m^2 as obese. Reported baseline use of MHT (unopposed estrogen and/or estrogen plus progesterone) pills or patches were recoded as current, past, or never use. Baseline vitamin D insufficiency was defined as <800 IU by applying previously published cut points[41] to data from the FFQ and self-reported supplement use.

Statistical analysis

First we reported the sociodemographic (age, race/ethnicity, education, health insurance status), clinical (years since menopause, BMI, alcohol use, MHT use, vitamin D intake), and smoking characteristics (age started smoking, cigarettes smoked per day, years smoked regularly, smoking pack-years, and age at smoking cessation) by smoking status. Next, multivariable linear regression models were used to estimate associations between differences in three-year HrQOL, ADL, and physical activity scores and number of menopausal symptoms by baseline smoking status. When model building, we examined univariate distributions of each score differences and years since menopause to ensure normality. After examining missing values for determinants and outcomes conditional on potential confounders, we determined missing data were completely at random and would not produce biased estimates in these data. Therefore, complete case analyses were used for each model. Multicollinearity was ruled out by evaluating correlations between each potential confounder (e.g. years since

menopause, alcohol use, BMI, MHT use, vitamin D intake). We used an iterative approach to evaluate confounding. Variables whose addition to the model resulted in ≥ 10% change in the estimate of association were considered confounders and retained in the models. We also evaluated fully adjusted models which included all potential confounders. Model fit was evaluated in several ways. We visually inspected residual plots to ensure residuals were spaced around zero, confirming that a linear regression was appropriate for these data. Normality was confirmed by visually inspecting Q-Q plots for linearity. Outliers were not found when the studentized residuals were examined. We provided beta coefficients and corresponding 95% confidence intervals (CI) from the adjusted models. Statistical significance was determined using an alpha level of 0.05.

Results

Of the 251 women in this sample, only 6% changed smoking status from baseline measures to year 3. Nearly 9% of women were current smokers and 50.2% were past smokers (Table 2.1). More current smokers (65.2%) than past smokers (48.4%) were 59 years of age or younger at baseline. Most women identified as non-Hispanic White regardless of smoking status. Of all non-Hispanic Blacks, 18.6% were current smokers and 61.5% were past smokers. Regardless of smoking status, most women had some college or higher education levels, health insurance, and were of normal weight or underweight. While 81% of never smokers reported ever alcohol use, 83% of current and 80% of past smokers reported current alcohol use. At least half of never smokers and 57% of current smokers reported MHT use while 48% of past

smokers reported MHT use. All women, regardless of smoking status, had less than 800 IU Vitamin D intake per day from food, over the counter supplements, and/or prescribed supplements.

Most women began smoking at age 25 years of age or older and most reported regularly smoking less than 15 cigarettes per day (Table 2.1). Seventy-five percent of current smokers and 25% of past smokers reported regularly smoking for ≥ 30 years. When converted to pack-years, 43% of current smokers and 23% of past smokers smoked for 30 pack-years or more. Most past smokers reported quitting at age 40 years or older.

From baseline to year three of follow-up, greater changes in HrQOL were shown in the MCS rather than PCS (Table 2.2). Age at smoking initiation was associated with significant changes in MCS during menopause in patients with MS. Relative to women who began smoking at ≥ 25 years of age, women who began smoking aged less than 20 years had lower MCS scores at year 3 compared to baseline (adjusted β: -10.50, 95% Confidence Interval (CI): -18.9 to -2.1). PCS scores were unchanged. Similarly, women who began smoking at 20-24 years of age had lower MCS scores (adjusted β: -8.81, 95% CI: -18.1 to 0.4), but no change in PCS. No differences in change in MCS scores were observed based on overall smoking status (current vs. past vs. never smoker). Smoking pack-years were not associated with changes in PCS or MCS. Interestingly, past smokers who reported quitting at age 40 years or older had higher PCS scores (adjusted β: 3.43, 95% CI: -0.3 to 7.2) and lower MCS scores (adjusted β: -4.45, 95% CI: -9.2 to 0.3).

Table 2.3 shows the association between various definitions of smoking and change in ADLs and physical activity from baseline to year 3. From baseline to year 3, the mean ADL change was 0.01 in never smokers and -0.02 in ever smokers. None of the associations between ADL change and smoking were statistically significant. For physical activity, women who reported never smoking experienced a decrease of 3.66 MET task hours per week in physical activity, former smokers a decline of 0.60, and current smokers a decline of 0.10. Relative to women who never smoked, we observed a slower decline in physical activity for current smokers (adjusted β: 4.15, 95% CI: -0.8 to 9.1) and former smokers (adjusted β: 3.48, 95% CI: 0.5 to 6.4) in physical activity.

The five most prevalent menopausal symptoms reported at baseline included joint pain/stiffness (74%), forgetfulness (68%), difficulty concentrating (48%), headaches (45%), mood swings (42%), and vaginal dryness (31%). Aside from joint pain (10%), few ranked symptoms as severe. The least common menopausal symptom reported was a decrease in appetite, regardless of smoking status or time point. Except for vaginal dryness, these estimates were similar at year 3. Differences in change in menopausal symptoms by overall smoking status were not observed (Table 2.4). On average, women who reported never smoking experienced no mean change in menopausal symptoms (0.01), while former smokers (0.37) and current smokers (0.48) reported more symptoms in year 3 relative to baseline. Compared to women who began smoking at age 25 years or older, increases in the number of menopausal symptoms from baseline to year 3 were found for women who began smoking aged less than 20 years (adjusted β: 2.94, 95% CI: 0.4 to 5.5) and for women who began smoking between ages 20 to 24 (adjusted β: 3.27, 95% CI: 0.5 to 6.0). Women who smoked for

30 pack-years or more experienced a reduction in menopausal symptoms than women who smoked less than 10 pack-years (adjusted β: -2.75, 95% CI: -4.7 to -0.8).

Conclusions

To our knowledge, this is the first study to estimate the associations between smoking status and outcomes in post-menopausal women living with MS. Nearly half of all women with MS in the WHI-OS were past smokers, and most had ceased at age 40 years or older. Women with MS who began smoking at a young age had substantially worse mental HrQOL at year 3 than at baseline, indicating a decline in cognition during menopause for those who began smoking at age 20 years or younger. A similar trend in change mental HrQOL during menopause was observed for women with MS who began smoking between ages 20 to 24. Change in in physical HrQOL was not associated with age at smoking initiation. The association between early age of smoking initiation and decline in mental HrQOL during menopause was not explained by current smoking status or by a dose-effect since greater smoking pack-years did not correspond to decline in MCS. Past smokers who had ceased at age 40 years or older had improved physical HrQOL and worsened mental HrQOL at year 3 relative to baseline. Little change was observed in ADLs regardless of smoking status, but current and former smokers experienced increases in physical activity from baseline to year 3 relative to never smokers. The most frequently reported menopausal symptoms were joint pain or stiffness and forgetfulness, regardless of smoking status and time of data collection. Women who began smoking at younger ages (24 years or younger) experienced more

menopausal symptoms from baseline to year 3 relative to women who began smoking aged 25 years or older. Yet women who smoked at least 30 pack-years experienced fewer menopausal symptoms from baseline to year 3 than women who smoked less than 10 pack years.

Estimates of prevalence of smoking are much lower in this study than in previous reports of 40%,[13] as only 9% of women reported current smoking and 59% reported that they had ever smoked. This difference may be due to previous findings that WHI-OS participants are healthier than the general population. Previous studies have shown 6.3% of all WHI-OS participants at baseline were current smokers.[42] Differences in findings may also be related to the majority of past smokers relative to current smokers. While previous studies have only linked ever smoking to worsened outcomes in the MS disease process,[13] changes in HrQOL and physical functioning and activity measures may be strongly related to current smoking than past smoking. For example, our findings of increased physical activity for current smokers also differ from previous findings in participants with MS and in the WHI-OS. Previous studies report decreases in motor function for participants with MS within 10 minutes of smoking a cigarette,[43] Studies in the general WHI-OS population also report current smokers were less likely to engage in more intense physical activity over eight years of followup.[44] The small change in physical activity for current smokers with MS but decline in never smokers suggests current smokers may compensate for smoking by maintaining physical activity.

The results of this study show that classifying smoking status as only never, past, or current use may limit interpretability. Smoking has been linked to increases in MS

incidence through its alterations to the blood-brain barrier[45] by nitric oxide[46] and is affected by ages at smoking initiation and smoking cessation. Younger age at smoking initiation has been linked to increased risk of MS[47] and worsened prognosis from onset.[48] In our study, younger age at smoking initiation was associated with decrease in mental HrQOL. Women with MS in the WHI-OS who ceased smoking at age 40 years or older also experienced increases in physical HrQOL but decreases in mental HrQOL over 3 years. Because ever smokers are more likely to develop progressive disease faster than never smokers,[13] smoking cessation at older ages may be too late to improve mental HrQOL in post-menopause.

The strengths of this study include the unique population and diverse outcomes afforded in WHI-OS data. While the WHI was not an MS-only population, efforts were made during enrollment to represent the general population of post-menopausal women. Additionally, while no MS-specific measures were collected in the WHI, many of the outcomes measured in follow-up data (e.g. SF-36 scales, ADLs) are included in MS-specific composite measures. The WHI-OS also provides data not always present in other MS registries, such as specific questions regarding menopausal symptoms and their severities, frequency and duration of smoking (e.g. number of cigarettes per day, years of smoking before cessation), BMI calculated from physically measured weight and height, and vitamin D intake from supplements and food.

Some may question the participant-reported physician diagnoses of MS used in the WHI. A validation study of self-reported diagnosis of MS in the North American Research Committee on MS registry showed a 98.79% sensitivity of self-report when compared to chart review and/or physician report.[49] The validation subsample

comprised of 59.8% women with a mean age of 54 years, indicating many of these women were similar in age to WHI-OS participant and were probably experiencing menopause or post-menopause at time of study. While no data were available to ascertain time of MS diagnosis, duration of MS, type of MS, or other disability measures, we were comfortable with our decision to use self-reported diagnoses.

In summary, this study evaluated the effects of smoking on HrQOL and physical measures in post-menopausal women with MS. As these women were healthier than the general population and few were current smokers, effects were not found for all outcomes by all smoking frequencies or duration. Regardless, women with MS should be encouraged to quit smoking. Patterns were found pointing to an association between smoking initiation at younger ages and decline mental HrQOL during menopause. It is known that smoking increases risk of MS, but longitudinal studies of age at smoking initiation and outcomes in older age for MS patients are needed.

Table 2.1. Baseline characteristics of postmenopausal women with multiple sclerosis (MS) by smoking status in the Women's Health Initiative Observational Study.

Baseline Characteristics	Current Smoker (n = 23)	Past Smoker (n = 126)	Never Smoker (n = 102)
	Median (Standard Deviation)		
Years since menopause	11.9 (7.2)	13.2 (8.4)	13.8 (9.4)
	Percentages		
Age			
<50 – 59 years	65.2	48.4	46.1
60 – 69 years	34.8	40.5	37.3
70 – 79+ years	0	11.1	16.7
Race/ethnicity			
Non-Hispanic White	89.5	90.0	90.5
Non-Hispanic Black	10.5	6.4	2.4
Hispanic	0	3.6	3.6
Other	0	0	3.6
Education			
≤ High school	13.0	16.0	16.8
Some college	47.8	36.0	36.6
≥ College graduate	39.1	48.0	46.5
Have any health insurance	100	98.4	95.1
Body mass index (kg/m^2)			
<18.5 (underweight)	8.7	4.8	7.8
18.5 to <25 (normal)	47.8	48.4	42.2
25 to <30 (overweight)	26.1	26.2	33.3
30+ (obese)	17.4	20.6	16.7
Alcohol Use			
Never drinker	0	4.0	18.6
Past drinker	17.4	15.9	16.7
Current drinker	82.6	80.2	64.7
Menopause Hormone Therapy			
Never User	34.8	34.1	35.3
Past User	8.7	18.3	12.8
Current User	56.5	47.6	52.0
Vitamin D <800 IU per day	100	100	100
Age started smoking (years)			
< 20	16.1	12.0	N/A
20 to 24	30.1	31.0	N/A
25 or older	53.8	57.1	N/A
Cigarettes smoked (per day)			
< 15	52.0	55.1	N/A
15 or more	48.0	44.9	N/A
Years smoked regularly			
< 10	4.3	27.3	N/A
10 to 29	20.2	47.6	N/A

30 to 49	63.4	23.7	N/A
50 and more	12.0	1.4	N/A
Pack years			
< 10	22.2	44.9	N/A
10 to 29	35.1	31.7	N/A
30 to 49	29.2	14.5	N/A
50 or more	13.6	8.9	N/A
Age quit smoking (years)			
< 20	N/A	1.8	N/A
20 to 29	N/A	19.2	N/A
30 to 39	N/A	25.2	N/A
40 or older	N/A	53.8	N/A

Table 2.2. Association between smoking status and change in health related quality of life measures over 3 years among postmenopausal women with multiple sclerosis (MS) in the Women's Health Initiative Observational Study.

	Δ Physical Component Score (3 year-baseline)			*Δ Mental Component Score (3 year-baseline)*		
Exposure	*Mean Change (Standard Deviation)*	*β-Coefficient Crude*	*β-Coefficient Adjusted[1] (95% Confidence Interval)*	*Mean Change (Standard Deviation)*	*β-Coefficient Crude*	*β-Coefficient Adjusted[1] (95% Confidence Interval)*
Smoking history						
Never smokers	-0.65 (8.6)	Ref.	Ref	-0.84(12.1)	Ref.	Ref.
Ever smokers	-1.10 (9.5)	-0.45	-0.58 (-3.1 to 2.0)	0.12 (11.5)	0.96	0.24 (-3.1 to 3.6)
Smoking status						
Former smokers	-0.74 (9.1)	-0.10	0.89 (-1.7 to 3.4)	-0.25 (11.2)	0.59	-0.09 (-3.4 to 3.2)
Current smokers	-2.97 (11.7)	-2.33	-1.09 (-5.4 to 3.2)	2.08 (13.4)	2.91	2.03 (-3.7 to 7.7)
Age started smoking (years)						
< 20	-1.25 (9.6)	1.25	1.52 (-5.1 to 8.2)	-0.93 (11.4)	-10.03	-10.50 (-18.9 to -2.1)
20 to 24	-0.58 (9.0)	1.93	2.15 (-4.9 to 9.2)	0.72 (11.2)	-8.37	-8.81 (-18.1 to 0.4)
25 or older	-2.51 (12.3)	Ref.	Ref.	9.09 (12.4)	Ref.	Ref.
Cigarettes smoked (per day)						
< 15	-1.73 (8.3)	Ref.	Ref.	0.71 (10.3)	Ref.	Ref.
15 or more	-0.46 (10.7)	1.27	1.60 (-1.5 to 4.7)	-0.47 (12.7)	-1.18	-1.41 (-5.5 to 2.7)
Years smoked regularly						
< 30	-1.89 (8.8)	Ref.	Ref.	1.12 (10.6)	Ref.	Ref.
30 or more	-0.12 (11.1)	1.77	1.80 (-1.5 to 5.1)	-1.89 (13.3)	-3.01	-2.93 (-7.2 to 1.4)
Number of smoking pack-years						
< 10	-1.65 (8.2)	Ref.	Ref.	-0.05 (11.2)	Ref.	Ref.
10 to 29	-2.31 (9.0)	-1.49	-1.60 (-4.9 to 1.7)	2.89 (10.1)	3.61	3.89 (-0.6 to 8.4)
30 or more	1.21 (9.9)	2.03	2.30 (-2.8 to 7.4)	-4.15 (13.9)	-3.43	-3.65 (-10.3 to 3.0)
Age quit smoking (years)						
< 40	-2.94 (8.9)	Ref.	Ref.	1.79 (10.8)	Ref.	Ref.
40 or older	0.46 (9.9)	3.38	3.43 (-0.3 to 7.2)	-2.82 (11.9)	-4.47	-4.45 (-9.2 to 0.3)

[1] Adjusted for the following baseline confounders: years since menopause, alcohol use (current and past drinking, with referent group as never drinker), and body mass index (<18.5 kg/m as underweight, 25 $kg/m^2 \leq$ BMI < 30 kg/m^2 as overweight, and ≥ 30 kg/m^2 as obese, with the referent group as 18.5 $kg/m^2 \leq$ BMI < 25 kg/m^2, or normal weight).

Table 2.3. Association between smoking status and change in physical functioning and activity scores over 3 years among postmenopausal women with multiple sclerosis (MS) in the Women's Health Initiative Observational Study.

	Δ Activities of Daily Living (3 year-baseline)			*Δ Physical Activity (3 year-baseline)*		
Exposure	*Mean Change (Standard Deviation)*	*β-Coefficient Crude*	*β-Coefficient Adjusted[1] (95% Confidence Interval)*	*Mean Change (Standard Deviation)*	*β-Coefficient Crude*	*β-Coefficient Adjusted[1] (95% Confidence Interval)*
Smoking history						
Never smokers	0.01 (0.5)	Ref.	Ref.	-3.66 (12.3)	Ref.	Ref.
Ever smokers	-0.02 (0.6)	-0.03	-0.06 (-0.3 to 0.1)	-0.53 (9.8)	3.12	3.59 (0.8 to 6.3)
Smoking status						
Former smokers	-0.01 (0.53)	-0.02	-0.05 (0.2 to 0.1)	-0.60 (10.2)	3.06	3.48 (0.5 to 6.4)
Current smokers	-0.10 (0.62)	-0.11	-0.14 (-0.3 to 0.1)	-0.19 (7.0)	3.46	4.15 (-0.8 to 9.1)
Age started smoking (years)						
< 20	0.0 (0.6)	0.25	0.24 (-0.2 to 0.6)	-0.52 (9.3)	-1.70	-1.43 (-9.3 to 6.4)
20 to 24	-0.03 (0.4)	0.22	0.22 (-0.2 to 0.6)	-0.89 (11.3)	-2.06	-1.75 (-10.2 to 6.7)
25 or older	0.25 (0.5)	Ref.	Ref.	1.17 (8.9)	Ref.	Ref.
Cigarettes smoked (per day)						
< 15	-0.04 (0.39)	Ref.	Ref.	0.14 (11.0)	Ref.	Ref.
15 or more	0.0 (0.7)	0.04	0.04 (-0.2 to 0.2)	-1.2 (8.4)	-1.33	-1.40 (-4.9 to 2.1)
Years smoked regularly						
< 30	-0.08 (0.6)	Ref.	Ref.	0.04 (11.1)	Ref.	Ref.
30 or more	0.06 (0.5)	0.14	0.14 (-0.1 to 0.3)	-1.07 (6.8)	-1.11	-1.04 (-4.8 to 2.7)
Number of smoking pack-years						
< 10	-0.06 (0.4)	Ref.	Ref.	-0.84 (9.6)	Ref.	Ref.
10 to 29	-0.02 (0.3)	-0.04	-0.05 (-0.2 to 0.1)	-0.96 (11.8)	2.4	2.65 (-1.2 to 6.5)
30 or more	-0.27 (1.2)	-0.29	-0.30 (-0.7 to 0.1)	-0.40 (4.6)	1.07	1.25 (-4.8 to 7.3)
Age quit smoking (years)						
< 40	0.01 (0.5)	Ref.	Ref.	-0.60 (10.1)	Ref.	Ref.
40 or older	-0.10 (0.6)	-0.16	-0.16 (-0.4 to 0.0)	-1.09 (8.8)	-0.31	-0.48 (-4.6 to 3.6)

[1] Adjusted for the following baseline confounders: years since menopause, alcohol use (current and past drinking, with referent group as never drinker), and body mass index (<18.5 kg/m as underweight, 25 $kg/m^2 \leq$ BMI < 30 kg/m^2 as overweight, and $\geq$ 30 kg/m^2 as obese, with the referent group as 18.5 $kg/m^2 \leq$ BMI < 25 kg/m^2, or normal weight).

Table 2.4. Association between smoking status and change in menopausal symptoms over 3 years among postmenopausal women with multiple sclerosis (MS) in the Women's Health Initiative Observational Study.

	Δ Menopausal Symptoms (3 year-baseline)		
		β-Coefficient	
Exposure	*Mean Change (Standard Deviation)*	*Crude*	*Adjusted[1] (95% Confidence Interval)*
Smoking history			
Never smokers	0.01 (3.5)	Ref.	Ref.
Ever smokers	0.38 (3.5)	0.37	0.46 (-0.5 to 1.4)
Smoking status			
Former smokers	0.37 (3.4)	0.35	0.43 (-0.6 to 1.4)
Current smokers	0.48 (4.1)	0.47	0.61(-1.0 to 2.2)
Age started smoking (years)			
< 20	0.44 (3.7)	2.69	2.94 (0.4 to 5.5)
20 to 24	0.70 (2.6)	2.95	3.27 (0.5 to 6.0)
25 or older	-0.16 (3.5)	Ref.	Ref.
Cigarettes smoked (per day)			
< 15	0.50 (2.9)	Ref.	Ref.
15 or more	0.27 (3.9)	-0.23	-0.26 (-1.4 to 0.9)
Years smoked regularly			
< 30	0.08 (3.2)	Ref.	Ref.
30 or more	0.88 (4.1)	0.80	0.74 (-0.4 to 1.9)
Number of smoking pack-years			
< 10	0.35 (3.1)	Ref.	Ref.
10 to 29	0.67 (3.1)	0.0	-0.1 (-1.3 to 1.1)
30 or more	-2.13 (4.0)	-2.80	-2.75 (-4.7 to -0.8)
Age quit smoking (years)			
< 40	0.31 (3.3)	Ref.	Ref.
40 or older	0.35 (3.4)	0.12	0.06 (-1.3 to 1.4)

[1] Adjusted for the following baseline confounders: years since menopause, alcohol use (current and past drinking, with referent group as never drinker), and body mass index (<18.5 kg/m as underweight, 25 $kg/m^2 \leq$ BMI < 30 kg/m^2 as overweight, and ≥ 30 kg/m^2 as obese, with the referent group as 18.5 $kg/m^2 \leq$ BMI < 25 kg/m^2, or normal weight).

