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Non-pharmacologic and Alternative Management of Chronic Pain in Multiple Sclerosis

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Abstract

Chronic pain associated with multiple sclerosis (MS) is prevalent in many phenotypes. Pharmacologic therapy of this pain often fails to provide analgesia. This research is intended to determine which nonpharmacological interventions may be recommended for treatment of chronic extremity pain in individuals with MS. This research was primarily conducted through a comprehensive literature review of publications within the past five years on three databases, PubMed, EMBase, and CINAHL. Additional resources were added from "similar" sections of the databases, directly from included studies, and when used to inform background information, for a total of 26 resources. Studies were excluded if not specifically addressing chronic pain treatment in MS or if beyond the scope of this research. Background information presented discusses pathophysiology of pain in MS and previously published literature regarding pharmacologic and nonpharmacologic interventions for MS-related pain. New data suggests that improving MS-related pain characterization has potential to alter current understanding of phenotype prevalence and subsequently impact selection of pharmacologic treatment agents for pain in pwMS, but impact on nonpharmacological intervention selection is unknown. Much of the research analyzed focuses on novel studies investigating various nonpharmacological modalities including physical interventions, mental and emotional cognitive strategies, and neuromodulation. Many of these nonpharmacological interventions show promise of analgesia for chronic MS-related pain but lack the large sample sizes and standardization necessary to generalize findings and make subsequent recommendations. Research into nonpharmacological MS-related pain treatment continues, and is currently investigating interventions like optimal psychotherapy techniques, on-demand MS programs, and telehealth group conferences.

Keywords: multiple sclerosis, chronic pain, pain management, neuropathic pain, non-pharmacological treatment

Statement of the Problem

Multiple sclerosis (MS) - the most common autoimmune, neurodegenerative disease - is associated with a cacophony of symptoms that can range from merely bothersome to debilitating for affected patients. Chronic pain is commonly present in patients with MS (pwMS) and can also be difficult to treat due to its heterogeneity and pathophysiology. This can appear in one of many isolated, overlapping, or concurrent phenotypes. Symptoms and named pain syndromes pwMS often suffer from include, but are not limited to, central or peripheral neuropathic pain, nociceptive pain, nociplastic pain, trigeminal neuralgia, migraine headaches, and chronic pelvic pain. Treatment of chronic pain - irrespective of the presence of MS - is notoriously difficult in and of itself. Medications often fail to provide adequate pain control and these agents are also associated with adverse effects. Additionally, potent pain medications have a well-known potential for abuse and misuse and are not appropriate for some patients Specifically for MS, the data is limited regarding treatment options, and pharmaceutical options and alternative modalities for treatment are often implemented despite disputed efficacy or unapproved status. Therefore, it is clinically relevant to research recent literature regarding what options, both pharmacologic and non-pharmacologic, are available for management and treatment of chronic pain in multiple sclerosis,

Research Question

For adults with multiple sclerosis, what non-pharmacological or alternative treatment modalities may be recommended for treatment of chronic pain of the lower extremities?

Methods

A comprehensive literature review was utilized to inform this research. PubMed electronic database was the primary location of the studies referenced in this research. Keyword

and mesh terms for multiple sclerosis, chronic pain and pain management were used in the initial search, but the results were too narrow, so pain management was removed to yield a broader spectrum of studies. Only journal articles within the last 5 years were considered which produced a total number of 174 entries. This search revealed many phenotypes of MS-related pain, to narrow the focus only studies considering general chronic pain or chronic lower extremity pain - regardless of origin- were considered. Similar searches in CINAHL and EMBase databases were also performed, and articles from "similar" were included when relevant, as well as dated studies that were directly referenced or reanalyzed in recent publications. To be included in this research, studies/metanalyses needed to specifically focus on prevalence or pathophysiology of chronic pain in MS or focus on non-pharmacological treatment of chronic pain in pwMS. Comprehensive reviews were also reviewed and included where relevant to inform background information for the research; the methods used produced a total of 24 studies and other references. Studies were excluded if irrelevant to the criteria above, if beyond the scope of this research, if not in the English language, if considering a remarkably small or inappropriate sample, and if not focusing on chronic pain in MS specifically.

Literature Review

A review of the literature has shown that chronic pain is commonly present in those with multiple sclerosis (MS), and there are many phenotypes into which this pain can fall. Although there are standard treatments used to treat chronic pain in persons with MS (pwMS), the heterogeneity and pathophysiology of this pain - as well as the disease itself - can render drug therapy inefficacious. Due to suboptimal pain treatment with pharmacologic agents, ongoing research continues to investigate the realm of alternative treatments for chronic pain in MS. Some alternative interventions considered include exercise, massage, psychosocial interventions,

and complementary and alternative medicine (CAM.) The data collected from this recent research has shown mixed results, but some interventions do show some promise of diminishing pain intensity in pwMS. For patients to receive the most benefit from analgesic modalities, clinicians must be willing to consider a multifaceted treatment approach that can include pharmacologic, nonpharmacologic, and CAM options.