Chapter 3: Association between Smoking and Health Outcomes in Postmenopausal Women Living with Multiple Sclerosis

Abstract

Background: Lowered estrogen levels during the menopausal transition may worsen quality of life for people living with multiple sclerosis (MS) by further worsening physical function and symptomology.

Objective: To evaluate the extent to which menopausal hormone treatment (MHT) improves health outcomes and health-related quality of life (HrQOL) for post-menopausal patients with MS.

Methods: There were 256 women with MS in the Women's Health Initiative Observation Study with valid information at baseline and year 3. Outcomes included changes from baseline to 3 years in activities of daily living, physical activity, HrQOL mental and physical component scales (MCS, PCS) of the SF-36, and menopausal symptoms.

Results: Fifty-one percent reported current MHT use and 14.8% reported past use. MHT had no effect on physical functioning, activities of daily living, or menopausal symptoms. Relative to never MHT users, ever MHT users had higher MCS scores at year 3 compared to baseline (adjusted β: 3.0, 95% Confidence Interval: 0.4 to 5.6), but no change in PCS.

Conclusion: Women with MS may experience HrQOL gains with MHT, but its use must be carefully evaluated in the context of risks and benefits. Contemporaneous data on MHT use is needed.

Introduction

Multiple sclerosis (MS) is a progressive disease of the central nervous system which occurs more often in women than men.[50] It is known that patient symptoms impact quality of life across the lifespan,[16] yet it is unknown how menopause may affect outcomes in MS patients. Menopause (median age of onset 52 years)[25] begins a period of rapid decline in serum estradiol levels in women.[51] Fluctuations in estrogen levels are linked to disease activity in women with MS. Higher estradiol levels during pregnancy are associated with reduced frequency of relapses, and the precipitous decline in estradiol levels post-partum is associated with increased frequency of relapses.[52] Furthermore, experimental evidence indicates that estrogens have immunomodulatory and neuroprotective effects, [52] potentially mediating remyelination.[53] Therefore, lowered estrogen levels during the menopausal transition might be expected to worsen MS-related symptoms and quality of life.

Despite the increasing incidence of MS in women[54] and the millions of women approaching or experiencing menopause[32] in the aging population,[26] most studies concerning estrogen and MS have examined women of reproductive ages. Thus, further examination of outcomes in older women with MS is needed, particularly during the period of natural decrease in estrogen levels in menopause and beyond. Using a prospective study of American postmenopausal women, we aimed to evaluate the extent to which health outcomes and health-related quality of life (HrQOL) improve for MS patients who have ever used MHT (currently or in the past) compared to never-using MS patients.

Methods

Participants

The Women's Health Initiative Observation Study (WHI-OS), sponsored by the National Institutes of Health and the National Heart, Lung, and Blood Institute, is a multi-center study which followed 93,676 racially diverse women ages 50 to 79 years throughout the U.S.[33] Eligible women were post-menopausal, not enrolled in other WHI clinical trials, and unlikely to relocate or die within 3 years. Protocols for WHI-OS were reviewed and approved by human subjects review committees at each participating institution.[34] Analyses included 256 WHI-OS participants with MS at baseline who completed year three assessments by December 2012 and completed questions regarding MHT. Participants were considered diagnosed with MS if they reported 'yes' when answering the question, "Has a doctor ever told you you had MS?"

Determination of MHT use

Self-reported MHT use at baseline was collected in two different ways. WHI participants were asked to bring in all medications currently used. For those not currently using MHT, information regarding duration of previous use and type of MHT used (unopposed estrogen or estrogen-progesterone, in pills or patches) were collected. These were categorized as MHT history (current, past, or never use), duration of estrogen-alone or estrogen-progesterone use (<5, 5 to 9, or 10 or more years), recency of estrogen-alone use (current, past <9, past 10 or more years), and recency of estrogen-progesterone use (current, past <5, past 5 or more years).

Outcome ascertainment

We evaluated changes in menopausal symptoms, HrQOL, and indicators of physical functioning and activity from baseline to year three. Using the Postmenopausal Estrogen/Progestin Interventions trial[40] symptom tool, we considered the following to be menopausal symptoms: forgetfulness, difficulty concentrating, mood swings, joint pain or stiffness, headaches or migraines, breast tenderness, increased or decreased appetite, hot flashes, night sweats, vaginal/genital irritation, and vaginal/genital dryness. For each symptom, participants were asked how bothersome the symptom was during the past 4 weeks, with four possible values (0=did not occur, 1=mild, 2=moderate, and 3=severe). We collapsed the response categories for each symptom to a binary indicator variable (1=present (mild, moderate, or severe), 0=not present). We summed the number of symptoms present at baseline and at year 3, separately (range 0 to 11). We treated the outcome as a yes/no indicator of an increase in the number of symptoms from baseline to year 3 (yes=increase in number of symptoms; no=decrease or no change).

HrQOL was measured with the RAND 36-Item Health Survey[36] using the SF-36 scoring method, which has been validated in the MS population.[37] Two summary scores, the Mental Component (MCS) and Physical Component Scores (PCS), were calculated from eight subscales (vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health). Scores ranged from 0 to 100 points with 50 representing the mean score in the general population; a score below 50 indicated worse mental or physical health than the general population. Change scores from year 3 to baseline were computed, with a positive change score indicating an increase in HrQOL.

A similar approach was used to evaluate changes in activities of daily living (ADL) and physical activity. ADLs recorded in the WHI (modified from the original Katz et al[38] index) consisted of four separate items regarding the participant's ability to eat, get in and out of bed, dress, and/or take a bath on her own. Each item had three possible values (1=without help, 2=some help, and 3=completely unable), and scores were summed (ranging from 4 to 12) to represent overall ADLs with a lower score indicating better health. The baseline ADL score was subtracted from the year 3 ADL score such that a positive change score represented a decline in ADLs. Physical activity was computed from self-reported energy expenditures for recreational activities, including walking and other mild/moderate/strenuous activity, which are comparable to physical activity diaries.[39] These responses were scored as total metabolic equivalent tasks (MET)-hours per week. Change scores from year 3 to baseline were computed with a positive change score indicating an increase in physical activity.

Covariates

Potential confounders included years since menopause, body mass index (BMI), vitamin D intake, and smoking status. Years since menopause was calculate as the difference between reported youngest age when menses ceased (age when participant experienced last menstruation, oophorectomy, or initiated MHT)[55] and reported age at baseline. BMI was calculated in kg/m^2 units from heights and weights measured with calibrated balances and stadiometers. BMI was categorized according to the 2012 World Health Organization guidelines:[56] BMI <18.5 kg/m^2 as underweight, BMI between 18.5 kg/m^2 and less than 25 kg/m^2 as normal weight, 25 kg/m^2 to less than 30 kg/m^2 as overweight, and at least 30 kg/m^2 as obese. Vitamin D intake was recorded using self-

reported responses to the Food Frequency Questionnaire, which has been validated in the WHI cohort,[57] and questions regarding supplement use. Using previously published cut points,[41] vitamin D insufficiency was defined as <800 IU. Smoking status was determined from baseline self-report and categorized as current, past, or never smoker.

Statistical analysis

We reported the sociodemographic (age, race/ethnicity, education, health insurance status), clinical (years since menopause, vitamin D intake, BMI, alcohol use, smoking history), and MHT use (duration of unopposed estrogen use, recency of unopposed estrogen use, duration of estrogen-progesterone use, and recency of estrogen-progesterone use by MHT use. Binary logistic regression models were used to estimate odds of increased number of menopausal symptoms from baseline to year 3. Confounding was evaluated in an iterative approach. Variables whose addition to the model resulted in ≥ 10% change in the estimate of association were considered confounders and retained in the model. We also evaluated fully adjusted models which included all potential confounders. We also considered reproduction-specific covariates such as parity and past oral contraceptive use when modeling. As these covariates had no impact on outcomes evaluated, they were excluded from adjusted models. Odds ratios and 95% confidence intervals (CI) are provided for both crude and fully adjusted models.

For continuous outcome variables, multivariable linear regression models were used to estimate associations between differences in three-year HrQOL, ADL, and physical activity scores by baseline MHT use. When model building, univariate distributions of each score difference and years since menopause were examined to

ensure normality. After examining missing values for determinants and outcomes conditional on potential confounders, we determined missing data were completely at random and would not produce biased estimates in these data. Therefore, complete case analyses were used for each model. Multicollinearity was ruled out by evaluating correlations between each potential confounder (e.g. years since menopause, BMI, vitamin D intake, and smoking status). To evaluate confounding, we used the same iterative approach described above. Model fit was evaluated in several ways. We visually inspected residual plots to ensure residuals were spaced around zero, confirming that a linear regression was appropriate for these data. Normality was confirmed by visually inspecting Q-Q plots for linearity. Outliers were not found when the studentized residuals were examined. We provided beta coefficients and corresponding 95% CI from the adjusted models. Statistical significance was determined using an alpha level of 0.05.

Sensitivity analysis

In a sensitivity analysis, we evaluated the number of women who changed MHT use from baseline to year 3 measures. Previous studies have shown more than 20% of women in the WHI-OS reported using MHT for less than 5 years at baseline.[42] As MHT is primarily prescribed to treat vasomotor symptoms[25] and these symptoms are usually strongest within the two years after menopause,[51] we predicted some women in this study would change MHT use status from baseline to year 3. Substantial changes in MHT use (e.g. occurred in at least 10% of women) would cause exposure misclassification and would potentially bias our analyses. Therefore we evaluated the

number of women who reported different MHT status at year 3 and performed the statistical analyses listed above for this subset.

Results

Among women with MS, 51.2% were current MHT users at baseline and 14.8% were past users (Table 3.1). More than 20% of past MHT users and 7.6% of current users were 70 years of age or older. Most current users identified as non-Hispanic White (93.8%) and 42.8% of non-Hispanic Black participants were ever users. Nearly 52% of current users reported their highest education level as high school diploma or less, relative to 35.1% of past users who reported the same. An equivalent number of past or never users were underweight (past users: 10.5%, never: 10.3%) while 2.3% of current MHT users were underweight. Most current and past MHT users reported current alcohol use, and 89.7% of current MHT users were ever smokers. All women had less than 800 IU Vitamin D intake per day from food, over the counter supplements, and/or prescribed supplements. Higher proportions of current MHT users had hysterectomies (47.3%) or oophorectomies (33.8%) relative to past users and never users.

More than one half of ever MHT users had used unopposed estrogen (Table 3.1). Most past MHT users reported using unopposed estrogen for less than 5 years, while 40.5% of current users of unopposed estrogen had been using MHT for 5 or more years. Forty-seven percent of past MHT users reported using estrogen and progesterone for less than 5 years relative to 22.1% of current MHT users reporting the

same. Nearly 8% of current MHT users had switched between unopposed estrogen and estrogen and progesterone.

The most common menopausal symptom, regardless of MHT use or time point, was joint pain or stiffness (Table 3.2). Overall, a similar number of women had increases in symptoms from baseline to year 3, regardless of MHT use. In particular, 40.5% of current MHT users reported joint pain or stiffness at year 3 relative to 29% at baseline. After adjusting for years since menopause, smoking status, and BMI, the odds ratios for increased symptoms at year 3 was 0.81 for current users (95% Confidence Interval (CI): 0.43 to 1.51) and 0.68 for past users (95% CI: 0.28 to 1.69) when compared to never users.

Table 3.3 shows the association between MHT use and change in HrQOL from baseline to year 3 in subjects with MS. Relative to never MHT users, ever MHT users had a non-statistically significant increase in MCS scores at year 3 compared to baseline (adjusted β: 3.0, 95% CI: -0.3 to 6.3), but no change in PCS. Never users experienced an average 1.96 point decline (standard deviation: 10.4) in MCS from baseline to year 3, whereas women with MS who ever used MHT on average experienced a 0.63 increase in MCS (standard deviation: 12.3). For women who had ever used unopposed estrogen, greater increases in HrQOL were shown in MCS rather than PCS. Women who used unopposed estrogen for less than 5 years had little change in PCS but higher MCS scores at year 3 compared to baseline (adjusted β: 3.09, 95% CI: -2.0 to 8.2), although not statistically significant. Past users tended to have higher MCS scores at year 3 compared to baseline compared to never users (<10 years: adjusted β: 3.14, 95% CI: -3.7 to 10.0; 10+ years: adjusted β: 4.18, 95% CI: -3.5

to 11.8). Interestingly, the effect of MHT use on MCS was not observed for estrogen-progesterone users. For women with MS who had ever used estrogen and progesterone no changes in MCS scores were apparent. PCS scores were lower at year 3 than at baseline for women who had used estrogen and progesterone for less than 5 years (adjusted β: -3.6, 95% CI: -7.5 to -0.3) and past users who ceased 5+ years ago (adjusted β: -6.0, 95% CI: -11.3 to -0.7).

The association between MHT use and change in ADLs and physical activity from baseline to year 3 are shown in Table 3.4. None of the associations between ADL change and MHT use were statistically significant. Little change in ADL scores were observed from baseline to 3 years. The mean ADL change was -0.02 in never MHT users and -0.01 in ever users. For physical activity, 45.5% of women with MS had greater than 8 MET-hours/week of physical activity at baseline. The overall patterns observed indicated that women decreased their activity on average ~2 MET task hours/week from baseline to year 3. Women who used unopposed estrogen for 10 or more years maintained their activity levels resulting in a net increase of 2.57 MET task hours/week from baseline to year 3, compared to never users. None of the associations between MHT and changes in physical activity were statistically significant.

In our sensitivity analyses, we found 39 women (15.2% of the sample) had changed MHT status at year 3 assessments (Table 3.5). Most of these women were never or past users at baseline who began using MHT by year 3 (76.9%), while only 9 women who reported using MHT at baseline stopped at year 3. Similar to all women included in our sample, this subset was also mostly non-Hispanic White, overweight or obese, and current alcohol users. Most baseline MHT users stopped using unopposed

estrogen after less than 9 years duration. As in the general sample, the most common menopausal symptoms were joint pain or stiffness and forgetfulness (Table 3.6). Unlike the general sample, at least half of all women who had changed MHT status experienced increases in symptoms by year 3. Non-significant associations were found for increased symptoms at year 3 by baseline MHT status.

Directions of associations between baseline MHT status and MCS and PCS for women who changed MHT use by year 3 were similar to those found in the total sample, but greater in magnitude (Table 3.7). Ever users at baseline experienced non-statistically significant decreases in PCS (adjusted β: -3.39, 95% CI: -10.8 to 4.1) and increases in MCS (adjusted β: 3.0, 95% CI: -0.3 to 6.3) at year 3, relative to never users. Never users at baseline experienced an average 2.56 point decline (standard deviation: 8.5) in MCS from baseline to year 3, while ever users at baseline on average experienced a 3.52 increase in MCS (standard deviation: 16.2). For women who had ever used unopposed estrogen at baseline, greater increases in HrQOL were shown in MCS rather than PCS. Women who used unopposed estrogen for less than 9 years had little change in PCS but higher MCS scores at year 3 compared to baseline (adjusted β: 12.73, 95% CI: -0.8 to 26.3), although not statistically significant. Past users tended to have higher MCS scores at year 3 compared to baseline compared to never users (adjusted β: 11.12, 95% CI: -3.8 to 26.0). For women with MS who had ever used estrogen and progesterone, decreases in MCS scores were greater in magnitude than in the total sample. Women who had ever used estrogen-progesterone at baseline experienced non-significant increases in PCS and decreases in MCS scores at year 3 compared to baseline. Past users who stopped using MHT less than 5 years

before baseline had significant decreases in MCS at year 3 (adjusted β: -18.75, 95% CI: -33.8 to -3.7) compared to never users at baseline.

As in the total sample, no significant associations were found between changes in limitations due to ADLs and MHT use at baseline for women who changed their MHT status at year 3 (Table 3.8). Additionally, none of the associations between MHT and changes in physical activity were statistically significant. Relative to never users, ever MHT users at baseline maintained their physical activity at year 3. Current users of unopposed estrogen at baseline increased physical activity at year 3 (adjusted β: 6.16, 95% CI: -7.8 to 19.9) relative to never users, while current users of estrogen-progesterone at baseline experienced no changes. Women who had used estrogen-progesterone for less than 5 years at baseline had fewer decreases in physical activity relative to never users than women who had used estrogen-progesterone for at least 10 years. Yet women who had used unopposed estrogen for at least 10 years at baseline had increases in physical activity at year 3 relative to never users (adjusted β: 7.84, 95% CI: -8.0 to 23.7), while women who had used unopposed estrogen for less than 10 years at baseline decreased physical activity at year 3 (adjusted β: -6.69, 95% CI: -18.3 to 4.9).

Conclusions

To our knowledge, this is the first study to estimate the associations between MHT and outcomes in women living with MS. MHT use was common in women with MS. In our study, 51% percent reported current use and 14.8% past use. This is consistent with previous reports of the general WHI population report 45.5% current

use.[42] The extent to which these estimates would be consistent with a contemporary cohort is unclear as the 2002 results of the WHI clinical trial in estrogen-progestin in healthy women[58] resulted in nationally reduced MHT use.[59] In our study, unopposed estrogen was the most cited choice for managing menopausal symptoms. Additionally, the women in our study who had stopped using MHT by enrollment in the WHI-OS but resumed use at year 3 experienced more menopausal symptoms and worse mental HrQOL than the total sample, indicating that women with MS may be seeking MHT for relief of symptoms.

The findings regarding HrQOL and MHT among women with MS are intriguing. Overall, women with MS reporting MHT use had less declines in mental HrQOL measures (MCS) compared to never users of MHT, suggesting a beneficial effect of estrogen use on mental health in women with MS during menopause. When evaluating this finding by type of MHT, we found that for women who had used unopposed estrogen, greater increases were found in MCS scores than in PCS scores over three years of follow-up. Yet for women who had used estrogen and progesterone, greater decreases in PCS scores than in MCS scores were found. Greater changes in MCS scores are consistent with recent experimental autoimmune encephalomyelitis models, which suggest that estrogen is protective for synaptic transmission and may improve memory and cognition in people living with MS.[60] Our findings of greater decreases in PCS than MCS for estrogen-progesterone users differ from other studies in postmenopausal women with intact uteri. A study in women[61] who had used estrogen-progesterone reported non-significant increases in PCS subscales over 9 months, all of which were below the population norms for Canadian women aged 45 to 54 years.

Additionally, estrogen-progesterone has been shown to have protective effects[62] in postmenopausal women with cognitive complaints. As most women in our study were aged 69 years or younger but had used estrogen-progesterone for up to nine years, it is possible that estrogen-progesterone was not initiated at the youngest appropriate age to effectively improve mental and physical HrQOL or physical functioning.

Our study found no overall association between MHT and measures of physical functioning and physical activity. This is consistent with reports from the WHI randomized trials which also demonstrated no association with self-reported outcomes[63, 64] and trials using change in performance-based measures of physical function.[65, 66] At baseline, 45.5% of women with MS had greater than 8 MET-hours/week of physical activity. This is consistent with previous reports of 55.5% of all women in the WHI-OS with similar levels of physical activity.[42]

We found no overall association between MHT and changes in menopausal symptoms. This is inconsistent with the state of the science report on management of menopausal symptoms suggests that there is a beneficial effect on some common symptoms.[25] The discrepancy between our study and the literature may be owing to several reasons. First, because of the limited number of women with MS, we could not evaluate each individual symptom. Instead we used a composite score which may have diluted our ability to show benefit of MHT. Second, our data showed a beneficial effect, but we may not have had sufficient power to demonstrate statistical significance. Third, in women with MS, the most frequently reported menopausal symptoms were joint pain or stiffness, regardless of MHT use and time of data collection. This is consistent with previous findings from the WHI clinical trials and consensus statements which show

frequent reports of joint pain during menopause, but no clear association between menopausal status and joint pain.[25, 67] Fourth, women with MS may experience fewer symptoms which are most amenable to MHT intervention. While previous reports of WHI indicated that vaginal dryness was reported in 27.0% and vaginal irritation or itching in 18.6% of all women,[68] women with MS had lower reports of these symptoms at baseline.

Strengths of this study include the study population and outcomes evaluated. The WHI-OS focused on enrollment so that the study participants would represent the general population of postmenopausal women, particularly those of different races/ethnicities. Our study population captured women in a more generalizable community setting, which offers an advantage to other MS studies conducted in clinical settings. Indeed, the sample size available for this study (n=256) exceeds most single-center studies of patients with MS. To our knowledge, only one study[20] attempted to capture menopausal symptoms experienced by women living with MS. This cross-sectional study was conducted over twenty years ago and included only 19 post-menopausal women. By evaluating the associations between MHT use and menopausal symptoms for women with MS in longitudinal WHI data, we were able to use menopause-specific measures and validated tools for physical functioning, physical activity, and HrQOL provided by the WHI.

The WHI, however, captured diagnosis of MS using participant-reported physician diagnoses of MS. No data were available in the WHI-OS to ascertain time of MS diagnosis, duration of MS, type of MS, or other MS-specific disability measures. While the WHI did not collect MS-specific measures, MS registries also rely on self-

reported symptoms and physical function[69] and validation studies have shown self-report is an accurate representation of the MS disease experience.[70] In a sample of MS patients (59.8% female with a mean age of 53.49 years), self-reported diagnoses was 98.79% sensitive when compared to chart review and/or physician report.[49] Additionally, while prevalence of MHT use in the WHI was higher than use in postmenopausal women today,[59] the 3-year analysis period in this study reflects current guidelines for MHT use and is relevant in women living with MS today.[71]

In summary, this study evaluated the effects of MHT use on HrQOL and physical measures in post-menopausal women with MS. Consistent with previous research, we found no overall effect of MHT on physical functioning and activity. However, our findings show MHT may positively impact mental HrQOL in women with MS, and those women who are experiencing worse symptoms may seek relief with MHT.[25] While more longitudinal assessments of frequency and duration of MHT use in MS patients are needed, previous surveys[72] have shown nearly 70% of post-menopausal women with MS do not use MHT for symptom relief. Healthcare professionals should consider available MHT regimens in the context of efficacy and risk of adverse events when treating symptoms during menopause and post-menopause.

Table 3.1. Baseline characteristics of postmenopausal women with multiple sclerosis (MS) by MHT use in the Women's Health Initiative Observational Study.

Baseline Characteristics	Current MHT user (n = 131)	Past MHT user (n = 38)	Never MHT user (n = 87)
		Median (Standard Deviation)	
Years since menopause	12.4 (8.3)	16.1 (10.6)	13.6 (8.2)
		Percentages	
Age			
<50 – 59 years	56.5	47.4	37.9
60 – 69 years	35.9	26.3	48.3
70 – 79+ years	7.6	26.3	13.8
Race/ethnicity			
Non-Hispanic White	93.8	89.7	85.3
Non-Hispanic Black	1.8	6.9	9.3
Hispanic	2.7	3.5	4.0
Other	1.8	0.0	1.8
Education			
≤ High school	51.5	35.1	43.7
Some college	36.2	48.7	35.6
≥ College graduate	12.3	16.2	16.2
Have any health insurance	98.5	100	94.2
Body mass index (kg/m^2)			
<18.5 (underweight)	2.3	10.5	10.3
18.5 to <25 (normal)	51.9	44.7	37.9
25 to <30 (overweight)	29.0	26.3	29.9
30+ (obese)	16.8	18.4	21.8
Alcohol Use			
Never drinker	8.4	10.5	10.3
Past drinker	15.3	21.1	16.1
Current drinker	76.3	68.4	73.6
Smoking History			
Never	42.1	34.2	41.4
Past	47.6	60.5	49.4
Current	10.3	5.3	9.2
Vitamin D intake <800 (µg/day)	100	100	100
Ever Hysterectomy	47.3	36.8	25.3
Ever Oophorectomy[1]	33.8	23.7	25.3
Ever Oral Contraceptive Use	57.3	31.6	44.8
Gravidity			
1 to 4 pregnancies	69.5	78.9	58.6
5+ pregnancies	18.0	13.2	27.6
Parity			
Never pregnant/term pregnancy	13.7	10.5	18.4
1 to 3 term pregnancies	71.8	65.8	58.6
4+ term pregnancies	14.5	23.7	23.0
MHT type used			
Ever unopposed estrogen	58.8	55.3	N/A

Ever estrogen-plus-progesterone	41.2	44.7	N/A
Unopposed estrogen duration			
< 5 years	18.3	34.2	N/A
5-9 years	13.0	7.9	N/A
10+years	27.5	13.2	N/A
Recency of estrogen-alone use			
Current	51.2	N/A	N/A
Past<9 years	5.3	23.7	N/A
Past 10+ years ago	2.3	31.6	N/A
Estrogen-plus-progesterone duration			
< 5 years	22.1	47.4	N/A
5-9 years	20.6	5.3	N/A
10+years	13.7	2.6	N/A
Recency of estrogen-plus-progesterone			
Current	48.9	N/A	N/A
Past < 5 years	2.3	36.8	N/A
Past 5+ years	5.3	18.4	N/A

[1] Includes the removal of one or both ovaries.

Table 3.2. Association between MHT use and menopausal symptoms at 3 year followup among post-menopausal women with MS

Menopausal Symptoms	Current MHT user (n = 131)		Past MHT user (n = 38)		Never MHT user (n = 87)	
	Baseline	Year 3	Baseline	Year 3	Baseline	Year 3
	Percentages					
Forgetfulness	14.5	14.5	21.1	21.1	17.2	20.7
Difficulty concentrating	10.7	9.9	13.2	13.2	9.2	11.5
Mood swings	9.2	7.6	10.5	10.5	11.5	14.9
Joint pain or stiffness	29.0	40.5	34.2	34.2	29.9	33.3
Headaches or migraines	13.0	10.7	10.5	13.2	12.6	13.8
Breast tenderness	5.3	3.1	2.6	7.9	1.2	2.3
Increased appetite	8.4	7.6	13.2	10.5	10.3	11.5
Decrease appetite	2.3	2.3	0	0	4.6	1.2
Hot flashes	5.3	6.1	7.9	10.5	9.2	2.3
Night sweats	8.4	8.4	10.5	7.9	9.2	9.2
Vaginal/genital irritation	4.6	5.3	2.6	2.6	1.2	2.3
Vaginal/genital dryness	3.8	7.6	10.5	18.4	9.2	6.9
Average number of symptoms (Standard Deviation)	1.15 (1.41)	1.24 (1.64)	1.37 (1.79)	1.50 (1.66)	1.25 (1.59)	1.30 (1.64)
Increase in symptoms		24.4		23.7		27.6
Crude OR[1] (95% CI)	0.85 (0.46 to 1.57)		0.82 (0.34 to 1.97)		*Reference*	
Adjusted[2] OR (95% CI)	0.81 (0.43 to 1.51)		0.68 (0.28 to 1.69)		*Reference*	

[1] Here, the outcome evaluated is a yes/no indicator of an increase in the number of symptoms from baseline to year 3 (yes = an increase in the number of symptoms; no = a decrease or no change), with no as the referent group.

[2] Adjusted for the following baseline confounders: years since menopause, smoking status, alcohol use, and body mass index (<18.5 kg/m as underweight, 25 $kg/m^2 \leq$ BMI < 30 kg/m^2 as overweight, and ≥ 30 kg/m^2 as obese, with the referent group as 18.5 $kg/m^2 \leq$ BMI < 25 kg/m^2, or normal weight).

Table 3.3. Association between MHT status and change in health-related quality of life measures over 3 years among postmenopausal women with multiple sclerosis (MS) in the Women's Health Initiative Observational Study.

	Δ Physical Component Score (3 year-baseline)			*Δ Mental Health Component Score (3 year-baseline)*		
Exposure	*Mean Change (Standard Deviation)*	*β-Coefficient Crude*	*β-Coefficient Adjusted[1] (95% Confidence Interval)*	*Mean Change (Standard Deviation)*	*β-Coefficient Crude*	*β-Coefficient Adjusted[1] (95% Confidence Interval)*
MHT history						
Never	-0.06 (9.2)			-1.96 (10.4)		
Ever	-1.36 (9.0)	1.30	-1.41 (-4.0 to 1.1)	0.63 (12.3)	2.59	3.00 (-0.3 to 6.3)
Unopposed estrogen duration						
< 5 years	-0.83 (10.9)	0.83	0.17 (-3.8 to 4.1)	2.71 (12.5)	2.24	3.09 (-2.0 to 8.2)
5-9 years	-0.33 (8.8)	1.33	0.33 (-4.8 to 5.4)	0.59 (12.9)	0.12	1.09 (-5.6 to 7.8)
10+years	-1.77 (9.2)	-0.11	-1.15 (-5.3 to 3.0)	-0.95 (11.5)	-1.42	-0.36 (-5.8 to 5.1)
Recency of unopposed estrogen use						
Current	-1.00 (9.7)	0.66	-0.04 (-3.6 to 3.5)	-0.10 (13.3)	-0.57	0.55 (-4.0 to 5.1)
Past <10 years	-2.3 (12.8)	-0.64	-0.76 (-6.1 to 4.6)	3.04 (7.5)	2.57	3.14 (-3.7 to 10.0)
Past 10+ years ago	-0.53 (6.2)	1.13	-0.76 (-6.6 to 5.1)	1.78 (11.0)	1.31	4.18 (-3.5 to 11.8)
Estrogen-plus-progesterone duration						
< 5 years	-4.44 (9.9)	-4.16	-3.60 (-7.5 to 0.3)	0.90 (10.5)	0.21	-1.07 (-6.2 to 4.0)
5-9 years	0.05 (7.2)	0.34	1.18 (-3.1 to 5.5)	-0.25 (10.7)	-0.94	-2.50 (-8.2 to 3.2)
10+years	-0.93 (9.4)	-0.64	-0.04 (-4.9 to 4.9)	1.24 (15.8)	0.54	0.06 (-6.5 to 6.4)
Recency of estrogen-plus-progesterone use						
Current	-0.77 (9.3)	-0.48	0.52 (-3.0 to 4.1)	0.49 (11.4)	-0.20	-1.49 (-6.2 to 3.2)
Past < 5 years	-3.2 (5.7)	-2.95	-1.80 (-7.1 to 3.5)	-0.11 (13.5)	-0.80	-2.24 (-9.3 to 4.8)
Past 5+ years	-7.03 (10.2)	-6.74	-6.00 (-11.3 to -0.7)	1.70 (10.3)	1.01	0.29 (-6.8 to 7.4)

[1] Adjusted for the following baseline confounders: years since menopause, alcohol use (current and past drinking, with referent group as never drinker), and body mass index (<18.5 kg/m as underweight, 25 $kg/m^2 \leq$ BMI < 30 kg/m^2 as overweight, and ≥ 30 kg/m^2 as obese, with the referent group as 18.5 $kg/m^2 \leq$ BMI < 25 kg/m^2, or normal weight).

Table 3.4: Association between MHT status and change in physical functioning and activity scores over 3 years among postmenopausal women with multiple sclerosis (MS) in the Women's Health Initiative Observational Study.

	Δ Activities of Daily Living (3 year-baseline)			*Δ Physical Activity (3 year-baseline)*		
		β-Coefficient			*β-Coefficient*	
Exposure	*Mean Change (Standard Deviation)*	*Crude*	*Adjusted[1] (95% Confidence Interval)*	*Mean Change (Standard Deviation)*	*Crude*	*Adjusted[1] (95% Confidence Interval)*
MHT history						
Never	-0.02 (0.51)			-1.76 (11.2)		
Ever	-0.01 (0.58)	0.01	-0.01 (-0.2 to 0.2)	-1.84 (10.8)	-0.08	0.51 (-2.4 to 3.5)
Unopposed estrogen duration						
< 5 years	-0.03 (0.5)	-0.03	0.05 (-0.1 to 0.2)	-3.22 (11.6)	-0.82	-0.90 (-5.4 to 3.6)
5-9 years	0.00 (0.3)	0.00	0.01 (-0.2 to 0.2)	-1.09 (15.6)	1.31	1.61 (-4.1 to 7.3)
10+years	-0.03 (0.3)	-0.03	0.00 (-0.2 to 0.2)	0.01 (10.0)	2.42	2.57 (-2.3 to 7.5)
Recency of unopposed estrogen use						
Current	-0.06 (0.3)	-0.06	0.00 (-0.2 to 0.2)	-0.52 (12.7)	1.89	1.85 (-2.1 to 5.8)
Past<9 years	0.06 (0.3)	0.06	0.08 (-0.3 to 0.5)	-6.23 (13.0)	-3.83	-3.61 (-9.7 to 2.5)
Past 10+ years ago	0.07 (0.5)	0.07	0.12 (-0.3 to 0.5)	-0.42 (2.4)	1.99	1.95 (-4.7 to 8.6)
Estrogen-plus-progesterone duration						
< 5 years	0.05 (0.6)	0.07	0.04 (-0.2 to 0.2)	-2.26 (8.9)	-1.79	-1.46 (-5.8 to 2.9)
5-9 years	0.0 (0.5)	0.03	-0.03 (-0.2 to 0.1)	-3.81 (9.7)	-3.34	-3.17 (-8.3 to 1.9)
10+years	-0.11 (1.1)	-0.08	-0.21 (-0.4 to 0.0)	-3.24 (8.6)	-2.78	-2.13 (-7.8 to 3.6)
Recency of estrogen-plus-progesterone use						
Current	-0.03 (0.7)	-0.01	-0.07 (-0.6 to 0.1)	-3.67 (10.2)	-3.2 (1.9)	-2.9 (-6.8 to 1.0)
Past < 5 years	0.19 (0.8)	0.22	0.16 (-0.2 to 0.6)	0.64 (4.1)	1.1 (2.9)	1.5 (-4.4 to 7.4)
Past 5+ years	-0.07 (0.3)	-0.04	-0.10 (-0.5 to 0.3)	-3.94 (7.1)	-3.5 (3.2)	-3.2 (-9.5 to 3.1)

[1] Adjusted for the following baseline confounders: years since menopause, alcohol use (current and past drinking, with referent group as never drinker), and body mass index (<18.5 kg/m as underweight, 25 $kg/m^2 \leq$ BMI < 30 kg/m^2 as overweight, and ≥ 30 kg/m^2 as obese, with the referent group as 18.5 $kg/m^2 \leq$ BMI < 25 kg/m^2, or normal weight).

Table 3.5. Baseline characteristics of postmenopausal women with multiple sclerosis (MS) who changed MHT use status by year 3 in the Women's Health Initiative Observational Study.

Baseline Characteristics	Baseline: Current MHT user (n = 9)	Baseline: Past MHT user (n = 13)	Baseline: Never MHT user (n = 17)
	Median (Standard Deviation)		
Years since menopause	11.8 (9.5)	11.0 (7.8)	12.3 (12.1)
	Percentages		
Age			
<50 – 59 years	66.7	46.2	64.7
60 – 69 years	22.2	46.2	17.7
70 – 79+ years	11.1	7.7	17.7
Non-Hispanic White	100.0	81.8	85.7
Education			
≤ Some college	33.3	50.0	58.8
≥ College graduate	66.7	50.0	41.2
Have any health insurance	100.0	100.0	100.0
Body mass index (kg/m^2)			
<25 (underweight to normal)	44.4	46.2	35.3
25 to <30 (overweight)	44.4	23.1	53.0
30+ (obese)	11.1	30.8	11.8
Alcohol Use			
Never drinker	0	15.4	17.7
Past drinker	11.1	7.7	11.8
Current drinker	88.9	76.9	70.6
Smoking History			
Never	37.5	23.1	52.9
Ever (Current or Past)	62.5	76.9	47.1
Vitamin D intake <800 (µg/day)	100.0	100.0	100.0
Ever Hysterectomy	55.6	15.4	23.5
Ever Oophorectomy[1]	44.4	7.7	29.4
Ever Oral Contraceptive Use	44.4	30.8	47.1
Gravidity			
1 to 4 pregnancies	77.8	69.2	58.8
5+ pregnancies	22.2	15.4	35.3
Parity			
Never pregnant/term pregnancy	33.3	15.4	5.9
1 to 3 term pregnancies	44.4	53.8	52.9
4+ term pregnancies	22.2	30.8	41.2
MHT type used			
Ever unopposed estrogen	66.7	23.1	N/A
Ever estrogen-plus-progesterone	33.3	76.9	N/A
Unopposed estrogen duration			
<10 years	44.4	15.4	N/A
10+years	22.2	7.7	N/A
Recency of estrogen-alone use			
Current	55.6	N/A	N/A
Past	11.1	23.1	N/A

Estrogen-plus-progesterone duration			
< 5 years	33.3	69.2	N/A
5+ years	11.1	7.7	N/A
Recency of estrogen-plus-progesterone			
Current	44.4	N/A	N/A
Past	0.0	76.9	N/A

[1] Includes the removal of one or both ovaries.

Table 3.6. Association between MHT use and menopausal symptoms at 3 year followup among post-menopausal women with MS who changed MHT use status by year 3.

Menopausal Symptoms	Baseline: Current MHT user (n = 9)		Baseline: Past MHT user (n = 13)		Baseline: Never MHT user (n = 17)	
	Baseline	Year 3	Baseline	Year 3	Baseline	Year 3
	Percentages					
Forgetfulness	11.1	11.1	30.8	23.1	35.3	35.3
Difficulty concentrating	11.1	0.0	0.0	23.1	5.9	23.5
Mood swings	0.0	0.0	23.1	23.1	5.9	11.8
Joint pain or stiffness	11.1	22.2	38.5	46.2	41.2	35.3
Headaches or migraines	11.1	11.1	23.1	15.4	11.8	23.5
Breast tenderness	0.0	0.0	7.7	15.4	0.0	0.0
Increased appetite	0.0	0.0	23.1	7.7	23.5	17.7
Decrease appetite	0.0	0.0	0.0	0.0	0.0	0.0
Hot flashes	11.1	22.2	15.4	15.4	11.8	5.9
Night sweats	0.0	11.1	15.4	7.7	17.7	11.8
Vaginal/genital irritation	0.0	0.0	7.7	0.0	0.0	0.0
Vaginal/genital dryness	0.0	0.0	7.7	7.7	0.0	11.8
Average number of symptoms (Standard Deviation)	0.56 (1.3)	0.78 (1.1)	1.92 (2.4)	1.85 (2.0)	1.53 (1.3)	1.76 (1.8)
Increase in symptoms		50.0		53.9		35.3
Crude OR[1] (95% CI)	1.20 (0.21 to 6.80)		0.44 (0.07 to 2.72)		*Reference*	
Adjusted[2] OR (95% CI)	1.02 (0.13 to 8.04)		0.37 (0.05 to 2.64)		*Reference*	

[1] Here, the outcome evaluated is a yes/no indicator of an increase in the number of symptoms from baseline to year 3 (yes = an increase in the number of symptoms; no = a decrease or no change), with no as the referent group.

[2] Adjusted for the following baseline confounders: years since menopause, smoking status, alcohol use, and body mass index (<18.5 kg/m as underweight, 25 $kg/m^2 \leq$ BMI < 30 kg/m^2 as overweight, and ≥ 30 kg/m^2 as obese, with the referent group as 18.5 $kg/m^2 \leq$ BMI < 25 kg/m^2, or normal weight).

Table 3.7. Association between MHT status and change in health-related quality of life measures over 3 years among postmenopausal women with multiple sclerosis (MS) who changed MHT use status by year 3.

	Δ Physical Component Score (3 year-baseline)			*Δ Mental Health Component Score (3 year-baseline)*		
		β-Coefficient			*β-Coefficient*	
Exposure	*7.ean Change (Standard Deviation)*	*Crude*	*Adjusted[1] (95% Confidence Interval)*	*Mean Change (Standard Deviation)*	*Crude*	*Adjusted[1] (95% Confidence Interval)*
MHT history						
Never	-0.11 (7.6)			-2.56 (8.5)		
Ever	-2.56 (8.5)	-2.45	-3.39 (-10.8 to 4.1)	3.52 (16.2)	4.21	3.89 (-6.3 to 14.1)
Unopposed estrogen duration						
< 10 years	-1.38 (9.5)	0.88	-0.62 (-12.6 to 11.3)	10.21 (14.6)	11.29	12.73 (-0.8 to 26.3)
10+years	-5.16 (18.0)	-2.9	0.94 (-12.8 to 14.7)	9.92 (19.2)	11.00	1.45 (-14.0 to 16.9)
Recency of unopposed estrogen use						
Current	-7.64 (15.4)	-5.39	-6.87 (-18.8 to 5.1)	-0.10 (17.5)	13.31	15.36 (-0.5 to 31.2)
Past	3.20 (3.3)	5.46	6.01 (-5.2 to 17.2)	7.22 (14.4)	8.31	11.12 (-3.8 to 26.0)
Estrogen-plus-progesterone duration						
< 5 years	-1.80 (5.8)	2.84	1.58 (-9.6 to 12.8)	-0.05 (16.9)	-11.73	-9.18 (-23.3 to 4.9)
5-9 years	-2.40 (2.4)	2.24	3.90 (-16.1 to 23.9)	-7.73 (7.7)	-19.42	-22.01 (-3.5 to 47.5)
10+years	2.93 (2.9)	2.84	5.82 (-15.5 to 27.2)	-2.21 (2.2)	-13.90	-12.94 (-40.2 to 14.3)
Recency of estrogen-plus-progesterone use						
Current	4.32 (8.1)	8.96	7.96 (-7.1 to 23.1)	1.26 (12.9)	-10.42	-3.99 (-22.4 to 14.4)
Past < 5 years	-2.80 (3.6)	1.84	1.09 (-11.3 to 13.4)	-5.70 (18.7)	-17.39	-18.75 (-33.8 to -3.7)
Past 5+ years	-5.90 (2.2)	-1.26	0.97 (-14.1 to 16.1)	10.03 (3.9)	-1.65	-4.89 (-23.3 to 13.5)

[1] Adjusted for the following baseline confounders: years since menopause, alcohol use (current and past drinking, with referent group as never drinker), and body mass index (<18.5 kg/m as underweight, 25 kg/m^2 ≤ BMI < 30 kg/m^2 as overweight, and ≥ 30 kg/m^2 as obese, with the referent group as 18.5 kg/m^2 ≤ BMI < 25 kg/m^2, or normal weight).