Multiple sclerosis basics: clinical presentations, pathophysiology, pain, and clinical importance

MS is an autoimmune neurologic disease that occurs when neurons in the central nervous system (CNS) become demyelinated by a misaligned immune system, and subsequent plaques are created in the brain and/or spinal cord (Cree & Hauser, 2018). There are several mechanisms present, and the resulting neuroinflammation of this aberrant attack of the CNS chronically contributes to neuronal damage, neuronal death, and axonal degeneration. The neurologic pathology present in MS also produces many symptoms in varying degrees and frequencies in affected individuals. Most commonly, MS occurs in Caucasian individuals living in moderate geographical regions (i.e., Northern Hemispheric.) MS is significantly more prevalent among women compared to men, as three times more females than males are affected. The typical age of onset is between 20 and 40 years of age, although the disease can be present throughout the life span, as MS has been diagnosed in children younger than 10 years old, according to Cree & Hauser.

According to Cree & Hauser (2018), the disease course of MS is very diverse, although affected individuals typically fall into one of three common classifications. The first and most severe form of MS is primary progressive MS (PPMS), which is a devastating diagnosis. After symptom onset, persons with PPMS have constant symptoms - with no reprieve - that gradually

worsen over time, typically leading to disability earlier in the disease course than other types of MS. PPMS is the least common type of MS. Interestingly, this form of MS has a later age of typical onset, with the mean being around 40 years of age, and men and women are affected almost equally.

The second and most common classification of MS, relapsing-remitting MS (RMS), is characterized by episodic presence of MS symptoms, with periods of normalcy between attacks. There is definite diversity within the subcategory of RMS; the episodes of symptoms (flares) may remain consistent in quality and/or quantity, increase in frequency, or even persist, with the relapses ceasing altogether. In cases where the relapses cease altogether, RMS then becomes the third and final classification of MS, secondary progressive MS (SPMS). Of individuals with RMS, about 2% of the population progress to SPMS per year. Following the onset of SPMS, it is virtually indistinguishable from PPMS, as eventually SPMS also causes significant fixed neurological deterioration in affected individuals (Cree & Hauser, 2018).

The most common symptoms present in MS include but are not limited to sensory symptoms (paresthesias, hypesthesia, pressure, pain,) optic neuritis, weakness, spasticity, ataxia, heat sensitivity, bladder dysfunction, Lhermitte's symptom, and depression. Of note, pain is present in >50% of MS patients, can be present in any location and it is not uncommon to change over time. The CNS lesions that are characteristic of MS form in different locations at different times (seen on MRI, a necessary diagnostic criterion) which partially explains the heterogenic presentation of the disease (Cree & Hauser, 2018).

Although chronic pain is a common and often debilitating symptom of MS, much about its pathophysiology is unknown. Due to the pervasive nature and difficulty treating chronic pain in pwMS, this is an active area of research. Recent advances in medical technology have made

specific neuroimaging possible. Plantone et al. (2021) investigated whether location of MS-caused brain lesions is correlated to presence or absence of chronic pain in individuals with this disease. This was accomplished by analyzing brain magnetic resonance imaging (MRIs) of 208 pwMS - both with pain, (PAIN+), and without pain, (PAIN-). Each demyelinating lesion found in the 208 brain MRIs was measured using volume and mapped according to voxel-based lesion symptom mapping (VLSM.)

Plantone et al. (2021) found no significant difference in the number ($p=0.086$) or volume ($p=0.064$) of lesions present in the PAIN+ group compared to the PAIN- group. However, when using VLSM analysis (explanation of this technique is outside the scope of this research) location of the lesions was significantly correlated to the presence or absence of pain. Patients without chronic pain more frequently had lesions in the right dorsolateral prefrontal area versus patients that did experience chronic MS-related pain more frequently had lesions (bilaterally) in the periventricular posterior area ($p <0.05$).When considering the function of lesion location, neuronal loss in the right dorsolateral prefrontal area may induce hypoalgesia while loss of neurons secondary to posterior periventricular lesions may interrupt pain processing pathways, leading to a disconnection syndrome and therefore chronic hyperalgesia.

The demonstrated correlation between plaque distribution and presence/absence of chronic pain in MS suggests that location of lesions may be partially responsible for diversity of this symptom. Furthermore, this information may help advance pathophysiologic knowledge of chronic pain in pwMS, and subsequently treatment: only 26.1% of individuals in the PAIN+ group reported using pain treatment (Plantone et al., 2021). A primary strength of this study is its relatively large sample size. However, the authors do note two primary limitations. First, MRIs included in the study were obtained by two different machines, although $p >0.1$ when

considering difference in image acquisition in PAIN+ and PAIN- groups. Second, this study lacked MRIs evaluation of to evaluate spinal cord lesions, which also could contribute to presence/absence of pain. Further research evaluating spinal lesions' locations and correlation to symptoms will deepen understanding of MS-related chronic pain.

As mentioned above, the disease course and symptoms commonly change over time in pwMS. Young et al. (2017) longitudinally analyzed the prevalence and course of chronic pain – present daily for > 3 months - in adults with MS, completed over a 10-year span. The participants (n = 70) had previously completed a 7-year longitudinal study, which researchers extended an additional three years to further investigate long-term changes and effects of chronic pain in MS. At the endpoint of this study, the average disease duration was 19.5 years. Although ~25.2 % of participants had RMS at the 7-year follow up, all patients in this category that continued to participate experienced progression to SPMS by the 10- year follow up, which highlights the nature of chronic MS as disease the intensifies over time. There was no change in number of individuals with PPMS from the baseline to 10-year follow up assessment (n = 9) (Young et al., 2017).

Like MS disease categorization, there were also evident changes among pain phenotypes and quality over the 10-year course. Throughout the study, dysesthetic pain (neuropathic pain that is central in origin) remained similar in prevalence. Nociceptive pain greatly increased with length of disease initially, then leveled off between 7 and 10 years (6.6% at baseline, 87.8% at 7-year follow-up, and 85.7% at 10-year follow up) (Young et al., 2017). When the visual analog scale (VAS) was used to track pain progression over the 10-year course there were no statistically significant changes in intensity. However, when participants categorized their pain based on intensity, pain did trend towards increasing severity as length of disease was prolonged:

at baseline only 13.1 % of participants rated their pain as severe or greater (very severe, worst pain possible) compared to 27 % and 35.9% at 7-year and 10-year follow ups, respectively. In this way, changes to pain intensity were different when considering different subjective measures of pain. Bilateral lower extremity was the most common location for pain throughout the study, from baseline to 10-year follow-up.

Chronic pain in pwMS is not limited to physical symptoms alone, as it also has substantial effects on the personal and social lives of those who suffer from this ailment. Gromisch et al. (2020) recruited 161 individuals with MS to a cross sectional study measuring illness intrusiveness and activity engagement, measured by electronic surveys. This was assessed through a modified (and therefore unvalidated) Illness Intrusiveness Rating Scale. The demographic makeup of the participants mirrored the epidemiological distribution of MS prevalence. Correlation analyses showed that pain negatively impacts activities away from home, social activities, and household chores ($r = -0.37$, $r = -0.26$, and $r = -0.16$ and $p < 0.001$, $p = 0.001$, and $p < 0.05$, respectively) in pwMS. When confounding factors (disability and depression symptoms) were controlled for using mediation analyses, only activities away from home were significantly impacted by pain. In this case, pain-related illness intrusiveness was directly correlated ($b = -0.03$, $p < 0.001$,) to reduced activities outside of the home.

Gromisch et al. further investigated the relationship between pain presence and reduced household chores by considering the mediatory of effects of two factors - emotional/cognitive strategies, and support from family and friends. Mediation analyses showed that emotional cognitive strategies did have a significant indirect effect ($b = - 0.01$, $p = 0.045$, 95% CI [-0.015, -0.001]) on activities away from home, although relatively small ($R^2_{med}=0.07$) and family/friend support did not have a significant impact ($b =0.01$, $p=0.084$, 95% CI [-0.014,0.000]) (Gromisch

et al., 2020). Therefore, it can be concluded from this study that cognitive strategies for pain management are associated with positive impacts on activities away from home in pwMS.

It is important to consider measures - such as cognitive strategies - that diminish pain interference in pwMS, as unmediated and untreated pain does decrease quality of life over time. Young et al. (2017) found that over a 10-year span many quality-of-life measures were remarkably impacted by MS, including illness ($p = .001$), social relationships ($p = .001$), independent living ($p < 0.001$) and physical senses ($p < 0.001$). The deterioration of these domains leads to pain-related disability and decreased capacity for independence. As MS progresses, the disease commonly necessitates a need for a full-time caregiver or altered living arrangements. Despite decreased subjective quality of life measures, the mental health of the participants in the Young et al. study did not show a significant change, which may indicate adaption to factors and circumstances associated with the course of MS (Young et. al 2017).

Given that MS is neurologic disease with pervasive effects, it would seem logical that the responsibility of care for those with this condition be largely left to specialists. This may, in part, be true - 63.9% of Medicare visits with the primary complaint related to MS were indeed performed by neurologists in 2015 (Lin et al., 2021). Certainly, neurologists are paramount in the diagnosis, treatment, and management of MS, but still over one-fourth (26.2%) of MS-related visits are with primary care providers (PCPs) (Lin et al.). Here, the number of MS-related visits to PCPs may be underestimated; When Lin et al. performed the analysis of this data, only office visits by Medicare beneficiaries were considered, so those pwMS not at a disease state leading to pervasive disability (i.e., more likely to maintain employment and private insurance) were not included. Furthermore, only office visits with an MS-related primary diagnosis (based on ICD-10 codes) were considered, so if an individual presented for another reason and neurologic

issues/treatments were addressed in addition the primary concern, these would not be included. This would mostly likely impact neurological visits with PCPs – common sense would suggest that a general practitioner would be more likely than a neurologist to address another concern (cardiovascular, psychological, etc.) and address neurologic complaints secondarily. In Young et al.'s longitudinal study of MS patients (2017), while utilization of health professionals, both neurologists and general practitioners increased with length of disease, as disease progressed pwMS visited PCPs in equal proportions to neurologists. This reinforces the need for general practitioners to be informed, prepared, and equipped to care for ailments of pwMS related to both general/other health as well as neurologic complaints.