Table 3.8. Association between MHT status and change in physical functioning and activity scores over 3 years among postmenopausal women with multiple sclerosis (MS) who changed MHT use status by year 3.

	Δ Activities of Daily Living (3 year-baseline)			*Δ Physical Activity (3 year-baseline)*		
		β-Coefficient			*β-Coefficient*	
Exposure	*Mean Change (Standard Deviation)*	*Crude*	*Adjusted[1] (95% Confidence Interval)*	*Mean Change (Standard Deviation)*	*Crude*	*Adjusted[1] (95% Confidence Interval)*
MHT history						
Never	-0.06 (0.4)			-1.75 (12.9)		
Ever	0.0 (0.9)	0.06	0.21 (-0.2 to 0.6)	-0.46 (0.5)	-2.21	1.20 (-7.0 to 9.4)
Unopposed estrogen duration						
< 10 years	-0.40 (0.9)	-0.58	-0.24 (-1.0 to 0.5)	-5.03 (11.1)	-4.01	-6.69 (-18.3 to 4.9)
10+years	0.0 (0.0)	-0.18	0.32 (-0.5 to 1.1)	11.14 (15.4)	12.16	7.84 (-8.0 to 23.7)
Recency of unopposed estrogen use						
Current	-0.50 (1.0)	-0.68	0.22 (-0.6 to 1.0)	6.92 (13.3)	7.94	6.16 (-7.6 to 19.9)
Past<9 years	0.0 (0.0)	-0.18	-0.32 (-1.1 to 0.5)	-10.44 (13.0)	-9.42	-10.45 (-24.6 to 3.7)
Past 10+ years ago	0.0 (0.0)	-0.18	0.27 (-1.1 to 1.6)	0.0 (0.0)	1.02	-3.48 (-27.2 to 20.2)
Estrogen-plus-progesterone duration						
< 5 years	0.20 (1.0)	0.49	-0.15 (-0.9 to 0.6)	-2.18 (8.0)	-5.72	-1.18 (-13.5 to 11.2)
5-9 years	0.0 (0.0)	0.29	-0.01 (-1.4 to 1.4)	0.0 (0.0)	-3.54	-3.00 (-27.7 to 21.7)
10+years	0.0 (0.0)	0.29	-0.08 (-1.5 to 1.3)	-12.25 (12.25)	-15.79	-13.15 (-39.4 to 13.1)
Recency of estrogen-plus-progesterone use						
Current	0.0 (0.0)	0.29	-0.56 (-1.5 to 0.4)	0.0 (0.0)	-14.69	-8.52 (-25.6 to 8.5)
Past < 5 years	0.29 (1.3)	0.57	-0.19 (-1.0 to 0.6)	0.78 (3.3)	-2.77	1.40 (-11.9 to 14.7)
Past 5+ years	0.0 (0.0)	0.29	0.20 (-0.8 to 1.2)	-11.15 (10.6)	-3.54	-5.98 (-24.2 to 12.2)

[1] Adjusted for the following baseline confounders: years since menopause, alcohol use (current and past drinking, with referent group as never drinker), and body mass index (<18.5 kg/m as underweight, 25 $kg/m^2 \leq$ BMI < 30 kg/m^2 as overweight, and ≥ 30 kg/m^2 as obese, with the referent group as 18.5 $kg/m^2 \leq$ BMI < 25 kg/m^2, or normal weight).

Chapter 4: A Systematic Review of Pharmacological Pain Management in Multiple Sclerosis

Abstract

Objective: To systematically review strategies for the reduction of pain in patients with multiple sclerosis (MS).

Methods: Experimental studies published after 1965 were chosen for review by searching electronic databases (e.g. PubMed, Cumulative Index to Nursing and Allied Health Literature, Science Citation Index Expanded, Conference Proceedings Citation Index- Science, and clinicaltrials.gov) and bibliographies/citations of previously published reviews. Studies were included if all participants were adults clinically diagnosed with MS, study sample was not restricted to participants with spasticity or trigeminal neuralgia, and participant-reported pain was a primary or secondary outcome measured with a validated tool. Records were screened and methodological qualities of included studies were assessed independently by two reviewers under the supervision of another reviewer.

Results: Fifteen studies met the inclusion and exclusion criteria for review; interventions included antidepressants, anticonvulsants, dextromethorphan/quinidine, cannabinoids, and opioids/opioid antagonists. Meta-analyses were not performed due to few trials identified per treatment within these classes. Four trials reported Class 1 evidence. Pain relief was reported compared to placebo for two of these trials (nabiximols: Cohen's d: -0.61; dextromethorphan/quinidine: Cohen's d: -0.22), but not reported in two other trials (nortriptyline: Cohen's d: 0.76; nabixomols: Cohen's d: 0.93). For these trials, dizziness was the most commonly reported adverse event, followed by nausea and somnolence.

Conclusions: Nabiximols and off-label use of dextromethorphan/quinidine may be effective in reducing central neuropathic pain in MS. More trials with rigorous design and reporting are needed to determine effective treatments for specific pain types presenting in people living with MS.

Introduction

Multiple sclerosis (MS) is a chronic disease of the central nervous system that affects nearly 2.5 million people worldwide.[1] The health-related quality of life for MS patients is strongly affected by the disease's accompanying symptoms.[17] Both chronic and acute pain have been cited as the most common symptoms amongst MS patients,[73-75] with recent prevalence estimates as high as 83%.[76] Sources of pain in MS are difficult to differentiate but certain pain syndromes are common in MS; trigeminal neuralgia[77] presents in 5% and spasticity[78] occurs in 50% of MS patients.[76] The evidence for spasticity and trigeminal neuralgia pharmacological treatments in MS has been systematically reviewed;[79-81] yet to our knowledge, no equivalent reviews have been published concerning MS pain unrelated to these two conditions. Therefore, we systematically reviewed pain management strategies for the reduction of non-spastic and non-trigeminal neuralgic pain in MS patients.

Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[82] for this review. The objective of our search was to identify all experimental studies published since 1965 (publication year of the first established MS diagnosis criteria by Schumacher et al)[83] which evaluated all pain management strategies in patients living with MS. Electronic databases, including PubMed (1965 to November 16, 2012), the Cumulative Index to Nursing and Allied Health Literature (CINAHL) database (1997 to December 31, 2012), the Science Citation Index Expanded database and Conference Proceedings Citation Index-

Science (CPCI-S) database (1965 to December 31, 2012), and clinicaltrials.gov, were searched for relevant experimental studies. The MEDLINE search strategy in Appendix was adapted for other databases using the following key words: MS AND pain AND therapy/management. Additionally, the bibliographies of review articles found during our queries and the studies citing these reviews were searched to find all available experimental studies.

Inclusion criteria

Studies were considered eligible for inclusion in this review according to the following criteria: 1) sample consisted wholly of adult human participants with definite diagnoses of MS; 2) sample was not restricted to only those with spasticity or only those with trigeminal neuralgia; 3) patient-reported pain was measured as a primary or secondary outcome using a previously validated tool; 4) study was published in English and 5) study involved a pharmacological intervention. Participants were adult humans aged 18 years or older with clinically diagnosed MS (according to the revised McDonald criteria[3], original McDonald criteria,[84] the Poser criteria,[85] or the Schumacher criteria[83]). Studies were excluded if patient-reported pain was mentioned in the publication as an adverse event; this avoided the inclusion of disease-modifying therapies whose main intent was not pain management. Validated tools to measure patient-reported pain included the visual analogue scale (VAS),[86] Patient's Global Impression of Change (PGIC),[87] McGill Pain Questionnaire (MPQ),[88] the Body Pain subscale of the 36-item Medical Outcome Study Short Form (SF-36),[36] and the numerical rating scale (NRS).[89];[87]

Because spasticity and trigeminal neuralgia are common in patients living with MS, a study whose population consisted of a mix of spastic/trigeminal neuralgic patients and MS patients experiencing other types of pain was considered eligible for inclusion in this review. Additionally, studies which did not evaluate comparison groups were also eligible for inclusion to allow for greater scope of review.

Initially we identified 280 records using the search algorithm in Appendix, including 143 articles from PubMed, 43 articles from CINAHL, 34 articles and records of conference proceedings in the Web of Science, and 60 records from clinicaltrials.gov (Figure 4.1). This pool yielded 50 relevant systematic reviews; after searching their bibliographies and citations, an additional 10 records were eligible for inclusion. Removing duplicates and screening records by title and abstract reduced the total number to 64 eligible records, with 15 included in our qualitative synthesis.

Data extraction and synthesis

Articles were independently selected and reviewed by R.J. and S.Y.; when opinions differed, consensus was reached between R.J., S.Y., and K.L.L. Agreements between R.J. and S.Y. were strong with a kappa statistic of 0.795. Data extracted included study type, population characteristics, pain management regimens, and mean patient-reported pain scores and standard deviations. Study type consisted of parallel or crossover designs, presence and type of comparison group, mean study duration, and pain scale used. Population characteristics included mean age, gender, type of MS, duration of disease, baseline use of pain medications, and baseline disability as measured by the Extended Disability Status Scale (EDSS).[90] Finally, pain management regimens were evaluated for dose and duration of treatment. For studies which

evaluated comparator groups, the average duration of treatment for comparison groups were also recorded. Pain scores were recorded as mean differences between or within groups weighted by the inverse of the pooled standard deviation (Cohen's d),[91, 92] as this standardization allowed comparison of effect sizes independent of pain measurement tools.[93] A negative Cohen's d indicates a relative reduction in pain associated with a treatment versus a comparator. For studies where the standard deviation was not reported or incalculable from the reported data, differences between scores were recorded.

Finally, the methodological qualities of all studies included were examined using the principles recommended in the Cochrane Handbook for Systematic Review of Interventions[94] and the levels of evidence espoused by the American Academy of Neurology.[95] This included an assessment of the following: randomization sequence generation, allocation concealment, clear definition of primary outcome, inclusion/exclusion criteria, and standard treatment for intervention and comparator groups, and blinding/masking of participants, personnel and outcome assessors. As this systematic review used previously published data, no ethical approval was sought.

Results

The 15 trials meeting our inclusion an d exclusion criteria are ranked according to class of evidence in Table 4.1. Seven trials evaluated the intervention with a separate comparison group while 5 trials used a crossover design and 3 trials were not controlled (Table 4.2). All except three trials examined participant-reported pain as the primary outcome. The most common pain scales used were variations of the NRS and VAS; no

trials used the MPQ but two trials used the Modified Memorial Pain Assessment Card[96] and the Brief Pain Inventory short form (BPI-SF),[97] respectively. Major classes of pharmacological interventions included anticonvulsants, antidepressants, cannabinoids, dextromethorphan/quinidine, and opioids/opioid antagonists. As no more than 3 trials were identified per pharmacological treatment within these classes, meta-analyses were not performed. Table 4.3 provides additional information on study design and baseline characteristics for all included trials.

Anticonvulsants

Six trials evaluated the use of anticonvulsants to treat pain in participants living with MS; the different types of pharmacological interventions included levetiracetam,[98, 99] lamotrigine,[100] gabapentin,[101] pregabalin,[102] and oxcarbamezapine.[103] Levetiracetam at a maximum dose of 3000 mg/day was reported as effective in reducing pain scores when compared to placebo in both Class 2 and Class 3 trials; this reduction persisted when measured by the 11-point NRS[98] and the 100 mm VAS[99] (Cohen's d: -0.52 and -1.36, respectively). The most common adverse events for those participants in the treatment group included tiredness, dizziness and mental changes.

In a Class 3 trial, lamotrigine[100] was reported effective in reducing worst and least pain (Cohen's d: -0.2 and -0.4, respectively) as measured by the BPI-SF, but ineffective in reducing average pain in comparison to placebo (Cohen's d: 0.4); nausea was the most commonly reported adverse event at a maximum dose of 400 mg/day. Class 4 trials in gabapentin[101] (maximum dose of 2400 mg/day) and pregabalin[102] (maximum dose of 300 mg/day) also reported a reduction in pain scores, with adverse events including mental cloudiness, somnolence, and nausea. Finally, oxcarbamezapine[103]

initiated at 150 mg/day and titrated to a maximum dose of 1200 mg/day reduced pain scores in one Class 4 trial (Cohen's d: -3.7) with a low rate of adverse events.

Antidepressants

Two trials evaluated antidepressants (nortriptyline and duloxetine) to treat pain in participants living with MS. While both varied in quality, both studies had similar inclusion criteria and allowed participants to concurrently use other stabilized pain medications with the experimental treatment. Nortriptyline,[104] when initiated at 10 mg/day and titrated to a maximum dose of 50 mg/day, was not reported to be effective in comparison to transcutaneous electrical nerve stimulation (TENS; Cohen's d: 0.76) in a Class 1 trial. Duloxetine[105] was reported to effectively reduce pain scores in participants of a Class 3 trial of central neuropathic pain (Cohen's d: -0.44); duloxetine was initiated at 30 mg/day and titrated to a maximum dose of 60 mg/day. Fewer and milder adverse events were reported for nortriptyline compared to duloxetine; for both antidepressants, adverse events included nausea, diarrhea, and somnolence.

Cannabinoids

The two types of cannabinoids assessed were nabixomols, an oromucosal spray containing 2.7 mg of delta-9-tetrahydrocannabinol (THC) and 2.5 mg cannabidiol (CBD), and dronabinol, an oral capsule of 2.5 mg of THC. Two Class 1 trials and one Class 3 trial assessed nabixomols with differing results. A Class 1 trial[78] in participants experiencing central pain reported improvement in pain scores compared to placebo (Cohen's d: -0.61); this effect was persistent in the Class 3 trial,[106] which also recruited participants with central pain (Cohen's d: -0.13). Yet, the other Class 1 trial[107] in nabixomols, which recruited participants experiencing spasticity, spasms, bladder

problems, tremor, and/or non-musculoskeletal pain, reported no improvement in pain compared to placebo (Cohen's d: 0.93). The Class 3 trial in dronabinol[108] also reported improvement in pain scores compared to placebo for participants with central pain (Cohen's d: -0.6).

The occurrence of adverse events was similar for all four trials. Dizziness was the most commonly reported event for any trial, experienced by 20% to 58% of participants in the intervention groups. Other adverse events included fatigue/somnolence, vertigo, and headaches. In one Class 1 trial in nabixomols,[107] burning at the site of application was reported by 26% of participants in the treatment group; because 23% of participants receiving placebo also reported this event, the authors hypothesized this was a result of the ethanol formulation of the oromucosal sprays. Later studies[78, 106] do not report this adverse event, indicating less irritating formulations may have been created.

Dextromethorphan/Quinidine

One Class 1 trial[109] evaluated capsules containing 30 mg dextromethorphan (DM) and 30 mg quinidine(Q) in participants who had scored at least 13 points on the Center for Neurologic Study-Liability Scale (CNS-LS) at baseline. While the treatment was intended for pseudobulbar affect, pain improvement was reported when compared to placebo (Cohen's d: -0.22). The most common adverse events reported were non-vertiginous dizziness (26% of participants in the treatment group), nausea (22% of treatment group), and headache (16% of treatment group).

Opioids/opioid antagonists

Two trials evaluated an opioid agonist (morphine) and an opioid antagonist (naltrexone) in separate placebo-controlled crossover studies. A Class 3 trial in naltrexone[110] at 4.5 mg/day reported a reduction in pain scores when compared to placebo (mean score difference between groups: -2.13). A Class 4 trial in intravenous morphine[111] also reported reduced pain scores compared to a saline placebo (Cohen's d: -0.48). Despite the differing effects of each drug, adverse events were similar between both trials. The most common adverse event was sedation, with vivid dreaming an added effect of naltrexone.

Quality assessment

Of the 15 trials included in this systematic review, only 4 had Class 1 evidence; the majority of trials were Class 3 or Class 4 (Table 4.2). One Class 4 trial[111] did not employ randomization when allocating treatments and more than 30% of participants in one Class 3 trial were lost to attrition and adverse events.[100] All controlled trials employed some blinding or masking methods, but 3 trials did not explicitly blind the physicians administering or overseeing treatment and 2 did not blind the outcome assessors. In general, all studies included had poor reporting standards regarding allocation concealment techniques and compliance differences between treatment and comparison groups. One Class 3 trial[110] noted that 14% of participants were lost due to poor database management and survey followup.

Conclusions

Pain is the symptom most commonly reported by people living with MS, yet few clinical trials have examined interventions for MS chronic pain with little consistency in treatment mechanisms. To our knowledge, this review is the first to evaluate treatments for pain unassociated with spasticity and trigeminal neuralgia in MS. Of the studies identified, the most common classes of drugs studied were anticonvulsants, antidepressants, cannabinoids, dextromethorphan/quinidine, and opioids/opioid antagonists.

Our systematic review revealed Class 1 evidence supporting the use of nabixomols and dextromethorphan/quinidine for pain reduction in MS. While Wade et al.[107] indicated no effect on pain scores due to nabixomols, this may be due to the inclusion of participants with mixed pain types (including spasticity and non-musculoskeletal pain). When excluding participants with spasticity, Rog et al[78] demonstrated Class 1 evidence for nabixomols reducing pain scores. While nabixomols are not currently approved for use in the US, it is approved for use in the United Kingdom where it has been shown to be effective in reducing pain in patients with MS.[112] Additionally, Panitch et al[109] demonstrated Class 1 evidence supporting off-label use of dextromethorphan/quinidine for pain reduction in MS. Currently marketed as Nuedexta® (20 mg DM/10 mg Q) and approved by the US Food and Drug Administration for treatment of pseudobulbar affect,[113] use of dextromethorphan/quinidine does not come without risks of QTc interval prolongation, falls, dizziness, headaches, diarrhea, and interactions with other medications. Indeed, the risk of ventricular arrhythmias as a result of QTc interval prolongation led to a

dosage change from 30 mg DM/30 mg Q used by Panitch et al[109] to its current market formulation.[114] While the new formulation has not been studied exclusively in MS patients, a Phase III trial[114] in a mixed sample of participants with amyotrophic lateral sclerosis and MS suggests greater pain improvement and fewer side effects. Careful clinical consideration of risks and benefits of nabixomols and dextromethorphan/quinidine are warranted before prescribing. In addition, the cost of treatment should be considered. Though dextromethorphan/quinidine consists of over-the-counter ingredients, current prices for a month's supply range from $400 to $600.[115]

We did not find evidence to support the use of nortriptyline in MS patients experiencing pain. Nortriptyline has been shown to be very effective in treating neuropathic pain in other studies,[116] yet did not reduce pain scores in the sole trial presented in this review. This discrepancy may be due to the trial's protocol of titrating nortriptyline up to a maximum dose of 50 mg/day,[104] while other neuropathic pain trials have often titrated to much higher doses. If nortriptyline is effective for treating chronic pain in MS at higher doses, the evidence-base is lacking.

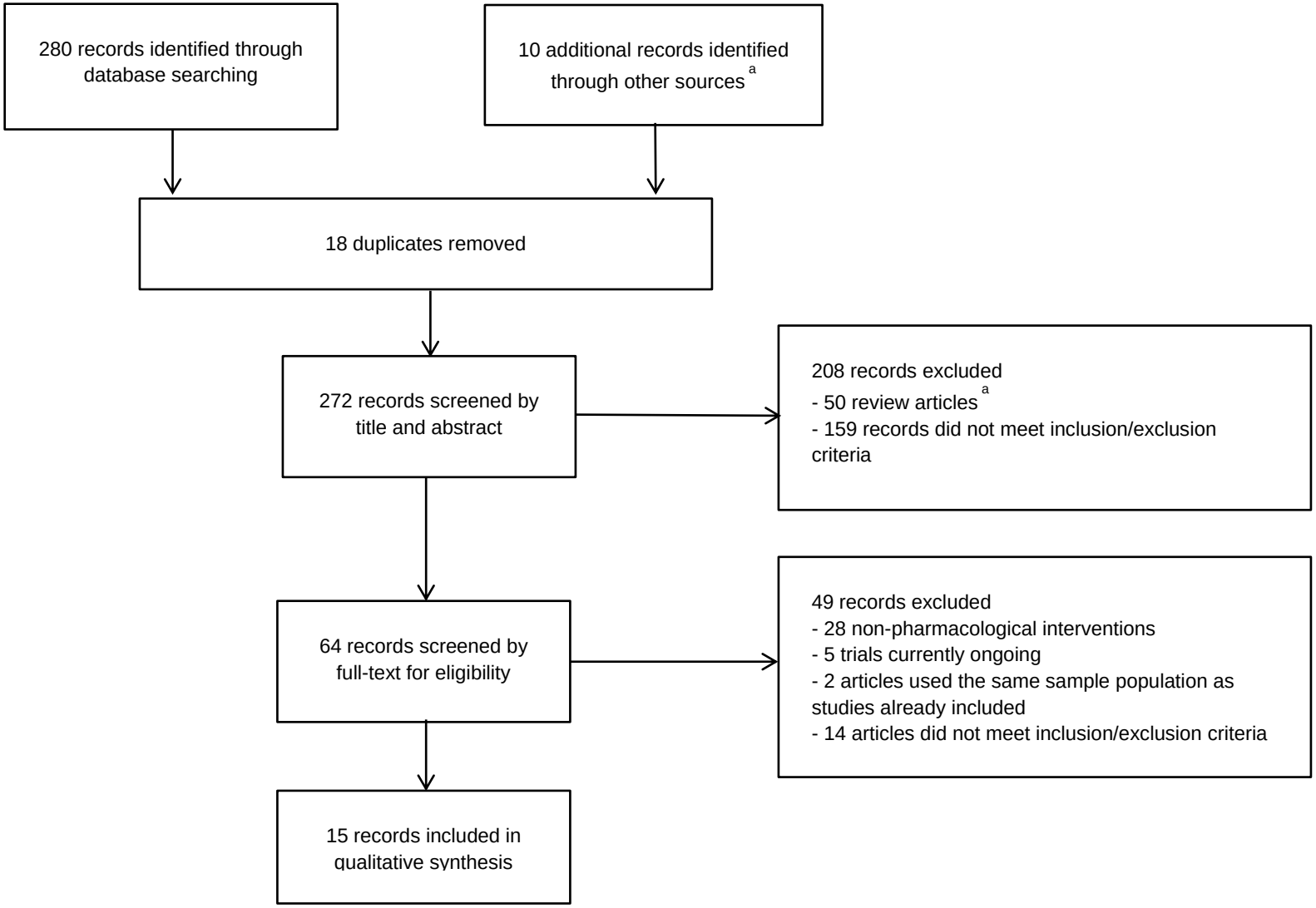
Our review did provide evidence consistent with literature on general neuropathic pain. In particular, the evidence from Class 2 through 4 trials of gabapentin,[117] pregabalin,[118] duloxetine,[119] intravenous morphine,[111] and naltrexone[110] are supported by previous reviews.[120, 121] As with Class 1 evidence, some reductions in pain occurred with treatment, but increases in gastrointestinal and central nervous system adverse events were non-trivial.

The strengths of our review lay in our search methodology, inclusion criteria, and rigorous review methodology. Standardized effect sizes and classification of studies by methodological and reporting quality are provided to facilitate understanding. Our inclusion criteria restricting the studies to chronic pain not associated with spasticity or trigeminal neuralgia allowed is novel. Because such studies in the MS literature are scarce, we included uncontrolled clinical trials and pilot studies. While the large effect sizes reported by the uncontrolled studies reflect an overestimation of the true treatment effect by not accounting for placebo effect, controlled studies are presented separately from the uncontrolled to aid interpretation. Of the 15 trials presented in this review, only three did not evaluate patient-reported pain as a primary outcome. The consistent effect sizes across multiple trials per drug (e.g. levetiracetam, nabixomols) indicate strength of evidence. While publication bias may be a possibility, our search strategy was built to minimize this possibility. Our search strategy included studies referenced in conference proceedings and search clinicaltrials.gov. Indeed, our review included two Class 1 evidence trials which reported negative effects.

The findings of this systematic review must be considered with a few caveats in mind. Our review focused on pharmacological management of pain in MS; additional non-pharmacologic treatments may offer benefits but were beyond the scope of this review. As evidenced by Chitsaz et al.,[104] TENS may be more effective in reducing MS pain than nortriptyline. Additionally, the relatively small number of trials in MS patients with chronic pain precludes our ability to make specific recommendations for treatment strategies. Finally, our review did not reveal any studies of drug combinations. In studies of general neuropathic pain, drug combinations, such as gabapentin and an

opioid, are more effective at reducing neuropathic pain than monotherapy.[122] Thus, the extent to which drug combinations would be beneficial in patients with MS is unknown.

In summary, our review identified nabiximols and off-label use of dextromethorphan/quinidine as promising treatments for chronic pain in MS. Side effect profiles for both treatments include dizziness, nausea, and headaches, but patients report acceptable tolerability.[114] Unfortunately, generic formulations are not available for either treatment and nabiximols is not approved for use in the United States. While nabiximols and off-label use of dextromethorphan/quinidine might be effective, the evidence base is insufficient to establish how to choose an optimal therapy for particular patients. In all but one study, the clinical studies were relatively short duration (<4 months). Long term assessment of the efficacy and safety of pharmacologic treatments of pain in MS patients is needed. In the absence of evidence to help clinicians select one therapy over another, clinicians and patients must careful consider available treatment regimens in the context of efficacy, risk of adverse events, cost, and clinical complexity of the patient (e.g. comorbid conditions and concomitant medication use).



[a] Sources include the bibliographies and citing articles of the 50 reviews found through database searches.

Figure 4.1. Flow chart of the systematic review.

Table 4.1. Included trials of pharmacological pain management for multiple sclerosis (MS) by evidence class and effect size.

Citation	Sample size, Pain management therapy and dose	Pain measurement tool, Main findings
Class 1 Evidence		
Rog, 2005	N = 66 Nabixomols (Oromucosal spray, 5 weeks) On first day up to 4 sprays delivered in 2 hours (2.7 mg THC/2.5 mg of CBD); participants advised to increase sprays up to 48 sprays (THC 129.6 mg THC/120 mg CBD) in 24 hours.	11-pt NRS Intervention mean score change (SD): -2.73 (1.9)* Placebo mean score change (SD): -1.41 (1.7) Cohen's d: -0.61
Panitch, 2006	N = 150 Dextromethorphan/Quinidine (Capsule, 85 days) Initiated and remained on 30mg DM/30mg Q every 12 hours throughout duration. Duration: 85 days	5-pt NRS Intervention mean score change (SD): -0.4 (0.88) Placebo mean score change (SD): -0.2 (0.86) Cohen's d: -0.22
Chitsaz, 2009	N = 59 Nortriptyline (Pill, 8 weeks) Initiated at 10 mg/day for first 3 days; increased to 25mg/day for next 4 days; maximum dose (50 mg/day) continued for remaining weeks.	10-pt VAS Intervention mean score change (SD): -1.6 (2.0) Comparator mean score change (SD): -2.5 (1.6) Cohen's d = 0.76
Wade, 2004	N = 160 Nabixomols (Oromucosal spray, 6 weeks) Initiated at 2.7 mg THC/2.5 mg CBD per day or when necessary; titrated to maximum dose (120 mg THC/120 mg CBD)	100-mm VAS Intervention mean score change: -11.4 Placebo mean score change: -20.17 Pooled SD: 9.4 Cohen's d: 0.93
Class 2 Evidence		
Rossi, 2009	N = 20 Levetiracetam (Tablet, 3 months) Initiated at 1000 mg/day for week 1; titrated up to maximum dose (3000 mg/day) at week 4 and continued for remaining weeks	100 mm VAS Intervention mean score change (SD): -45 (20) Placebo mean score change (SD): -15 (17) Cohen's d: -1.36
Class 3 Evidence		
Falah, 2012	N = 30 Levetiracetam (Tablet, 6 weeks) Initiated with 500 mg/day and titrated to maximum dose (3000 mg/day) for 15 days	11-pt NRS Intervention mean score change (SD): 5.3 (2.0) Placebo mean score change (SD): 5.7 (1.8) Cohen's d = -0.52
NCT00755807	N = 239 Duloxetine (Pill, 6 weeks) Initiated on 30 mg/day for 1 week; titrated to 60 mg/day for remaining weeks	11-pt NRS Group 1 mean score change (SD): -1.83 (1.73) Group 2 mean score change (SD): -1.07 (1.72) Cohen's d: -0.44

Breuer, 2007	N = 15 Lamotrigine (Pill, 13 weeks) Initiated with 25mg/day for weeks 1 and 2; increased to 50 mg/day (weeks 3 and 4), 100mg/day (week 5), 200 mg/day (week 6), 300 mg/day (week 7) up tp maximum dose at week 8 (400 mg/day) Final dose maintained for 3 weeks then dose-tapering occurred for 2 weeks	BPI Short Form Mean score changes (SD): Worst pain: -1.0 (2.7), Average pain: 0.8 (4.0), Least pain : -0.8 (2.0) Cohen's d: Worst pain: -0.2 Average pain: 0.4 Least pain: -0.4
NCT00391079	N = 339 Nabixomols (Oromucosal spray, 14 weeks) Initiated at 2.7 mg THC/2.5 mg CBD, 8 to 12 sprays per day; titrated to maximum dose (32.4 mg THC/30 mg CBD)	11-pt NRS Group 1 mean score change (SD): -2.02 (2.15) Group 2 mean score change (SD): -1.89 (2.33) Cohen's d: -0.13
Cree, 2010	N = 80 Naltrexone (Capsule, 8 weeks) Initiated and continued at 4.5 mg/day	SF-36 Bodily Pain subscale Intervention mean score change: 5.49 Placebo mean score change: 3.36 Difference: -2.13
Svendsen, 2004	N = 24 Dronabinol (Capsule, 15 to 21 days) Initiated on 2.5 mg/day, increased 2.5 mg every other day to maximum dose (10 mg/day)	11-pt NRS Group 1 median score change: -1.0 Group 2 median score change: -1.5 Median difference: −0.6
Class 4 Evidence		
Kalman, 2002	N = 14 Morphine (Infusion, at least 11 minutes) Initiated at rate of 1 mg/(kgBWh) until pain reduction > 50% on VAS; continued at this maximum dose for 10 min.	100 mm VAS Intervention mean score change (SD): -21.4 (19.0) Placebo mean score change (SD): -9.5 (14.7) Cohen's d: -0.48
Solaro, 2007	N = 12 Oxcarbamezapine (Pill, 3 months) Initiated at 150 mg/day and increased every 3 days until achieved pain relief or maximum dose (1200 mg/day)	4-pt NRS Initial mean score (SD): 2.5 (0.5) Final mean score (SD): 0.2 (0.4) Cohen's d: -3.7
Solaro, 2009	N = 16 Pregabalin (Pill, 3 months) Initiated at 75 mg/day and increased every 3 days until achieved pain relief or maximum dose (300 mg/day)	4-pt NRS Initial mean score (SD): 2.4 (0.5) Final mean score (SD): 0.4 (0.7) Cohen's d: -2.3
Houtchens, 1997	N = 25 Gabapentin (Pill, 17 months) Initiated at 300 mg/day; titrated over 3 weeks to maximum tolerated dose (ranged from 300 mg/day to 2400 mg/day)	Modified Memorial Pain Assessment Card 31.8% excellent relief (change of 5 to 9 pts) 36.3% moderate relief (change of 2 to 4 pts) 31.8% no relief (change of 1 to 0 pts)

Table 4.2. Quality Assessment of Included MS Pain Trials.

Citation	Treatment Allocation		Blinding/Masking			Parallel assignment	Compliance or attrition unlikely to introduce bias	Comparable Baseline characteristics	Primary Outcome is Pain
	Random-ization	Concealed allocation	Patients	Physicians	Outcome Assessors				
Class 1 Evidence									
Rog, 2005	+	+	+	+	+	+	+	+	+
Panitch, 2006	+	+	+	+	+	+	+	+	-
Chitsaz, 2009	+	+	-	-	+	+	+	+	+
Wade, 2004	+	+	+	+	+	+	+	+	-
Class 2 Evidence									
Rossi, 2009	+	?	+	-	-	+	+	+	+
Class 3 Evidence									
Falah, 2012	+	+	+	+	+	-	-	+	+
NCT00755807	+	?	+	+	+	+	?	+	+
Breuer, 2007	+	+	+	+	+	-	+	-	+
NCT00391079	+	?	+	+	+	+	?	+	+
Cree, 2010	+	?	+	+	+	-	-	+	-
Svendsen, 2004	+	+	+	+	+	-	+	+	+
Class 4 Evidence									
Kalman, 2002	-	?	+	-	-	-	+	+	+
Solaro, 2007	n/a	n/a	n/a	n/a	n/a	n/a	+	n/a	+
Solaro, 2009	n/a	n/a	n/a	n/a	n/a	n/a	+	n/a	+
Houtchens, 1997	n/a	n/a	n/a	n/a	n/a	n/a	+	n/a	+

+ = Yes; - = No; ? = Not reported; N/A = Not Applicable

Table 4.3. Description of included trials of pharmacological pain management for multiple sclerosis (MS).

Citation	Location, Clinicaltrials.gov ID, Funding source	Inclusion criteria, Operational definition of comparison group, Duration of use	Baseline Characteristics
Class 1 Evidence			
Rog, 2005	United Kingdom NCT01604265 Funded by GW Pharmaceuticals	1) Only central pain without a nociceptive cause of at least 3 months' duration 2) No spasticity or painless spasms alone or another non-central pain mechanism 3) No contraindications or comorbidities 4) No cannabinoid use in 7 days prior to screening 5) Concomitant use of stabilized pain medications allowed Placebo: Oromucosal spray of ethanol:propylene glycol (50:50) Duration: 5 weeks	Mean age (SD): 49.2 (8.3) yr 21% men 35% RRMS, 14% PPMS, 50% SPMS Mean MS duration (SD): 11.6 (7.7) yr Mean EDSS score (SD): 5.9 (1.3)
Panitch, 2006	United States, Israel Registration status is unknown Funded by Avanir Pharmaceuticals	1) On first day of clinic visit, participant scored at least 13 points on the Center for Neurologic Study-Liability Scale (CNS-LS). 2) No concomitant use of antidepressants, monoamine oxidase inhibitors, anticoagulants, or certain other inhibitors or substrates for P450 2D6 or P450 3A4 3) No contraindications or comorbidities Placebo: Identical capsules, no other description given Duration: 85 days	Mean age: 45.0 yr 17.3 % men Mean MS duration: 10.0 yr
Chitsaz, 2009	Iran Registration status unknown Funding not reported	1) EDSS ≤ 6 2) Natural disease course ≥ 2 years 3) Discontinued use of opioids for duration of study, but concomitant use of non-opioid pain medication allowed. 4) No contraindications Transcutaneous electrical nerve stimulation (TENS): Self-applied 3 times per day and when needed Initiated at 60 Hz and 40μs pulses for 20 to 30 minutes; increased to maximum tolerated pulse strength and continued for remaining weeks Duration: 8 weeks	Mean age (SD): 32.4 (7.8) yr 25% men
Wade, 2004	United Kingdom NCT01610700 Funded by GW Pharmaceuticals	1) VAS score at least 50 for one symptom: spasticity, spasms, bladder problems, tremor, or non-musculoskeletal pain 2) No contraindications or comorbidities Placebo: Oromucosal spray of excipients, used daily and when necessary Duration: 6 weeks	Mean age (SD): 50.7 (9.3) yr 38.1% men 24% spasticity
Class 2 Evidence			

Rossi, 2009	Italy Registration status is unknown Funded by Italian MS Foundation, Italian Ministries of Health and Education, Universities, and Research, and UCB Pharmaceuticals	1) Chronic neuropathic pain but not due to trigeminal neuralgia or other painful manifestations 2) No MS relapse in 30 days prior to randomization 3) No contraindications or comorbidities 4) Concomitant use of stabilized pain medications not allowed <u>Placebo:</u> Tablets Duration: 3 months	Mean age (SD): 37.6 (8.3) yr 25% men 85% RRMS, 5% PPMS, 10% SPMS Mean MS duration (SD): 7.2 (5.9) yr Mean pain duration (SD): 8.2 (5.8) yr Mean EDSS score (SD): 2.5 (1.3)
Class 3 Evidence			
Falah, 2012	Denmark NCT00423527 Not funded, UCB Pharmaceuticals sponsored monitoring throughout trial	<u>Inclusion criteria</u> 1) Pain in a body area with sensory abnormality on clinical exam/quantitative sensory exam corresponding to at least one lesion of the central nervous system 2) Median total pain of at least 4 on an 11-point scale during 1 week off pain medication before randomization 3) Concomitant use of stabilized pain medication not allowed <u>Washout period:</u> 1 week <u>Placebo:</u> Tablets Duration: 6 weeks	Median age: 47 yr 27% men 60 % RRMS, 17% PPMS, 13% SPMS, Median MS duration: 8 yr Median pain duration: 5 yr Median EDSS score: 5
NCT00755807	United States, Belgium, Canada, and Poland NCT00755807 Funded by Eli Lilly	1) MS diagnosis at least 1 year prior to study 2) Daily central neuropathic pain due to MS for at least 3 months prior to study 3) No contraindications or comorbidities 4) Concurrent stabilized pain medication allowed <u>Placebo:</u> Oral pill taken once daily Duration: 6 weeks	Mean age (SD): 51.73 (9.4) yr 25% men, 64% RRMS, 11% PPMS, 21% SPMS, Mean MS duration (SD): 11.23 (7.99) yr Mean pain duration (SD): 6.9 (6.3) yr Mean EDSS score (SD): 4.0 (1.89)
Breuer, 2007	United States Registration status is unknown Funded by GlaxoSmithKline	1) Participant reported MS-related pain with neuropathic features for at least 3 months and scored at least 4 for any item on 11-point Neuropathic Pain Scale 2) No central pain related to other conditions 3) Did not experience 2 or more MS relapses within the prior 6 months and did not have rapidly progressive MS 4) Did not receive corticosteroid treatment for MS in the 30 days prior to screening 5) No contraindications or comorbidities 6) Concomitant stabilized pain medication allowed <u>Washout period:</u> 2 weeks <u>Placebo:</u> Oral pill taken daily Duration: 13 weeks	Mean age (SD): 49.3 (11.7) yr 16.7% men

NCT00391079	Canada NCT00391079 Funded by GW Pharmaceuticals	1) Central neuropathic pain (CNP) for 3 or more months and expected to remain stable for the study duration 2) Baseline pain score sum at least 24 3) Pain not likely to be nociceptive, musculoskeletal (including spasms) peripheral neuropathic or psychogenic in origin, or due to trigeminal neuralgia. 4) No contraindications or comorbidities Placebo: Oromucosal spray of excipients, 8 to 12 sprays per day Duration: 14 weeks	Mean age: 49 (10.47) yr 32% men Mean MS duration (SD): 11.99 (8.26) yr Mean pain duration (SD): 5.5 (5.5) yr
Cree, 2010	United States NCT00501696 Funded by private contributions from people living with MS	1) Did not begin disease-modifying therapy in 3 months prior to enrollment 2) No currently on natalizumab or IFN and/or glatiramer acetate 2) Not receiving treatment with chronic opiate agonists Washout period: 1 week Placebo: Capsules taken daily Duration: 8 weeks	Mean age: 49 yr 30% men, 39% RRMS, 19% PPMS, 16% SPMS
Svendsen, 2004	Denmark Registration status unknown Funded by Danish MS Society, private donations, and Solvay Pharmaceuticals	1) Central pain in a body area for abnormal sensation to pinprick, touch, warmth or cold (evaluated in person) or quantitative sensory testing corresponding to at least one lesion in the central nervous system 2) Pain at maximal pain site with score of at least 3 points on 11-pt NRS 3) No contraindications or comorbidities 4) No marijuana use in 3 months prior to study 5) Concurrent stabilized pain medication allowed Washout period: 15 to 21 days) Placebo: Capsules of sesame oil Duration: 15 to 21 days	Median age: 50 yr 42% men 38% RRMS, 25% PPMS, 38% SPMS Median MS duration: 7.0 yr Median pain duration: 4.5 yr Median EDSS score: 6.0
Class 4 Evidence			
Kalman, 2002	Sweden Registration status is unknown Funded by Country Council of Östergötland, Swedish Medical Research Council (MFR), The Bank of Sweden Tercentenary Foundation, and Swedish Association of Neurologically Disabled	1) Constant, non-fluctuating central pain for at least 6 months 2) 100 mm VAS score > 30 at baseline 3) No trigeminal neuralgia 3) No contraindications or comorbidities Washout period: 10 min Placebo: Infusion of physiological saline at a rate of 1 ml/(kgBWh) Duration: 20 min	Mean age (SD): 54.9 (11.5) yr 42.8% men, Mean MS duration (SD): 19.7 (8.8) yr Mean pain duration (SD): 15.6 (11.7) yr

Solaro, 2007	Italy Registration status is unknown Funding not reported	1) Had painful paroxysmal symptoms (transient pain in any area with abrupt onset, duration from a few seconds to a few minutes, and with repetitive and stereotyped features) 2) Non-responsive or intolerant to conventional medications 3) Concomitant use of pain medications not allowed No comparison group	Mean age (SD): 43.6 (10.9) yr 31% men, 83% RRMS, 8% PPMS, 8% SPMS 33% trigeminal neuralgia Mean MS duration (SD): 7.3 (4.9) yr Mean EDSS score (SD): 3.8 (1.6)
Solaro, 2009	Italy Registration status is unknown Funding not reported	1) Had painful paroxysmal symptoms (transient pain in any area with abrupt onset, duration from a few seconds to a few minutes, and with repetitive and stereotyped features) 2) No relapses or worsening greater than 1 point on the EDSS scale in prior 3 months 3) Previous treatment with conventional medication for paroxysmal pain 4) No contraindications or comorbidities 5) Concomitant use of neuropathic pain medications not allowed No comparison group	Mean age (SD): 52 (12.4) yr 38% men, 44% RRMS, 19% PPMS, 38% SPMS Mean MS duration (SD): 11.9 (8.0) yr Mean EDSS score (SD): 5.1 (1.7)
Houtchens, 1997	United States Registration status is unknown Funding not reported	1) Attended the MS Clinic at the University of Utah School of Medicine or Georgetown University MS Center 2) Concomitant use of pain medications allowed No comparison group	Mean age: 45.8 yr 32% men, 60% RRMS, 32% PPMS, 8% SPMS Range of MS duration: 1 to 20 yr Range of pain duration: 1 to 20 yr

Chapter 5: A Systematic Review of Non-Pharmacological Pain Management in Multiple Sclerosis

Abstract

Objective: To systematically review non-pharmacological strategies for the reduction of pain in patients with multiple sclerosis (MS).