Symptoms of MS- including pain- are treated based on the needs of each specific person; according to Cree & Hauser (2018) analgesia is attempted with many different agents. Pharmaceutical pain control attempts often include antiseizure medications (carbamazepine, phenytoin, etc.) gabapentinoids, antidepressants (amitriptyline, desipramine or venlafaxine) or antiarrhythmics (mexiletine) (Cree & Hauser, 2018). As length of disease extends, utilization of analgesics for MS-related pain increases and tends to become more potent, although non-opioid analgesics are the most used pharmaceutical vehicles for pain treatment regardless of severity (Young et al, 2017). In the 10-year longitudinal study by Young et al., utilization of opioids, muscle relaxers/anticonvulsants, and antidepressants/anxiolytics all increased, while use of non-steroidal anti-inflammatory drugs (NSAIDS) decreased. As medication often fails to adequately control pain in pwMS, nonpharmacologic avenues are often considered. The most common non-pharmacologic method of pain management is physical/electrical stimulation (Young et al., 2017). When typical approaches for pain treatment fail, the individual should be evaluated by a professional specializing in pain management (Cree & Hauser) although few pwMS utilize pain

or rehabilitation specialists for various reasons (Young et al.). Both pharmaceutical and non-pharmacologic methods of analgesia in persons with MS (pwMS) will be discussed in further detail in subsequent sections of this review.

Overview of Current Treatment Options

In order to understand the necessity of research into nonpharmacological pain treatment in MS, it is important to analyze previously published data regarding common medication-based approaches for analgesia in pwMS. It is relevant to mention that treatment of acute flares is typically accomplished with corticosteroids, and prevention of disease progression/disease modification is with immunosuppressive and immunomodulatory medications (Cree & Hauser, 2018). However, specific discussion of these topics is outside the scope of this research which is focused on analgesic interventions.

Duffy et al. (2018) published a comprehensive review regarding management of neuropathic pain (NP) in pwMS, as this is a commonly reported phenotype of chronic pain in this population. A defined understanding of NP is essential to achieving clarity and differentiation from other types of pain. Duffy et al. (2018) highlight the difference between nociceptive pain and NP in pwMS, stating “nociceptive pain arises from actual or potential damage to non-neural tissue” and whereas NP is “a direct consequence of a lesion or disease affecting the somatosensory system” (Duffy et al., 2018, p.107). Furthermore, NP has many different phenotypes and can originate either centrally (diffuse pain in legs, i.e dysesthetic pain) or from stimuli that activate peripheral chemoreceptors or mechanoreceptors. In pwMS, NP commonly presents following immobilization or spasticity that occurs later in the disease course. Of all NP presentations, dysesthetic extremity pain is the most common and has been estimated to affect about 26% of individuals with MS (Duffy et al.).

NP can occur with various conditions, just one of which is MS. Analgesics for pain in pwMS are often selected based on the commonly used medications for general NP, so Szok et al. (2019) compiled treatment recommendations for general NP that is not specific to pwMS. For all NP subtypes, encompassing first-line medication options are the tricyclic antidepressant (TCA) amitriptyline (strong recommendation, moderate quality evidence), gabapentinoids (strong recommendation, high quality evidence) and serotonin-norepinephrine reuptake inhibitor (SNRI) medications venlafaxine and duloxetine (strong recommendation, high quality evidence) (Szok et al., 2019). Second-line drugs for all NP subtypes include the opioid analgesics tramadol and tapentadol (weak recommendation, moderate quality evidence.) Topical agents such as lidocaine (weak recommendation, low quality evidence) or capsaicin (weak recommendation, high quality of evidence) are second-line medications for NP that is peripheral in origin. Third line drug treatment options for all NP subtypes include strong opioids morphine and oxycodone (weak recommendation, moderate quality of evidence). Again for only NP that originates peripherally, botulinum-A neurotoxin injections are also (weak recommendation, low quality of evidence) third-line options. Cannabinoids are neither recommended nor encouraged for any type of NP, but it is noted that oromucosal formulations may be beneficial in pwMS that have central NP. Other non-pharmacological interventions for drug-refractory NP are extensive and mostly consist of inconclusive evidence or weak recommendation in specific subtypes of NP; the exception to this statement is exercise training, which has shown beneficial analgesia (Szok et al. 2019).

As many of the mechanisms for chronic pain in pwMS are poorly understood, there have been very few large scale double-blind randomized controlled trials (RCTs,) so much of current treatment for this population is based off recommendations for other chronic pain conditions or provider preference (Duffy et al. 2018) as discussed above. In fact, there are no specific

guidelines for medication selection and initiation for chronic pain in pwMS. Commonly used agents include TCAs, gabapentinoids, and SNRIS (Szok et al., 2019) which mirror the typical agents selected first-line for general NP. Tetrahydrocannabinol: cannabidiol (THC: CBD) formulations have shown some benefit in providing analgesia for MS patients suffering from chronic central NP pain, but use of these agents remains questionable secondary to mixed study results and adverse effects (Szok et al.). Without MS-specific pain treatment guidelines recommendations, decisions based on evidence are lacking which ultimately may come at the cost of the patient.