Data Sources: Experimental studies published after 1965 were chosen for review by searching electronic databases (e.g. PubMed, Cumulative Index to Nursing and Allied Health Literature, Science Citation Index Expanded, Conference Proceedings Citation Index- Science, and clinicaltrials.gov) and bibliographies/citations of previously published reviews.

Study Selection: Studies were included if all participants were adults clinically diagnosed with MS, study sample was not restricted to participants with spasticity or trigeminal neuralgia, and participant-reported pain was a primary or secondary outcome measured with a previously validated tool.

Data Extraction: Records were screened and methodological qualities of included studies were assessed independently by two reviewers under the supervision of another reviewer. Pain scores were recorded as mean differences between or within groups weighted by the inverse of the pooled standard deviation (Cohen's d).

Data Synthesis: A total of 13 studies which met the inclusion and exclusion criteria were identified for review; interventions included education, electrical stimulation, and physical therapies. Meta-analyses were not performed due to few trials identified per treatment within these classes. Pain relief was reported compared to placebo for two trials in transcutaneous electrical nerve stimulation (TENS) with effect sizes of -3.37 and

-3.32, respectively. Inconclusive pain relief was reported for other education and physical therapies.

Conclusions: TENS may be effective in reducing central neuropathic pain in MS. More trials with rigorous design and reporting are needed to determine effective treatments for specific pain types presenting in people living with MS.

Introduction

Multiple sclerosis (MS) is a chronic disease of the central nervous system that affects nearly 2.5 million people worldwide.[1] The health-related quality of life (HrQOL) for MS patients is strongly affected by the disease's accompanying symptoms.[17] Both chronic and acute pain have been cited as the most common symptoms amongst MS patients,[73-75] with recent prevalence estimates as high as 83%.[76] Sources of pain in MS are difficult to differentiate but certain pain syndromes are common in MS; trigeminal neuralgia[77] presents in 5% and spasticity[78] occurs in 50% of MS patients.[76] The evidence for spasticity and trigeminal neuralgia treatments in MS has been systematically reviewed;[79-81] yet to our knowledge, no equivalent reviews have been published concerning MS pain unrelated to these two conditions. In particular, no reviews have focused on non-pharmacological pain management strategies. Therefore, we systematically reviewed pain management strategies for the reduction of non-spastic and non-trigeminal neuralgic pain in MS patients.

Methods

Search Strategy

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[82] in this review, we identified all experimental studies published since 1965 (publication year of the first established MS diagnosis criteria by Schumacher et al)[83] which evaluated any pain management strategies in patients living with MS. Electronic databases were searched, including PubMed (1965 to November 16, 2012), the Cumulative Index to Nursing and Allied Health Literature (CINAHL)

database (1997 to December 31, 2012), the Science Citation Index Expanded database and Conference Proceedings Citation Index- Science (CPCI-S) database (1965 to December 31, 2012), and clinicaltrials.gov.

The MEDLINE search strategy in Appendix was adapted for other databases using the following key words: MS AND pain AND therapy/management. We searched the bibliographies of review articles and the studies citing these reviews to find all available experimental studies.

Inclusion criteria

Studies were considered eligible for inclusion according to the following criteria: 1) sample consisted wholly of adult human participants with definite diagnoses of MS; 2) sample was not restricted to only those with spasticity or only those with trigeminal neuralgia; 3) patient-reported pain was measured as a primary or secondary outcome using a previously validated tool; 4) study was published in English and 5) study involved a non-pharmacological intervention. Participants were adult humans aged 18 years or older with clinically diagnosed MS (according to the revised McDonald criteria[3], original McDonald criteria,[84] the Poser criteria,[85] or the Schumacher criteria[83]). Studies were excluded if patient-reported pain was mentioned in the publication as an adverse event; this avoided the inclusion of disease-modifying therapies whose main intent was not symptomatic pain management. Validated tools to measure patient-reported pain included the visual analogue scale (VAS),[86] McGill Pain Questionnaire (MPQ),[88] the Bodily Pain subscale of the 36-item Medical Outcome Study Short Form (SF-36),[36] and the numerical rating scale (NRS).[87, 89] Because spasticity and trigeminal neuralgia are common in patients living with MS, a study whose population consisted of a mix of

spastic/trigeminal neuralgic patients and MS patients experiencing other types of pain was considered eligible for inclusion. Studies which did not evaluate comparison groups were eligible to allow for greater scope of review.

We identified 280 records using the search algorithm in Appendix, including 143 articles from PubMed, 43 articles from CINAHL, 34 articles and records of conference proceedings in the Web of Science, and 60 records from clinicaltrials.gov (Figure 5.1). This pool yielded 50 relevant systematic reviews; after searching their bibliographies and citations, an additional 10 records were eligible for inclusion. Removing duplicates and screening records by title and abstract reduced the total number to 64 eligible records, with 13 included in our qualitative synthesis.

Data extraction and synthesis

Articles were independently selected and reviewed by R.J. and S.Y.; when opinions differed, consensus was reached between R.J., S.Y., and K.L.L. Agreements between R.J. and S.Y. were strong with a kappa statistic of 0.795. Data extracted included study type, population characteristics, pain management regimens, and mean patient-reported pain scores and standard deviations. Study type consisted of parallel or crossover designs, presence and type of comparison group, mean study duration, and pain scale used. Population characteristics included mean age, gender, type of MS, duration of disease, concomitant use of pain medications or management strategies, and baseline disability as measured by the Extended Disability Status Scale (EDSS).[90] Finally, pain management regimens were evaluated for type, description, and duration of treatment. For studies which evaluated comparator groups, the average duration of treatment for comparison groups were also recorded. Pain scores were

recorded as mean differences between or within groups weighted by the inverse of the pooled standard deviation (Cohen's d),[91, 92] as this standardization allowed comparison of effect sizes independent of pain measurement tools.[93] A negative Cohen's d indicates a relative reduction in pain associated with a treatment versus a comparator. However, for the Bodily Pain subscale of the SF-36, a positive Cohen's d indicates an improvement in pain-related quality of life or a reduction in pain associated with a treatment versus a comparator. For these analyses, a Cohen's d of 0.2 is considered a small effect, 0.50 a medium effect, and 0.80 a large effect.[123] For studies where the standard deviation was not reported or incalculable from the reported data, differences between scores were recorded and labeled as such on the tables.

Finally, the methodological qualities of all studies included were examined using the principles recommended in the Cochrane Handbook for Systematic Review of Interventions,[94] which included an assessment of the following: randomization sequence generation, allocation concealment, clear definition of primary outcome, inclusion/exclusion criteria, and standard treatment for intervention and comparator groups, and blinding/masking of participants, personnel and outcome assessors. As this systematic review used previously published data, no ethical approval was sought.

Results

The 13 trials meeting our inclusion and exclusion criteria are ranked according to type of intervention in Table 5.1. Included studies are discussed in greater detail (e.g. inclusion criteria, baseline characteristics, type of comparison group) in Table 5.2. All but one trial evaluated an intervention with separate comparison group(s), and the most

commonly used pain scale was the SF-36 Bodily Pain subscale. Major types of interventions included education, electrical stimulation, and physical therapy. As no more than 3 trials were identified per treatment within these groups, meta-analyses were not performed.

Educational Interventions

Five trials evaluated the use of educational interventions to help manage pain in participants living with MS; these included energy conservation courses (ECC),[124-126] chronic disease self-management courses (CDSMC),[127] and hypnosis and/or cognitive restructuring courses (HCRC).[128] ECC, originally meant for fatigue management, had little[124, 126] to no[125] improvement in pain-related quality of life, regardless of the presence of a comparison group. CDSMC was reported as effective in reducing pain scores when compared to no treatment for participants on the waiting list, but ineffective when compared to no treatment for patients who did not participate.[127] Overall, the greatest reduction in pain scores was shown for a combination of self-hypnosis and cognitive restructuring.[128]

Electrical Stimulation

Two trials[129, 130] evaluated transcutaneous electrical nerve stimulation (TENS) in targeting chronic lower back pain amongst patients with MS. While both studies measured pain with different scales (MPQ[129] and 100 mm VAS[130]), both reported low frequency TENS at 4 Hz was more effective at reducing pain scores than high frequency TENS at 110 Hz.

Physical Therapy

Of the five trials which evaluated different types of physical therapies, studies which evaluated outpatient rehabilitation,[131-133] yoga and exercise,[134] and robotic-assisted gait training (RAGT)[135] reported the greatest differences in pain scores. The one trial which evaluated reflexology[136] reported no improvement in pain when compared sham massage. All physical treatments except for reflexology included educational sessions to address patients' individualized needs and to teach improved physical function. Both studies which evaluated directed outpatient rehabilitation showed improvement in pain-related quality of life compared to waiting list controls[131] and self-exercise.[132] Additionally, physiotherapy in a warmer climate was shown to be more effective at reducing pain scores than physiotherapy in a colder climate (Cohen's d: -0.12).[133] While use of RAGT did not decrease pain scores compared to the walking control group (Cohen's d: 0.61),[135] the intervention also included healthcare-professional-directed activities such as strengthening exercises, occupational therapy, and pool exercises.

Quality assessment

Of the 13 trials included in this systematic review, only one did not evaluate a comparator group (Table 5.3). Two pilot studies[125, 131] did not employ randomization when allocating treatments and attrition likely introduced bias in two more recent studies.[127, 128] As these studies evaluated non-pharmacological treatments, most investigators did not adequately blind participants or researchers administering treatments. Three studies[128, 134, 135] did not use intention-to-treat analyses when evaluating outcomes.

Conclusions

Pain is commonly reported by people living with MS, yet few clinical trials have examined interventions for MS chronic pain with consistency in treatment mechanisms. While pharmacological treatments for pain unassociated with spasticity and trigeminal neuralgia have been reviewed,[137] this is the first review to evaluate non-pharmacological treatments for chronic pain in MS. There were few studies found and most were of short duration. Of the identified studies, the most common treatment types were education, electrical stimulation, and physical therapies.

Of all pharmacological[137] and non-pharmacological placebo-controlled trials in non-spastic and non-trigeminal neuralgic pain, low-frequency TENS (4 Hz, 200 μs) has the greatest reported reduction in pain scores, regardless of scoring method or duration of treatment.[129, 138] Similar pain reduction has been reported by MS patients with spasticity[139, 140] or using other types of electrical stimulation,[141] which suggests TENS may be effective and cost-effective monotherapy for general MS pain. Yet, TENS has not been extensively studied in patients with MS and only one trial[104] has evaluated pain relief from TENS relative to a pharmacological agent. Recent reviews[142] support the use of TENS as part of a pain management package instead of monotherapy. Despite this, Medicare does not cover TENS for patients with MS.[143]

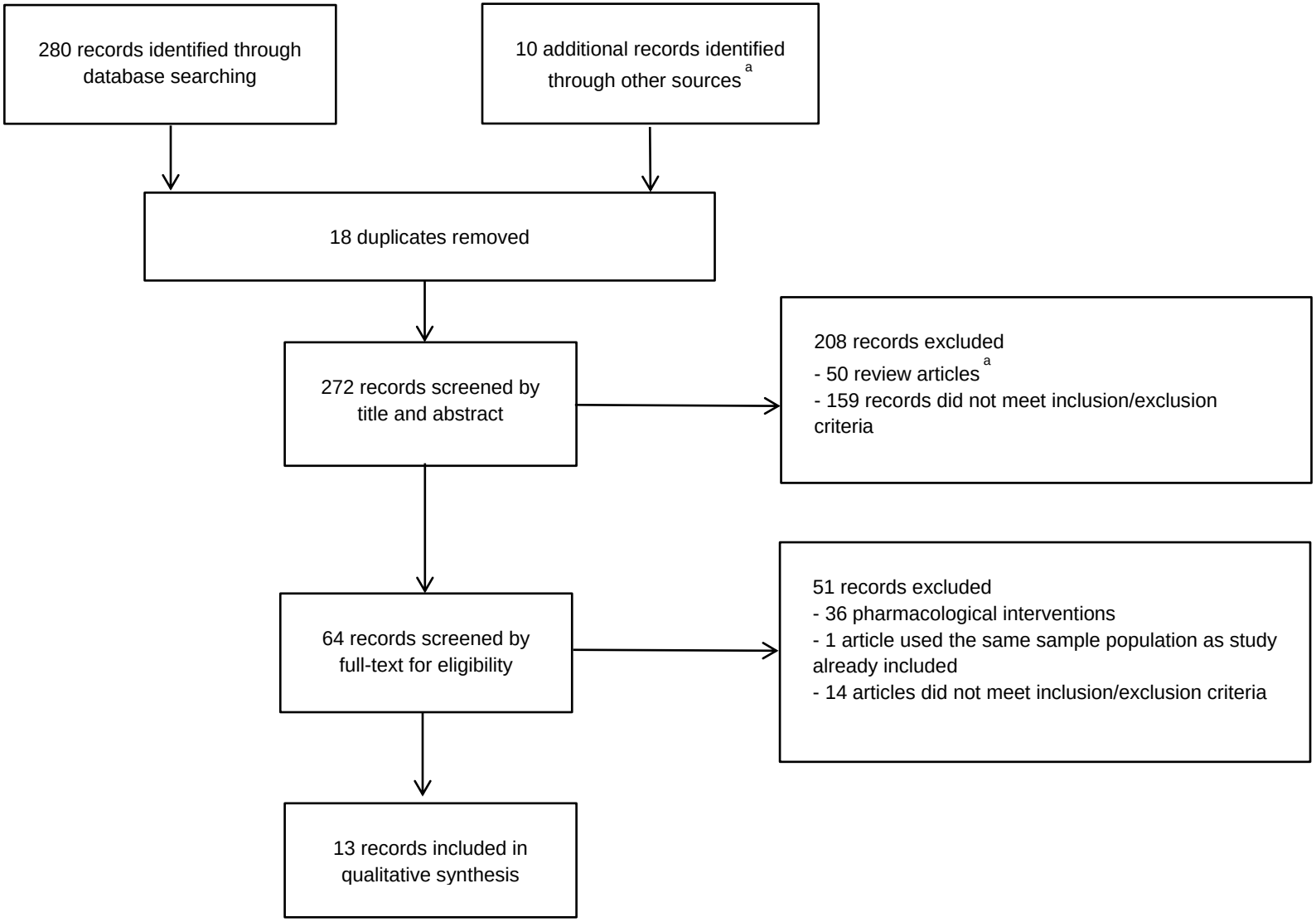
We did not find conclusive evidence to support the use of other education or physical therapies in MS patients experiencing pain. However, those therapies which did not reduce pain scores often improved HrQOL and/or physical function. Two studies which evaluated outpatient rehabilitation programs reported worsened pain scores but improvements in SF-36 scores and improved physical function, whether for a

duration of 12 weeks[132] or one year.[131] Yet, mind-body interventions such as hypnosis and/or cognitive restructuring[128] and yoga[134] were reported effective in treating pain but had little to no effect on HrQOL. Similar differences have been found for other MS patients[144] and for cancer-related pain.[145] These results suggest clinicians and patients should also consider overall health when choosing pain management strategies.

The strengths of our review lay in our search methodology, inclusion criteria, and review methodology. Standardized effect sizes are provided to facilitate understanding. Because studies in chronic MS pain not associated with spasticity or trigeminal neuralgia are scarce, we included uncontrolled clinical trials and pilot studies. While publication bias may be a possibility, our search strategy was built to minimize this by including studies referenced in conference proceedings and searches in clinicaltrials.gov. Additionally, the consistent effect sizes across multiple trials per therapy (e.g. TENS) indicate strength of evidence. The findings of this systematic review must be considered with a few caveats in mind. Our review focused on non-pharmacological management of pain in MS; additional pharmacologic treatments may offer benefits[137] but were beyond the scope of this review. The relatively small number of trials in MS patients with chronic pain precludes our ability to make specific recommendations for treatment strategies.

In summary, our review identified TENS as a promising non-pharmacological alternative to drug therapy for chronic pain in MS. Clinicians and patients must carefully consider the risks and benefits of supplanting pharmacological therapy with non-pharmacological therapy such as TENS. The clinical studies were of relatively short duration (up to one year). Long term assessment of the efficacy and safety of TENS

and other non-pharmacologic treatments of pain in MS patients is needed. Additionally, non-pharmacological pain scores are more often measured as a part of HrQOL scales (e.g. SF-36 Bodily Pain subscore), indicating non-pharmacological interventions are appropriate for a holistic treatment of neuropathic pain. Thus clinicians and patients must weigh the importance of using a non-pharmacological therapy solely for pain management. Physical and educational therapies which do not provide measurable pain relief may still improve physical function and HrQOL for patients living with MS.



[a] Sources include the bibliographies and citing articles of the 50 reviews found through database searches.

Figure 5.1. Flow chart of the systematic review.

Table 5.1. Included trials of non-pharmacological pain management for multiple sclerosis (MS) by treatment type and effect size.

Citation	Sample size, Study duration, Operational definition of pain management therapy	Main findings Cohen's d
Education		
Barlow, 2009	N = 216 Duration: 4 months <u>Chronic Disease Self-Management Course</u> (2 hr/week for 6 weeks) Education regarding self-management principles, communication, and goal setting; delivered by lay instructors in community settings.	10-pt NRS CDSMC mean change pain score (SD): -0.2 (2.8) Waiting List mean change pain score (SD): -0.4 (2.7) Informed non-attender mean change pain score (SD): -0.3 (2.8) Cohen's d: CDSMC vs. Waiting List: -0.04 CDSMC vs. Informed Non-attender: 0.04
Finlayson, 2005	N = 29 Duration: 6 sessions <u>Energy Conservation Course</u> (~1 hour/session for 6 sessions) Fatigue management education regarding living habits and communication; delivered via teleconference.	SF-36 Bodily Pain Subscale Mean change pain score (SD): 6.9 (25.9) Cohen's d: 0.27
Jensen, 2010	N = 22 Duration: 16 hours <u>Self-Hypnosis Training</u> (~1 hr/session for 4 sessions) Clinician-induced hypnosis with suggestions for analgesia and comfort; participants urged to practice at home. <u>Cognitive Restructuring</u> (~1 hr/session for 4 sessions) Education about role of cognition in pain, coping skills, and maintenance of skills. <u>Hypnosis/Cognitive Restructuring</u> (~1 hr/session for 4 sessions) Combination of both methods above to reinforce skills and increase sense of pain control.	10-pt NRS Hypnosis mean change pain score (SD): -0.9 (1.7) Cognitive mean change pain score (SD): -0.4 (1.9) Hyp/Cog mean change pain score (SD): -1.58 (1.7) Education mean change pain score (SD): -0.06 (1.7) Cohen's d: Hypnosis: -0.49 Cognitive: -0.18 Hypnosis/Cognitive: -0.89

Mathiowetz, 2001	N = 54 Duration: 19 weeks Energy Conservation Education (2 hr sessions/week, 6 weeks) Fatigue management course regarding living habits and communication.	SF-36 Bodily Pain Subscale Education mean change pain score (SD): -0.6 (23.5) Control mean change pain score (SD): 4.6 (25.0) Cohen's d: -0.19
Mathiowetz, 2005	N = 169 Duration:12 weeks Energy Conservation Education (2 hr sessions/week, 6 weeks) Fatigue management course regarding living habits and communication.	SF-36 Bodily Pain Subscale Education mean change pain score: 2.69 Cohen's d: 0.18
Electrical Stimulation		
Al-Smadi, 2003	N = 15 Duration:10 weeks Low-frequency TENS (4 Hz, 200 µs) Applied for 45 minutes 3 times/week for 6 weeks, and as needed. High-frequency TENS (110 Hz, 200 µs) Applied for 45 minutes 3 times/week for 6 weeks, and as needed.	McGill Pain Questionnaire Low freq TENS mean change pain score (SD): -13.6 (4.1) High freq TENS mean change pain score (SD): 0.3 (4.1) Placebo TENS mean change pain score (SD): 0.2 (3.5) Cohen's d: Low freq TENS: -3.37 High freq TENS: 0.02
Warke 2006	N = 90 Duration:32 weeks Low-frequency TENS (4 Hz, 200 µs for 45 minutes) Applied twice daily for 6 weeks and as needed. High-frequency TENS (110 Hz, 200 µs for 45 minutes) Applied twice daily for 6 weeks and as needed.	100 mm VAS Low freq TENS mean change pain score: -20.76 Hgh freq TENS mean change pain score: -8.21 Placebo TENS mean change pain score: -17.44 Mean Difference: Low freq TENS: -3.32 High freq TENS: 9.23
Physical Therapy		

Di Fabio, 1997	N = 31 Duration: 1 year <u>Outpatient Rehabilitation</u> (5 hours/day, 1 day/week) Physical and occupational therapy, structured recreational experiences, and counseling.	SF-36 Bodily Pain Subscale Outpatient Rehabilitation effect size: 0.16 Waiting List Control effect size: -0.03 Effect size difference: 0.19
Hughes, 2009	N = 71 Duration: 10 weeks <u>Reflexology</u> (45 min/week) Pressure massage sequences stimulating key reflex points on feet associated with pain throughout body.	10 mm VAS Reflexology median pain score difference: 3 Placebo median pain score difference: 3 Median value difference: 0
Oken, 2004	N = 69 Duration: 6 months <u>Yoga Sessions</u> (90 min/week) Iyengar yoga with 19 instructed poses; held for up to 30 sec with 30 sec to 1 min rest period between; all poses supported by chair or leaning against wall. <u>Aerobic Exercise Sessions</u> (1 class/week and home exercise) Recumbent/stationary bicycling or using a Swiss ball; kept moderate pace (participants able to converse while exercising) until stopped due to fatigue/exacerbated symptoms/reached 1 hour.	SF-36 Bodily Pain Subscale Yoga mean change pain score (SD): -1.4 (18.6) Exercise mean change pain score (SD): 15.7 (15.5) Control mean change pain score (SD): 3.8 (25.7) Cohen's d: Yoga: -0.22 Exercise: 0.87
Patti, 2002	N = 111 Duration: 12 weeks <u>Outpatient Rehabilitation</u> (50 to 60 min/day, 6 days/week) First 6 weeks were instruction; next 6 weeks were self-executed physiotherapy, occupational therapy, speech therapy, group therapy, and other personalized therapy.	SF-36 Bodily Pain Subscale Rehabilitation mean change pain score (SD): 14.9 (20.0) Self-exercise mean change pain score (SD): -0.1 (0.6) Cohen's d: 0.91

Smedal, 2010	N = 60 Duration: 18 months <u>Physiotherapy in Hakadal, Norway</u> (60 min/day, 4 weeks) Physiotherapy focused on improving patient's own movement control; measurements taken after 6 months of followup.	10-pt NRS Norway mean change pain score (SD): 0.5 (2.6) Spain mean change pain score (SD): 0.2 (2.7) Cohen's d: Spain vs. Norway: -0.12
Vaney, 2012	N = 67 Duration: 3 weeks <u>Robotic-Assisted Gait Training</u> (30 min/session, 9 sessions) Support began at 50% of body weight then reduced after observing gait pattern; also included strengthening exercises, horseback riding, pool exercises and occupational therapy.	10 mm VAS RAGT mean change pain score (SD): 1.0 (2.68) Walking group mean change pain score (SD): -0.70 (2.91) Cohen's d: 0.61

Table 5.2. Description of included trials of pharmacological pain management for multiple sclerosis (MS).

Citation	Location, Registration ID, Funding	Inclusion criteria, Study type, Operational definition of comparison group	Baseline Characteristics
Education			
Barlow, 2009	United Kingdom Registration status unknown Funded by UK MS Society	Inclusion criteria 1) Able to understand and participate in English Parallel assignment Waiting List Controls Included those on waiting list Informed Non-Attenders Aware of research and course, yet indicated they did not want to attend	Mean age (SD): 51.1 (11.1) yr 27.3% men, Mean MS duration (SD): 12 (9.3) yr
Finlayson, 2005	USA NCT00591721 Funded by University of Illinois	Inclusion criteria 1) Fatigue Severity Scale score ≥ 4 2) No cognitive impairments according to Blessed Orientation Memory Concentration test Uncontrolled	Mean age (SD): 47 (9.6) yr 17.2% men, 62.1% RRMS, 3.4% PPMS, 17.2% SPMS, Mean MS duration (SD): 9.8 (5.1) yr Mean symptom duration (SD): 14 (6.7) yr
Jensen, 2010	USA NCT00621374 Funding information not provided	Inclusion criteria 1) 10-pt NRS chronic pain score ≥ 4 for at least 6 months 2) Telephone Interview of Cognitive Status score > 20 3) In counseling/psychotherapy ≤ 1 session/week 4) No psychiatric hospitalizations, hypnosis, cognitive behavioral therapy, or active suicidal ideation in past 6 months Crossover Education Control (~1 hr/session for 4 sessions) Education on scope of pain in MS patients and management strategies; specific coping skills not taught.	Mean age: 52.6 yr 20% men

Mathiowetz, 2001 .	USA, Registration status unknown Funding information not provided	Inclusion criteria 1) Fatigue Severity Scale score ≥ 4 2) Community dwelling 3) Received personal care or homemaker services ≤ 10 hrs/week 4) Not in other rehabilitation programs 5) Stabilized concomitant fatigue treatments allowed Crossover Duration of washout period: 6 weeks Control Support Group (2 hr sessions/week, 6 weeks) Discussed living with MS with no mention of fatigue management	Mean age (range): 50 (31 to 74) yr 33% men, 36% RRMS, 22% PPMS, 13% SPMS, Mean MS duration (range): 9.5 (1 to 34) yr
Mathiowetz, 2005	USA Registration status unknown Funding information not provided	Inclusion criteria 1) Fatigue Severity Scale score ≥ 4 2) Community dwelling 3) Passed 3 of 4 subsets of Neuropsychological Screening Battery for MS Crossover Control Period (6 weeks) No intervention, so washout period not used.	Mean age (SD): 48.3 (8.4) yr 17.2% men, 61.5% RRMS, 5.9% PPMS, 18.9% SPMS, Mean MS duration (SD): 9.5 (7.4) yr Mean symptom duration (SD): 14.9 (9.7) yr
Electrical Stimulation			
Al-Smadi, 2003	Northern Ireland Registration status unknown Funding information not provided	Inclusion criteria 1) Chronic lower back pain for ≥ 3 months 2) No contraindications to transcutaneous electrical nerve stimulation (TENS), analgesic abuse, or sacral pressure ulcers 3) Stabilized concomitant pain treatments Parallel assignment Placebo TENS Used same machinery with no frequency	No information provided

Warke 2006	Northern Ireland Registration status unknown Funded by the MS Society of Great Britain and Northern Ireland	Inclusion criteria 1) Chronic lower back pain for ≥ 3 months 2) No contraindications to transcutaneous electrical nerve stimulation (TENS), analgesic abuse, or sacral pressure ulcers 3) Stabilized concomitant pain treatments allowed Parallel assignment Placebo TENS Used same machinery with no frequency	Mean age: 47.4 yr 23.3% men, Mean MS duration: 10.7 yr Mean pain duration: 10.4 yr
Physical Therapy			
Di Fabio, 1997	USA Registration status unknown Funding information not provided	Inclusion criteria 1) Progressive MS course 2) EDSS score between 5 and 8 Parallel assignment Waiting List Control On waiting list for treatment, not receiving outpatient rehabilitation	Mean age: 47.4 yr 19.4% men, Mean MS duration: 15.5 yr
Hughes, 2009	Northern Ireland Registration status unknown Funded by U.S. National Multiple Sclerosis Society	Inclusion criteria 1) EDSS score ≤ 7.5 2) Pain VAS score > 4 3) No previous experience with reflexology Parallel assignment Placebo (45 min/week) Standardized foot massage with same sequence as treatment, but avoided key reflex points.	Mean age: 51.5 yr 16.9% men, 39.4% RRMS, 11.3% PPMS, 26.8% SPMS, Mean MS duration: 12.5 yr Mean EDSS score: 6.0

Oken, 2004	USA Registration status unknown Funding information not provided	Inclusion criteria 1) EDSS score < 6.0 2) No comorbidities or cognition impairment 3) Did not perform yoga/tai chi in past 6 months 4) Did not regularly perform aerobic exercise for > 30 min/day Parallel assignment Waiting List Controls Received no intervention.	Mean age: 49.0 yr 5.8% men, Mean EDSS score: 2.0
Patti, 2002	Italy Registration status unknown Funding information not provided	Inclusion criteria 1) EDSS score between 4.0 and 8.0 2) Mini-Mental State Exam score > 24 3) No comorbidities or contraindications 4) No rehabilitation, MS disease-modifying drugs, or other experimental drugs 6 months prior to study Parallel assignment Self-exercise Program Control group performed self-exercise program at home for 12 weeks.	Mean age: 45.6 yr 42.3% men, Mean MS duration: 17.2 yr Mean EDSS score: 6.2
Smedal, 2010	Norway and Spain NCT01057719 Funded by Oslo University Hospital, Haukeland University Hospital, and Western Regional Health Authority	Inclusion criteria 1) EDSS score of 4.0 to 6.5 2) No past experiences with heat intolerance or excessive fatigue 3) Non-severe cognitive dysfunction 4) No comorbidities Crossover Washout period duration: 6 months Physiotherapy in Tenerife, Spain (60 min/day, 4 weeks) Physiotherapy focused on improving patient's own movement control; measurements taken after 6 months of followup.	Mean age (SD): 48.5 (9.0) yr 40% men, 63.3% RRMS, 5% PPMS, 31.7% SPMS, Mean EDSS score (SD): 4.5 (1.5)

Vaney, 2012	Switzerland Registered in Switzerland: ISRCTN69803702 Funded by Berner Klinik Montana, ReSAR/HES-SO of Switzerland	<u>Inclusion criteria</u> 1) EDSS score between 3.0 and 6.5 2) Able to walk 14 meters with or without assistive devices 3) Non-severe osteoporosis or scoliosis 4) Even leg lengths 5) No comorbidities Parallel assignment <u>Walking Group</u> (30 min/session, 9 sessions) Walked in a group with physiotherapist, in gym, or on uneven ground outdoors.	Mean age: 56.3 yr Mean EDSS score: 5.8

Table 5.3. Quality Assessment of Included MS Pain Trials.

	Treatment Allocation		Blinding									
Citation	Randomization	Blinded allocation	Patients	Physicians	Outcome Assessors	Comparison group	Primary Outcome as Pain	Compliance unlikely to introduce bias	Attrition unlikely to introduce bias	Comparable follow-up time	Intention to Treat Analysis	Baseline characteristics comparable
Barlow, 2009	+	+	-	-	?	+	-	?	+	+	+	-
Finlayson, 2005	N/A	N/A	N/A	N/A	N/A	-	-	+	-	N/A	+	N/A
Jensen, 2010	+	?	?	?	+	+	+	?	+	+	-	+
Mathiowetz, 2001	-	?	?	?	?	+	-	-	-	+	+	+
Mathiowetz, 2005	+	?	-	-	?	+	-	-	-	+	+	+
Al-Smadi, 2003	+	+	+	-	+	+	+	-	-	+	+	?
Warke 2006	+	+	+	-	+	+	+	-	-	+	+	+
Di Fabio, 1997	-	N/A	-	-	?	+	-	-	-	+	+	+
Hughes, 2009	+	+	+	-	+	+	+	-	-	+	+	+
Oken, 2004	+	+	-	-	+	+	-	-	-	+	-	+
Patti, 2002	+	+	+	+	+	+	-	-	-	+	+	+
Smedal, 2010	+	?	-	-	-	+	-	-	-	+	+	+
Vaney, 2012	+	+	-	-	-	+	-	-	-	+	-	+

+ : Present; - : Not Present; ? : Not Reported; N/A : Not Applicable

Reference List

Reference List

1. Compston A, Coles A. Multiple sclerosis. *Lancet*. 2002;359:1221-1231.

2. Richards RG, Sampson FC, Beard SM, Tappenden P. A review of the natural history and epidemiology of multiple sclerosis: implications for resource allocation and health economic models. *Health Technol Assess*. 2002;6:1-73.

3. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". *Ann Neurol*. 2005;58:840-846.

4. Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis results of an international survey. *Neurology*. 1996;46:907-911.

5. Tremlett H, Devonshire V. Is late-onset multiple sclerosis associated with a worse outcome? *Neurology*. 2006;67:954-959.

6. Ascherio A, Munger K. Epidemiology of multiple sclerosis: from risk factors to prevention. *Semin Neurol*. 2008;28:17-28.

7. Bove RM, Healy B, Augustine A, Musallam A, Gholipour T, Chitnis T. Effect of gender on late-onset multiple sclerosis. *Multiple Sclerosis Journal*. 2012.

8. Di Pauli F, Reindl M, Ehling R, et al. Smoking is a risk factor for early conversion to clinically definite multiple sclerosis. *Mult Scler*. 2008;14:1026-1030.

9. Jafari N, Hintzen RQ. The association between cigarette smoking and multiple sclerosis. *J Neurol Sci*. 2011;311:78-85.

10. Hernan MA, Olek MJ, Ascherio A. Cigarette smoking and incidence of multiple sclerosis. *Am J Epidemiol*. 2001;154:69-74.

11. Antico A, Tampoia M, Tozzoli R, Bizzaro N. Can supplementation with vitamin D reduce the risk or modify the course of autoimmune diseases? A systematic review of the literature. *Autoimmunity reviews*. 2012.

12. Pugliatti M, Harbo HF, Holmoy T, et al. Environmental risk factors in multiple sclerosis. *Acta Neurol Scand Suppl*. 2008;188:34-40.

13. Hernan MA, Jick SS, Logroscino G, Olek MJ, Ascherio A, Jick H. Cigarette smoking and the progression of multiple sclerosis. *Brain*. 2005;128:1461-1465.

14. Runia TF, Hop WCJ, de Rijke YB, Buljevac D, Hintzen RQ. Lower serum vitamin D levels are associated with a higher relapse risk in multiple sclerosis. *Neurology*. 2012;79:261-266.

15. Forbes A, While A, Taylor M. What people with multiple sclerosis perceive to be important to meeting their needs. *J Adv Nurs*. 2007;58:11-22.

16. Samkoff LM, Goodman AD. Symptomatic management in multiple sclerosis. *Neurol Clin*. 2011;29:449-463.

17. Brichetto G, Messmer Uccelli M, Mancardi GL, Solaro C. Symptomatic medication use in multiple sclerosis. *Mult Scler*. 2003;9:458-460.

18. Caminero A, Manuel Bartolomé. Sleep disturbances in multiple sclerosis. *J Neurol Sci*. 2011;309:86-91.

19. Davis SL, Wilson TE, White AT, Frohman EM. Thermoregulation in multiple sclerosis. *J Appl Physiol*. 2010;109:1531-1537.

20. Smith R, Studd J. A pilot study of the effect upon multiple sclerosis of the menopause, hormone replacement therapy and the menstrual cycle. *J R Soc Med*. 1992;85:612.

21. Bronner G, Elran E, Golomb J, Korczyn A. Female sexuality in multiple sclerosis: the multidimensional nature of the problem and the intervention. *Acta Neurol Scand*. 2010;121:289-301.

22. Nortvedt MW, Riise T, Myhr K, Landtblom A, Bakke A, Nyland H. Reduced quality of life among multiple sclerosis patients with sexual disturbance and bladder dysfunction. *Multiple Sclerosis*. 2001;7:231-235.

23. Tepavcevic D, Kostic J, Basuroski I, Stojsavljevic N, Pekmezovic T, Drulovic J. The impact of sexual dysfunction on the quality of life measured by MSQoL-54 in patients with multiple sclerosis. *Multiple Sclerosis*. 2008;14:1131-1136.

24. Demirkiran M, Sarica Y, Uguz S, Yerdelen D, Aslan K. Multiple sclerosis patients with and without sexual dysfunction: are there any differences? *Multiple Sclerosis*. 2006;12:209-211.

25. National Institutes of Health. National Institutes of Health State-of-the-Science Conference statement: management of menopause-related symptoms. *Ann Intern Med*. 2005;142:1003-1013.

26. Werner C. 2010 Census Briefs: The Older Population. U.S. Census Bureau; Nov 2011;9. Available from: http://www.census.gov/prod/cen2010/briefs/c2010br-09.pdf. Accessed Sept. 17, 2012.

27. Khan F, Gray O. Disability management and rehabilitation for persons with multiple sclerosis. *Neural Regeneration Research*. 2010;5:301-309.

28. Overs S, Hughes CM, Haselkorn JK, Turner AP. Modifiable Comorbidities and Disability in Multiple Sclerosis. *Current Neurology and Neuroscience Reports*. 2012:1-8.

29. Gold EB, Sternfeld B, Kelsey JL, et al. Relation of demographic and lifestyle factors to symptoms in a multi-racial/ethnic population of women 40–55 years of age. *Am J Epidemiol*. 2000;152:463-473.

30. Luoto R. Hot flushes and quality of life during menopause. *BMC Womens Health*. 2009;9:13.

31. Pittas F, Ponsonby AL, van der Mei IA, et al. Smoking is associated with progressive disease course and increased progression in clinical disability in a prospective cohort of people with multiple sclerosis. *J Neurol*. 2009;256:577-585.

32. Centers for Disease Control and Prevention. Women's Reproductive Health: Menopause. Available at: http://www.cdc.gov/reproductivehealth/womensrh/menopause.htm. Accessed Sept. 17, 2012, .

33. Woods NF, Woods F. Frailty: emergence and consequences in women aged 65 and older in the Women's Health Initiative Observational Study. *J Am Geriatr Soc*. 2005;53:1321.

34. Cauley JA, Reiner. Inflammation and Thrombosis Biomarkers and Incident Frailty in Postmenopausal Women. *Am J Med*. 2009;122:947.

35. Luo J, Horn K, Ockene JK, et al. Interaction between smoking and obesity and the risk of developing breast cancer among postmenopausal women: the Women's Health Initiative Observational Study. *Am J Epidemiol*. 2011;174:919-928.

36. Ware JE,Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*. 1992;30:473-483.

37. Freeman J, Hobart J, Langdon D, Thompson A. Clinical appropriateness: a key factor in outcome measure selection: the 36 item short form health survey in multiple sclerosis. *Journal of Neurology, Neurosurgery & Psychiatry*. 2000;68:150-156.

38. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged. *JAMA: the journal of the American Medical Association*. 1963;185:914-919.

39. Manson JAE, Greenland P, LaCroix AZ, et al. Walking compared with vigorous exercise for the prevention of cardiovascular events in women. *N Engl J Med*. 2002;347:716-725.

40. Greendale GA. Symptom relief and side effects of postmenopausal hormones: results from the Postmenopausal Estrogen/Progestin Interventions Trial. *Obstet Gynecol*. 1998;92:982.

41. Cauley JA, Danielson ME, Boudreau R, et al. Serum 25-hydroxyvitamin D and clinical fracture risk in a multiethnic cohort of women: The women's health initiative (WHI). *Journal of Bone and Mineral Research*. 2011;26:2378-2388.

42. Langer RD, White E, Lewis CE, Kotchen JM, Hendrix SL, Trevisan M. The Women's Health Initiative Observational Study: baseline characteristics of participants and reliability of baseline measures. *Ann Epidemiol*. 2003;13:S107.

43. Emre M, de Decker C. Effects of cigarette smoking on motor functions in patients with multiple sclerosis. *Arch Neurol*. 1992;49:1243.

44. Nguyen HQ, Herting JR, Kohen R, Perry CK, Lacroix A, Adams-Campbell LL. Recreational Physical Activity in Postmenopausal Women is Stable Over 8-Years of Follow-Up. *J Phys Act Health*. 2012.

45. Shirani A, Tremlett H. The effect of smoking on the symptoms and progression of multiple sclerosis: a review. *J Inflamm Res*. 2010;3:115-126.

46. Hill KE, Zollinger LV, Watt HE, Carlson NG, Rose JW. Inducible nitric oxide synthase in chronic active multiple sclerosis plaques: distribution, cellular expression and association with myelin damage. *J Neuroimmunol*. 2004;151:171-179.

47. Salzer J, Hallmans G, Nystrom M, Stenlund H, Wadell G, Sundstrom P. Smoking as a risk factor for multiple sclerosis. *Mult Scler*. 2012.

48. Sundstrom P, Nystrom L. Smoking worsens the prognosis in multiple sclerosis. *Mult Scler*. 2008;14:1031-1035.

49. Marrie RA, Cutter G, Tyry T, Campagnolo D, Vollmer T. Validation of the NARCOMS registry: diagnosis. *Mult Scler*. 2007;13:770-775.

50. Kantarci O, Wingerchuk D. Epidemiology and natural history of multiple sclerosis: new insights. *Curr Opin Neurol*. 2006;19:248-254.

51. Harlow SD, Gass M, Hall JE, et al. Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. *J Clin Endocrinol Metab*. 2012;97:1159-1168.

52. Gold SM, Voskuhl RR. Estrogen and testosterone therapies in multiple sclerosis. *Prog Brain Res*. 2009;175:239.

53. Kipp M, Amor S, Krauth R, Beyer C. Multiple sclerosis: neuroprotective alliance of estrogen-progesterone and gender. *Front Neuroendocrinol*. 2012;33:1-16.

54. Koch-Henriksen N, Sørensen PS. The changing demographic pattern of multiple sclerosis epidemiology. *The Lancet Neurology*. 2010;9:520-532.