Despite lack of specific guidelines, the consensus is that neuropathic pain in MS is usually treated with antidepressant (amitriptyline, duloxetine, venlafaxine) and/or anticonvulsant medications (carbamazepine, topiramate) (Duffy et al., 2018) which is consistent with reccommendations for general NP (Szok et al., 2019.) Duffy et al. (2018) summarize the findings of all published studies on pharmacological interventions for NP in pwMS. For each agent there are three or fewer studies, each with a small sample size, so data is overall limited. When considering NP in pwMS that affects lower extremities or is central in origin, the efficacy and support for the following drugs were analyzed (dosage not discussed here, many values reported.): duloxetine (SNRI, 2 studies) showed significant pain reduction (>30%) compared to placebo; topiramate (anticonvulsant, 1 study) showed significant VAS improvement in 75% of patients; levetiracetam (anticonvulsant, 2 studies) produced mixed results, with one study showing significant VAS improvement in treatment compared to placebo groups and the other study showing subgroups but not all groups with improvement compared to placebo; lamotrigine (anticonvulsant, 1 study) produced no significant reduction in central NP; gabapentin (gabapentinoid, 1 study) showed profound or moderate relief of mixed pain; pregabalin

(gabapentinoid, 1 study) showed improvement in paroxysmal pain in some patients; morphine (opioid analgesic, 1 study) showed reduction of pain in 28% of patients; THC:CBD oromucosal spray (cannabinoid, 3 studies) showed no significant reduction in VAS scores when compared to placebo for NP, and mixed results for central NP- one study demonstrated significant pain relief and one study showed statistically significant pain relief but a remarkable placebo effect; dronabinol (cannabinoid, 1 study) demonstrated modest efficacy for pain treatment, though clinically significant. For all pharmaceutical agents discussed here, one or more studies exhibited participant withdrawal from the trial secondary to significant adverse effects, which varied depending on class of medication. The exception to this statement is lamotrigine, which had no withdrawal from its study due to adverse effects, but recall was not efficacious in treatment of pain in this population (Duffy et al.).

Certainly, based on lack of standardized results and small sample sizes,it can be concluded that there is little to no high-quality evidence evaluating the treatment efficacy of analgesics on chronic pain in pwMS. Overall, the evidence that Duffy et al. (2018) compiled showed that pharmacological interventions such as antidepressants and anticonvulsants are first line for treatment of chronic NP in pwMS, but these medications fail to consistently provide sufficient analgesia. Therefore, alternative therapies have been considered to assist in treatment of NP in pwMS. The focus of this research is to evaluate recent studies regarding non-pharmacological and alternative methods for chronic pain in pwMS, but for context and comparison it is relevant to review previously published literature of these modalities.

Amatya et al. (2018) performed a meta-analysis evaluating the safety and efficacy of non-pharmacological interventions for chronic pain in pwMS. This meta-analysis considered studies published in the Cochrane MS Group Trials Register prior to 2017. All RCTs, cross-over studies,

and clinical controlled trials regarding non-pharmacological therapies for treatment of pain in pwMS were eligible, but only when an intervention was compared against a sham (control) group. Ten total studies met the inclusion criteria which comprised a total number of 565 participants. Several studies considering different modalities (bulleted below) for chronic pain treatment in MS were evaluated for their efficacy in pain intensity reduction, which was assessed using the VAS and McGill Pain Questionnaire (MPQ). Transcutaneous electrical nerve stimulation (TENS,) was also evaluated by this meta-analysis, but data was not appropriate for this research based on outcome measures.

- Hydrotherapy/ Ai Chi (1 RCT, n= 73): One qualifying study demonstrated significant change in musculoskeletal pain (both MPQ and VAS improved) in pwMS after 20 weeks of treatment in experimental group, but no significant pain reduction in control group.
- Transcranial direct current stimulation (tDCS) (2 RCT, n = 35): One study showed significant decrease in VAS following treatment, but no decrease after sham treatment in control group; The second study demonstrated significant time effect for decreased pain on VAS, suggesting that the intervention was not the driver of reduced pain (as opposed to time x treatment effect, which indicates that the intervention is a significant factor in reducing pain). Therefore, mixed results were reported regarding tDCS.
- Transcranial random noise stimulation (tRNS) (1 RCT, n =16): The sole study evaluated showed no significant changes to VAS pre-and post-treatment between experimental and control groups.

- Telephone-delivered education (1RCT, n =163): One study included showed statistically significant reduction in pain, although this was a secondary measure of the study.
- Hypnosis (1 RCT, n= 22): Compared to control (relaxation) group, individuals participating in self-hypnosis for the management of chronic pain in MS showed statistically significant decrease in average pain intensity on a numeric scale.
- Neurofeedback (1 RCT, n=20): This study showed that both control and treatment groups had improvement in pain intensity both after intervention and 1-month post-intervention, but pain reduction was not significant.
- Reflexology (2 RCT, n = 110): One study included in the evaluation of this modality showed that VAS had statistically significant improvement following 10 weeks of reflexology treatment, but the sham/control group also had statistically significant improvement. There was no significant difference between the groups. Similar to tDCS, this indicates that for this study there was a strong time effect, rather than time x treatment effect. The second study also showed reduction in VAS scores - from 2 months to baseline - in both control and treatment groups. Again, mixed results considering reflexology were reported.

In summary, the data from this study endorse hydrotherapy, telephone-based education, and tDCS as having the potential for significant pain reduction based on published research, although tDCS studies showed mixed results. A significant time effect (aka placebo effect, or effects not produced directly via intervention) emerged in studies of neurofeedback, tDCS and reflexology, indicating that there was no significant difference in pain reduction prior to and after utilization of the non-pharmacological intervention. Finally, tRNS showed no improvement in

either the experimental or sham groups, which point to ineffectiveness of pain reduction for this modality (Amatya et al., 2018).