55. Kabat GC, Kim MY, Woods NF, et al. Reproductive and menstrual factors and risk of ductal carcinoma in situ of the breast in a cohort of postmenopausal women. *Cancer Causes and Control*. 2011;22:1415-1424.

56. World Health Organization. BMI Classification. *WHO Global Database on Body Mass Index.* 2012.

57. Patterson RE, Kristal AR, Tinker LF, Carter RA, Bolton MP, Agurs-Collins T. Measurement characteristics of the Women's Health Initiative food frequency questionnaire. *Ann Epidemiol*. 1999;9:178-187.

58. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA: the journal of the American Medical Association*. 2002;288:321-333.

59. Steinkellner AR, Denison SE, Eldridge SL, Lenzi LL, Chen W, Bowlin SJ. A decade of postmenopausal hormone therapy prescribing in the United States: long-term effects of the Women's Health Initiative. *Menopause*. 2012;19:616-621.

60. Ziehn MO, Avedisian AA, Dervin SM, O'Dell TJ, Voskuhl RR. Estriol preserves synaptic transmission in the hippocampus during autoimmune demyelinating disease. *Lab Invest*. 2012;92:1234-1245.

61. Ryan N, Rosner A. Quality of life and costs associated with micronized progesterone and medroxyprogesterone acetate in hormone replacement therapy for nonhysterectomized, postmenopausal women. *Clin Ther*. 2001;23:1099-1115.

62. Maki PM, Gast MJ, Vieweg AJ, Burriss SW, Yaffe K. Hormone therapy in menopausal women with cognitive complaints: a randomized, double-blind trial. *Neurology*. 2007;69:1322-1330.

63. Brunner RL, Gass M, Aragaki A, et al. Effects of conjugated equine estrogen on health-related quality of life in postmenopausal women with hysterectomy: results from the Women's Health Initiative Randomized Clinical Trial. *Arch Intern Med*. 2005;165:1976-1986.

64. Hays J, Ockene JK, Brunner RL, et al. Effects of estrogen plus progestin on health-related quality of life. *N Engl J Med*. 2003;348:1839-1854.

65. Greenspan SL, Resnick NM, Parker RA. The effect of hormone replacement on physical performance in community-dwelling elderly women. *Am J Med*. 2005;118:1232-1239.

66. Michael YL, Gold R, Manson JAE, et al. Hormone therapy and physical function change among older women in the Women's Health Initiative: a randomized controlled trial. *Menopause (New York, NY)*. 2010;17:295.

67. Chlebowski RT, Cirillo DJ, Eaton CB, et al. Estrogen alone and joint symptoms in the Women's Health Initiative randomized trial. *Menopause*. 2013.

68. Pastore LM, Carter RA, Hulka BS, Wells E. Self-reported urogenital symptoms in postmenopausal women: Women's Health Initiative. *Maturitas*. 2004;49:292-303.

69. Hurwitz BJ. Registry studies of long-term multiple sclerosis outcomes. *Neurology*. 2011;76:S3.

70. Ingram G, Colley E, Ben-Shlomo Y, et al. Validity of patient-derived disability and clinical data in multiple sclerosis. *Mult Scler*. 2010;16:472-479.

71. North American Menopause Society. The 2012 hormone therapy position statement of: The North American Menopause Society. *Menopause*. 2012;19:257-271.

72. Shabas D, Weinreb H. Preventive healthcare in women with multiple sclerosis. *J Womens Health Gend Based*. 2000;9:389-395.

73. Aring CD. Pain in multiple sclerosis. *JAMA*. 1973;223:547.

74. O'Connor AB, Schwid SR, Herrmann DN, Markman JD, Dworkin RH. Pain associated with multiple sclerosis: systematic review and proposed classification. *Pain*. 2008;137:96-111.

75. Solaro C, Uccelli MM. Management of pain in multiple sclerosis: a pharmacological approach. *Nat Rev Neurol*. 2011;7:519-527.

76. Truini A, Galeotti F, Cruccu G. Treating pain in multiple sclerosis. *Expert Opin Pharmacother*. 2011;12:2355-2368.

77. Attal N, Cruccu G, Baron R, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J Neurol*. 2010;17:1113-e88.

78. Rog DJ, Nurmikko TJ, Friede T, Young CA. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. *Neurology*. 2005;65:812-819.

79. Paisley S, Beard S, Hunn A, Wight J. Clinical effectiveness of oral treatments for spasticity in multiple sclerosis: a systematic review. *Mult Scler*. 2002;8:319-329.

80. De Santi L, Annunziata P. Symptomatic cranial neuralgias in multiple sclerosis: clinical features and treatment. *Clin Neurol Neurosurg*. 2012;114:101-107.

81. Shakespeare DT, Boggild M, Young C. Anti-spasticity agents for multiple sclerosis. *Cochrane Database Syst Rev*. 2003;(4):CD001332.

82. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535.

83. Schumacher M, Hussain R, Gago N, Oudinet JP, Mattern C, Ghoumari AM. Progesterone synthesis in the nervous system: implications for myelination and myelin repair. *Frontiers in neuroscience*. 2012;6.

84. McDonald W, Halliday A. Diagnosis and classification of multiple sclerosis. *Br Med Bull*. 1977;33:4-8.

85. POSER C, Poser. Diagnostic criteria for multiple sclerosis. *Clin Neurol Neurosurg*. 2001;103:1-11.

86. Huskisson EC. Measurement of pain. *Lancet*. 1974;2:1127-1131.

87. Farrar JT, Young JP,Jr, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain*. 2001;94:149-158.

88. Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. *Pain*. 1975;1:277-299.

89. Downie WW, Leatham PA, Rhind VM, Wright V, Branco JA, Anderson JA. Studies with pain rating scales. *Ann Rheum Dis*. 1978;37:378-381.

90. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology*. 1983;33:1444-1452.

91. Nakagawa S, Cuthill IC. Effect size, confidence interval and statistical significance: a practical guide for biologists. *Biol Rev Camb Philos Soc*. 2007;82:591-605.

92. Morris SB, DeShon RP. Combining effect size estimates in meta-analysis with repeated measures and independent-groups designs. *Psychol Methods*. 2002;7:105-125.

93. Fritz CO, Morris PE, Richler JJ. Effect size estimates: current use, calculations, and interpretation. *J Exp Psychol Gen*. 2012;141:2-18.

94. Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions.* The Cochrane Collaboration; 2011; No. Version 5.1.0 [updated March 2011].

95. French J, Gronseth G. Lost in a jungle of evidence: we need a compass. *Neurology*. 2008;71:1634-1638.

96. Fishman B, Pasternak S, Wallenstein SL, Houde RW, Holland JC, Foley KM. The Memorial Pain Assessment Card. A valid instrument for the evaluation of cancer pain. *Cancer*. 1987;60:1151-1158.

97. Keller S, Bann CM, Dodd SL, Schein J, Mendoza TR, Cleeland CS. Validity of the brief pain inventory for use in documenting the outcomes of patients with noncancer pain. *Clin J Pain*. 2004;20(5):309-318.

98. Falah M, Madsen C, Holbech JV, Sindrup SH. A randomized, placebo-controlled trial of levetiracetam in central pain in multiple sclerosis. *Eur J Pain*. 2012;16:860-869.

99. Rossi S, Mataluni G, Codeca C, et al. Effects of levetiracetam on chronic pain in multiple sclerosis: results of a pilot, randomized, placebo-controlled study. *Eur J Neurol*. 2009;16:360-366.

100. Breuer B, Pappagallo M, Knotkova H, Guleyupoglu N, Wallenstein S, Portenoy RK. A randomized, double-blind, placebo-controlled, two-period, crossover, pilot trial of lamotrigine in patients with central pain due to multiple sclerosis. *Clin Ther*. 2007;29:2022-2030.

101. Houtchens MK, Richert JR, Sami A, Rose JW. Open label gabapentin treatment for pain in multiple sclerosis. *Mult Scler*. 1997;3:250-253.

102. Solaro C, Boehmker M, Tanganelli P. Pregabalin for treating paroxysmal painful symptoms in multiple sclerosis: a pilot study. *J Neurol*. 2009;256:1773-1774.

103. Solaro C, Restivo D, Mancardi GL, Tanganelli P. Oxcarbazepine for treating paroxysmal painful symptoms in multiple sclerosis: a pilot study. *Neurol Sci*. 2007;28:156-158.

104. Chitsaz A, Janghorbani M, Shaygannejad V, Ashtari F, Heshmatipour M, Freeman J. Sensory complaints of the upper extremities in multiple sclerosis: relative efficacy of nortriptyline and transcutaneous electrical nerve stimulation. *Clin J Pain*. 2009;25:281-285.

105. Eli Lilly & Co. Duloxetine for Multiple Sclerosis Pain. *ClinicalTrials Gov, National Institutes of Health [http://www.clinicaltrials gov]. NLM Identifier: NCT00755807.* 2010.

106. GW Pharmaceuticals Ltd. Sativex Versus Placebo When Added to Existing Treatment for Central Neuropathic Pain in MS. *ClinicalTrials Gov, National Institutes of Health [http://www.clinicaltrials gov]. NLM Identifier: NCT00391079.* 2009.

107. Wade DT, Makela P, Robson P, House H, Bateman C. Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients. *Mult Scler*. 2004;10:434-441.

108. Svendsen KB, Jensen TS, Bach FW. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. *BMJ*. 2004;329:253.

109. Panitch HS, Thisted RA, Smith RA, et al. Randomized, controlled trial of dextromethorphan/quinidine for pseudobulbar affect in multiple sclerosis. *Ann Neurol*. 2006;59:780-787.

110. Cree BA, Kornyeyeva E, Goodin DS. Pilot trial of low-dose naltrexone and quality of life in multiple sclerosis. *Ann Neurol*. 2010;68:145-150.

111. Kalman S, Osterberg A, Sorensen J, Boivie J, Bertler A. Morphine responsiveness in a group of well-defined multiple sclerosis patients: a study with i.v. morphine. *Eur J Pain*. 2002;6:69-80.

112. Lakhan SE, Rowland M. Whole plant cannabis extracts in the treatment of spasticity in multiple sclerosis: a systematic review. *BMC Neurol*. 2009;9:59-2377-9-59.

113. Olney N, Rosen H. AVP-923, a combination of dextromethorphan hydrobromide and quinidine sulfate for the treatment of pseudobulbar affect and neuropathic pain. *IDrugs*. 2010;13:254-265.

114. Pioro EP, Brooks BR, Cummings J, et al. Dextromethorphan plus ultra low-dose quinidine reduces pseudobulbar affect. *Ann Neurol*. 2010;68:693-702.

115. Hobson K. Lawmakers Aren't Laughing About Avanir's Price for Nuedexta. *WSJ.* Wall Street Journal; 2011. Available from: http://blogs.wsj.com/health/2011/05/25/lawmakers-arent-laughing-about-avanirs-price-for-nuedexta/. Accessed 2013 Mar 6.

116. Saarto T, Wiffen PJ. Antidepressants for neuropathic pain: a Cochrane review. *J Neurol Neurosurg Psychiatry*. 2010;81:1372-1373.

117. Moore RA, Wiffen PJ, Derry S, McQuay HJ. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev*. 2011;(3):CD007938. doi:CD007938.

118. Moore RA, Straube S, Wiffen PJ, Derry S, McQuay HJ. Pregabalin for acute and chronic pain in adults. *Cochrane Database Syst Rev*. 2009;(3):CD007076. doi:CD007076.

119. Lunn MP, Hughes RA, Wiffen PJ. Duloxetine for treating painful neuropathy or chronic pain. *Cochrane Database Syst Rev*. 2009;(4):CD007115. doi:CD007115.

120. Eisenberg E, McNicol E, Carr DB. Opioids for neuropathic pain. *Cochrane Database Syst Rev*. 2006;(3):CD006146.

121. O'Connor AB, Dworkin RH. Treatment of neuropathic pain: an overview of recent guidelines. *Am J Med*. 2009;122:S22-32.

122. Chaparro LE, Wiffen PJ, Moore RA, Gilron I. Combination pharmacotherapy for the treatment of neuropathic pain in adults. *Cochrane Database Syst Rev*. 2012;7:CD008943.

123. Cohen J. A power primer. *Psychol Bull*. 1992;112:155-159.

124. Finlayson M. Pilot study of an energy conservation education program delivered by telephone conference call to people with multiple sclerosis. *NeuroRehabilitation*. 2005;20:267-277.

125. Mathiowetz V, Matuska KM, Murphy ME. Efficacy of an energy conservation course for persons with multiple sclerosis. *Arch Phys Med Rehabil*. 2001;82:449-456.

126. Mathiowetz VG, Finlayson ML, Matuska KM, Chen HY, Luo P. Randomized controlled trial of an energy conservation course for persons with multiple sclerosis. *Mult Scler*. 2005;11:592-601.

127. Barlow J, Turner A, Edwards R, Gilchrist M. A randomised controlled trial of lay-led self-management for people with multiple sclerosis. *Patient Educ Couns*. 2009;77:81-89.

128. Jensen MP, Ehde DM, Gertz KJ, et al. Effects of self-hypnosis training and cognitive restructuring on daily pain intensity and catastrophizing in individuals with multiple sclerosis and chronic pain. *Int J Clin Exp Hypn*. 2011;59:45-63.

129. Al-Smadi J, Warke K, Wilson I, et al. A pilot investigation of the hypoalgesic effects of transcutaneous electrical nerve stimulation upon low back pain in people with multiple sclerosis. *Clin Rehabil*. 2003;17:742-749.

130. Warke K, Al-Smadi J, Baxter D, Walsh DM, Lowe-Strong AS. Efficacy of transcutaneous electrical nerve stimulation (tens) for chronic low-back pain in a multiple sclerosis population: a randomized, placebo-controlled clinical trial. *Clin J Pain*. 2006;22:812-819.

131. Di Fabio RP, Choi T, Soderberg J, Hansen CR. Health-related quality of life for patients with progressive multiple sclerosis: influence of rehabilitation. *Phys Ther*. 1997;77:1704-1716.

132. Patti F, Ciancio MR, Reggio E, et al. The impact of outpatient rehabilitation on quality of life in multiple sclerosis. *J Neurol*. 2002;249:1027-1033.

133. Smedal T, Myhr KM, Aarseth JH, et al. The influence of warm versus cold climate on the effect of physiotherapy in multiple sclerosis. *Acta Neurol Scand*. 2011;124:45-52.

134. Oken BS, Kishiyama S, Zajdel D, et al. Randomized controlled trial of yoga and exercise in multiple sclerosis. *Neurology*. 2004;62:2058-2064.

135. Vaney C, Gattlen B, Lugon-Moulin V, et al. Robotic-assisted step training (lokomat) not superior to equal intensity of over-ground rehabilitation in patients with multiple sclerosis. *Neurorehabil Neural Repair*. 2012;26:212-221.

136. Hughes CM, Smyth S, Lowe-Strong AS. Reflexology for the treatment of pain in people with multiple sclerosis: a double-blind randomised sham-controlled clinical trial. *Mult Scler*. 2009;15:1329-1338.

137. Jawahar R, Oh U, Yang S, Lapane KL. A systematic review of pharmacological pain management in multiple sclerosis. *Neurology* [Under Review.].

138. Warke K, Al-Smadi J, Baxter D, Walsh DM, Lowe-Strong AS. Efficacy of transcutaneous electrical nerve stimulation (tens) for chronic low-back pain in a multiple sclerosis population: a randomized, placebo-controlled clinical trial. *Clin J Pain*. 2006;22:812-819.

139. Armutlu K, Meric A, Kirdi N, Yakut E, Karabudak R. The effect of transcutaneous electrical nerve stimulation on spasticity in multiple sclerosis patients: a pilot study. *Neurorehabil Neural Repair*. 2003;17:79-82.

140. Miller L, Mattison P, Paul L, Wood L. The effects of transcutaneous electrical nerve stimulation (TENS) on spasticity in multiple sclerosis. *Mult Scler*. 2007;13:527-533.

141. Amatya B, Khan F, La Mantia L, Demetrios M, Wade DT. Non pharmacological interventions for spasticity in multiple sclerosis. *Cochrane Database Syst Rev*. 2013;2:CD009974.

142. Johnson MI, Bjordal JM. Transcutaneous electrical nerve stimulation for the management of painful conditions: focus on neuropathic pain. *Expert Rev Neurother*. 2011;11:735-753.

143. Jacques L, Jensen TS, Rollins J, Burton B, Hakim R, Miller S. Final Decision Memorandum for Transcutaneous Electrical Nerve Stimulation for Chronic Low Back Pain (CAG-00429N). Available at: http://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=256. Accessed April 21, 2013.

144. Khan F, Turner-Stokes L, Ng L, Kilpatrick T. Multidisciplinary rehabilitation for adults with multiple sclerosis. *Cochrane Database Syst Rev*. 2007;(2):CD006036.

145. Cassileth BR, Keefe FJ. Integrative and behavioral approaches to the treatment of cancer-related neuropathic pain. *Oncologist*. 2010;15 Suppl 2:19-23.

Appendix

MEDLINE search strategy

(1965/01/01:2012/11/16[dp]) AND (Clinical Trial[pt] OR Randomized Controlled Trial[pt] OR Controlled Clinical Trial[pt] OR trial*[all] OR intervention*[all]) AND (((multiple sclerosis[majr]) OR ("multiple sclerosis"[tiab]) OR multiple sclerosis[all]) NOT (trigeminal neuralgia[mh]) NOT (muscle spasticity[mh])) AND (pain[majr] OR “pain”[tiab] OR (pain[mh] NOT chemically induced[sh]) OR (pain management[mh] OR pain measurement[mh]))

[1]Filters for human- and English-only studies were not applied in this algorithm to capture all available articles in the database, including newer, non-indexed articles. Articles were later screened to exclude non-human studies (0 articles found) and non-English publications (14 articles found).

Vita

Rachel Hannah Jawahar was born June 24, 1983 in Boonton, New Jersey and is a United States citizen. She graduated from Plainview-Old Bethpage John F. Kennedy High School, Plainview, New York in 2001. She received her Bachelor of Science in Engineering from Cornell University, Ithaca, New York in 2007. She received a Masters of Public Health in Epidemiology from New York Medical College, Valhalla, New York in 2010.

Honors and Awards

2011, Summer Fellow, F.D.A. Medical Device Fellowship Program
2009, Popper Scholar Grant, Robert L. Popper Hudson Valley Health Fund, NY
2004, Research Experience for Undergraduates Award, National Science Foundation
2001, Highest Honors, NY Intel Science Talent Search

Professional and Research Positions

2013 Graduate Research Assistantship, Virginia Commonwealth University
Dept. of Pharmacotherapy & Outcomes Science
Mentor: Amy L. Pakyz, Ph.D,

2012 Contractor, Pfizer, New York, NY
Global Health Economics Outcomes Research, Global Market Access
Supervisor: Arthi Balachandran, Ph.D.

2012 Graduate Research Assistantship, Virginia Commonwealth University
Division of Epidemiology, Dept. of Family Medicine and Population Health
Mentor: Kate L. Lapane, Ph.D,

2011 Fellow, U.S. Food and Drug Administration
Centers for Device and Radiological Health/OSB/EDPI/EERB2
Supervisor: Mary Beth Ritchey, Ph.D.

2010 Teaching Assistant, Virginia Commonwealth University
Division of Epidemiology, Dept. of Family Medicine and Population Health
Mentor: Saba W. Masho, M.D.

2009 Program Evaluator, My Sister's Place, White Plains, NY
Supervisor: Bincy Jacob

2005 Undergraduate Researcher, Cornell University
Research Experience for Undergraduates, National Science Foundation
Mentor: Clifford Pollock, Ph.D.

2000 Researcher, State University of New York at Stony Brook
Mentor: Michael A. Bender, Ph.D.

PUBLICATIONS

Jawahar R, Oh U, Yang S, Lapane KL. A systematic review of pharmacological pain management in multiple sclerosis. Under review in Neurology.

Lapane KL, Yang S, Brown MJ, Jawahar R, Pagliasotti C, Rajpathak S. Sulfonylureas and risk of falls and fractures: a systematic review. Drugs Aging. 2013 Apr 23.

Yang S, Jawahar R, McAlindon TE, Eaton CB, Lapane KL. Racial differences in symptom management approaches among persons with radiographic knee osteoarthritis. BMC Complement Altern Med. 2012 Jul 6;12:86.

Jawahar R, Yang S, Eaton CB, McAlindon TE, Lapane KL. Gender-specific correlates of complementary and alternative medicine use among people with radiographically-confirmed knee osteoarthritis. J Womens Health (Larchmt). 2012 Oct; 21(10):1091-9.

PRESENTATIONS

Jawahar R, Yang S, Lapane KL, Eaton CB. (2011, November) Approaches to pain management in women with osteoarthritis. Poster presented at 139th Annual Meeting of the American Public Health Association, Washington, DC.

Jawahar R, Yang S, Lapane KL, Eaton CB. (2011, August) Risky NSAID use in adults with osteoarthritis. Poster presented at 27th Annual Scientific Meeting of the International Society for Pharmacoepidemiology, Chicago, IL.

Jawahar R, Yang S, Lapane KL, Eaton CB. (2011, March) Pain management in women: Are conventional treatments enough? Poster presented at 7th Annual VCU Women's Health Research Day, Richmond, VA.