Although many of the studies showed some improvement or statistically significant improvement in pain intensity or frequency, the authors (Amatya et al.) felt that each of the non-pharmacological interventions for chronic pain - regardless of treatment efficacy - should be given an evidence-based rating as "very low" due to a high risk of bias in available data; for each of the interventions, only 1-2 qualifying studies were available with small sample sizes throughout and contain various errors in study methodology. There are also many other non-pharmacological interventions that have been utilized for the treatment of chronic pain in MS that did not meet the inclusion criteria for this meta-analysis, such as yoga and massage therapy. Considering that some interventions were excluded and the studies that were included displayed broad heterogeneity, a complete recommendation for or against non-pharmacological interventions to treat chronic pain in MS cannot be made based on this meta-analysis. However, the conclusion can be made that there is very little high-quality published data regarding the topic, which will need to be addressed in the future to inform evidence-based medicine.

Szok et al. (2019) also reviewed non-pharmacological therapeutic approaches for both peripheral and central NP in pwMS and reported similar findings to Amatya et al. Szok et al. also mention additional other neuromodulatory interventions [intrathecal muscle relaxants, electrical stimulation (not limited to tDCS), deep brain stimulation (DBS) and spinal cord stimulators (SCS)] with evidence of pain reduction (Szok et al., 2019). The final intervention addressed, SCS, was not included in previous meta-analyses, perhaps in part due to its somewhat controversial nature.

Although invasive and certainly not a first-line treatment option for pain, SCS have been utilized in the past for treatment of resistant chronic pain, including in pwMS. SCS work by sending electrical impulses to the spinal cord that interfere with pain transmission; if patients are candidates for this intervention, it is accomplished in two steps: firstly, a trial device is placed. If this trial succeeds (>50% pain reduction,) a permanent device is placed (Sivanesan, n.d.).

In the past, the utilization of SCS in MS was lacking due to MRI incompatibility. MRIs are frequently needed in pwMS to monitor disease activity and efficacy of disease modifying treatment. Previous models of SCS were incompatible with magnetic MRI machines, which rendered the intervention less than optimal in treatment of pain, as monitoring could no longer be completed. In recent years, MRI-compatible SCS have become available, and are now an option for treatment of intractable chronic pain in certain pwMS. Since this intervention is newer in regard to pwMS, there is little research specific to SCS in MS.

Provenzano et al. (2016) published a comprehensive literature review of all published studies, though limited as mentioned above, evaluating SCS efficacy specifically in pwMS. A case report was also included but is not discussed within this research due to lack of validated data. Thirty-three studies (496 trialed patients, n = 744 implanted patients) were included in the review, 64% of which showed author-defined success rate and 42% which demonstrated success in more than half of study population. Thirty-six percent (12) of the articles – including 137 trialed and 381 implanted patients - evaluated reported complications (n= 88.) The most common complications were lead fracture/dislocation and infection (Provenzano et al., 2016). There are limitations to the findings of Provenzano et al.'s review for several reasons - the studies included lacked statistical analyses for significance of pain reduction following treatment, and there was no standardization of measures or results which makes inter-study comparison and compilation

of data unreliable. Finally, there was no placebo in any of the studies, as this would be unethical given invasive nature of the intervention.

New research: nonpharmacological and alternative treatment for MS-related chronic pain and chronic pain phenotypes

It has been established that for chronic pain in pwMS, common pharmacotherapy lacks consistent treatment efficacy. Furthermore, previously published reviews of nonpharmacological treatment options have not identified modalities that cannot be strongly recommended as providing significant analgesia. Therefore, it is important to evaluate and discuss findings of new research regarding nonpharmacological pain treatment in pwMS; thankfully there is adequate content to include in this research including physical interventions, behavioral interventions, and improved pain classification and stratification that could impact future treatment strategies.

In a recently published meta-analysis and systematic review, Salarvand et al. (2021) investigated the efficacy of a commonly utilized CAM modality, massage therapy (MT), for which previous compiled data was lacking. MT is defined as treatment administered through physical manipulation of the body, by touch and/or pressure. Only studies and RCTs comparing a treatment group against a control group were considered, which produced to total of 10 studies. However, only four studies evaluated pain as a primary or secondary outcome, so overall sample size of the desired meta-analysis metric was very small (n=67.) Additionally, the parameters of each study were markedly different; massage types included in the four considered studies include standard MT, Swedish massage, reflexology, and sham-reflexology. Duration and frequency of treatment also varied, further complicating ability to standardize and generalize findings. Pain was assessed using three different measures across the three studies (VAS, Pain Effects Scale, Numeric Rating Scale (NRS.)

Three of the four studies showed significant ($p < 0.05$) reduction in pain severity, two of which were able to demonstrate a significant difference between experimental and control groups ($p < .01$, $p < -.001$ respectively) (Salarvand et al., 2021). Findings of this meta-analysis may suggest that MT is helpful in treatment of chronic pain in pwMS, but the overall heterogeneity of included studies limits the ability to accurately assess efficacy of either MT generally or subcategories of this intervention. The diversity of the studies also renders it unreasonable to make recommendations for or against treatment of chronic pain in pwMS based on the compiled results. Lack of adverse events reported in the studies is helpful, however, as it suggests that this intervention is safe. Although unproven, MT will likely not cause any harm to patients who wish to pursue MT for treatment of their pain.

Exercise has also been recently investigated as a potentially helpful intervention for pain in pwMS, and like MT, results are difficult to analyze secondary to study heterogeneity. A systematic review and meta-analysis of 10 RCTs (n=389) (Demaneuf et al., 2019) evaluated exercise as an intervention (vs passive control groups) for chronic pain in pwMS. The 10 evaluated studies used various validated tools to measure pain severity, so standardized mean difference (SMD) was calculated for each study to aid in comparison. The meta-analysis found that when compared to the passive control group, pain intensity was lower in the exercise group (SMD = -.46) however these results would not generally be considered as significant due to a 95% confidence interval (CI) that includes 0. Each of the 10 studies was deemed high-risk for presence of bias based on the Cochrane risk of bias tool, and heterogeneity among studies was significant (I^2=77%.) Together these factors limit the usefulness of this information which the authors recognized and subsequently advised caution in interpretation of results.

Somatic stimulation is not the only intervention that has been evaluated for efficacy of chronic pain relief in pwMS. An alternative therapy that stimulates the CNS tissue, tDCS, has also been recently investigated. This technique is a nonpharmacological modality that uses scalp electrodes to continuously stimulate the nervous system with low-intensity electricity and is thought to modify the activity of neurons associated with pain perception and processing (Young et al., 2020). Young et al. performed a single-blind RCT comparing a 5-day course of tDCS to placebo in treatment of chronic central pain in MS. Pain scores in pwMS had previously been shown to decrease with tDCS, but under different treatment conditions. The total number of study participants was 30, half being treated with the intervention and half with a sham intervention. The primary outcome of the study was to determine if tDCS would significantly decrease the VAS in pwMS with chronic pain – this survey was completed at baseline (T0), before and after each tDCS treatment session, and at 4-week follow-up (T1). Another pain questionnaire, the Neuropathic Pain Scale (NPS), was evaluated at the same intervals as a secondary outcome of the study. This study tested a new protocol consisting of 5 consecutive days of a 10-minute 2-mA stimulation period followed by 25-minute break, then an additional 10-minute stimulation period.

Statistical analyses assessed the effect of tDCS on VAS and NPS. The results showed that 5 days of tDCS treatment was more effective at decreasing VAS than placebo ($p = 0$) starting at day 4 and continuing through two weeks after final treatment ($p = 0.01$). At T1 the differences in mean VAS between treatment and sham groups did not remain significant, but the reduction in VAS remained significant within the treatment group ($p = 0.001$). NPS showed no significant difference between T0 and T1 in treatment or sham groups. Preliminary results, as discussed by the authors, indicate that a 5-day regimen of tDCS may be effective in reduction of chronic

central neuropathic pain in pwMS. However, a larger sample size and repeat studies would need to be completed prior to recommending tDCS as a preferred option for pain treatment in this population. At this point it would not be warranted due to being the lone study evaluating this protocol. Additionally, it is unknown if repeat tDCS would extend the length of benefit for the intervention, which is pertinent to the long-term feasibility of use for chronic pain treatment. No concerning adverse effects occurred during this study, which is promising; if further research corroborates the potential success found in this trial, it could be a noninvasive and effective method for chronic pain treatment in pwMS (Young et al., 2020).

Like tDCS, previous research has shown self-hypnosis training to be safe and effective in chronic pain management - including in pwMS. This method is recommended by some experts as a first-line treatment for chronic pain, though this is debated due to mixed results and barriers to treatment that are often in present (Jensen et al., 2016). Jensen et al. investigated whether neurofeedback [biofeedback optimization of theta brain waves through use of an electroencephalogram (EEG)] can provide improved pain relief by increasing response to hypnosis. The study population (n =20) was comprised of otherwise-healthy adults with MS experiencing daily, chronic (> 6 months) pain ≥4 on a scale of 1-10, and demographic composition like prevalence of pwMS (primarily highly educated Caucasian females with RMS.) All participants in this proof of principle study received one face-to face and four prerecorded self-hypnosis training sessions. Prior to the prerecorded sessions, individuals received either 20 minutes of neurofeedback training (NF-HYP, n =10) or 20 minutes of relaxation techniques (RLX-HYP, n = 10.) The NRS was utilized to quantify the amount of hypnotic analgesia provided by the treatment. The NRS was assessed at baseline, prior to and following each hypnosis session, and one month following final treatment.

The findings of Jensen et al. (2016) demonstrated a large time interaction effect for average pain intensity following completion of the final treatment session. However, a medium Time x Treatment interaction effect also emerged for each condition (NYF-HYP and RLX-HYP), respectively. Given the proof of principle design, statistical significance cannot be interpreted, only interaction effects. This study did provide some very weak evidence that neurofeedback may be able to enhance hypnotic analgesia. Based on the sample size and evidence of large time interaction effect, it would be unwise to grant any significant weight to these findings in the absence of a larger-scale study including a passive control group. The authors state that the findings of this study support the hypothesis of increased hypnotic analgesia with the use of neurofeedback, as "the medium interaction effect [for Time x Treatment Condition] … can be explained by the large pre-to posttreatment and pretreatment to 1-month follow-up decreases in average pain intensity" (Jensen et al. , 2016, p. 12) when comparing participants in the NF-HYP and RLX-HYP groups. The Time x Treatment condition interaction was maintained at the one-month follow up (Jensen et al., 2016).

In a subsequent 2018 study, Jensen et al. further investigated the enhancement of hypnotic analgesia preceded by NF in treating chronic pain in pwMS, with an improved model. The demographic population of the follow-up study was like the initial study, but a control group was included. An additional pre-hypnosis treatment - which has also been postulated to slow brain activity by increasing theta waves - was also assessed for enhancement of hypnotic analgesia: mindfulness meditation (MM.) Rather than physical/external stimulation, mindfulness aims to redirect brain activity from pain activity using disengagement (Jensen et al., 2018).

Thirty-two participants were randomly assigned to one of three treatment groups: MM, NF or control. The pre-treatment conditions in this study were delivered as three consecutive weeks of twice-weekly NF, twice weekly MM, or a waiting period. The three weeks of pre-treatment were followed by one in-person self-hypnosis training session, and finally four audiotape-delivered self-hypnosis sessions (NF-HYP, MM-HYP, AND HYP-ONLY, respectively.) The NF-HYP and MM-HYP groups also received their respective enhancing treatments prior to each self-hypnosis session (Jensen et al, 2018). Outcome data were assessed at baseline, prior to initial hypnosis treatment, after final hypnosis treatment, and 1 month following final hypnosis treatment.

The results of statistical analyses (repeated two-way ANOVA test) showed that a large time effect was present when considering the primary outcome of average pain intensity measured by the NRS. This means that regardless of treatment group, pain did decrease as time progressed. Secondarily, a large Time x Treatment condition interaction effect was also revealed: the interaction was largest for the NF-HYP group, followed by the MM-HYP condition, and finally the HYP-ONLY group. These results suggest that all interventions do decrease pain over time (hypnosis alone OR with one of the two adjunct treatments) but efficacy is highest when hypnosis is preceded by neurofeedback or mindfulness mediation (Jensen et al., 2018).

Again, like the 2016 Jensen et al. study, the sample size and pilot design of Jensen et al. (2018) prevent the ability to determine statistical significance for any measures assessed in this RCT. However, the authors noted that the purpose of this study was to support or refute the appropriateness of future research into these enhancements for use with hypnotic algesia (Jensen et al., 2018). The improved study design enabled more accurate measurement of effectiveness of hypnotic analgesia pre-treatments, as the inclusion of a control group with a waiting period

allowed adjustment for main time effect. Therefore, the promising results of pain reduction in this study are encouraging. EEGs were used in this study to objectively measure alteration of brain wave oscillation frequencies per treatment and condition. Interestingly, although each condition did produce different frequencies of brain waves, the results were not consistent with the hypothesis, indicating that brain waves alone are not responsible for the enhancement of hypnotic analgesia with use of NF and MM. Complete discussion of this topic falls outside the scope of this research (Jensen et al., 2018).

MM is not the only cognitive intervention that has been investigated as a potential intervention for pain management in pwMS. Additional research has considered the possibility of other mental strategies as being helpful in relieving chronic pain. Senders et al. (2018) utilized a cross-sectional survey to examine the relationship between pain presence and mindfulness in pwMS. The survey population was comprised of 132 individuals of various demographics, paralleling usual disease distribution. The results of this survey demonstrated a significant ($p < 0.0001$) association ($t = -5.52$) between pain and mindfulness when the model is adjusted for possible confounding factors (age and MS type.) The R^2 value of this model is 0.26, indicating that up to 26% of variability in pain can be explained by the variables or mindfulness, age, and MS type. The significant results unveiled in this study support appropriateness of further research in this topic, as they suggest mindfulness (which requires trained techniques) may be a feasible moderator for chronic pain in MS (Senders et al., 2018). This is consistent with the findings of Gromisch et al. (2020), who determined that cognitive strategies mediate illness intrusiveness in pwMS when considering reduced activities away from home.

Ehde et al. (2015) evaluated the efficacy of emotional/cognitive strategies delivered by telephone self-management on chronic pain reduction in pwMS, as well as other variables. This

study was originally excluded from this research due to publication year, but a subsequent analysis (Ehde, Arewasikporn, et al., 2018) met inclusion criteria, so it is necessary to include for discussion. The design of the trial was single-blind, randomized, and evaluated a telephone self-management intervention (T-SM, n = 75) compared to a telephone-delivered MS education intervention (T-ED, n = 88.) The interventions were delivered once weekly for a period of eight consecutive weeks. The topics included in the T-SM sessions were introduction to self-management, goal setting and identifying stressors, problem solving and relaxation, energy management, working with thoughts, managing emotions, and building resilience in weeks one through eight, respectively. There were two consecutive weeks based on working with thoughts. In the same manner, educational content in weeks one through eight in the parallel T-ED included introduction and overview of MS, fatigue, pain, mood, sleep, nutrition and activity, communication and health care relationships, and social support. For both T-ED and T-SM, homework was assigned weekly and follow–up phone calls were made four and eight weeks after eighth treatment session (Ehde et al., 2015).

Study population (n= 163) was diverse, including adults across the United States that experienced moderate depression, fatigue, and/or pain secondary to an MS diagnosis. Three-quarters of participants qualifying for study met criteria for two primary outcome measures, and 68% met criteria for all three symptoms. When examining the characteristic makeup between groups, there were no significant differences in age, race, sex, education, income, marital status, location, MS type, disability, depression, years since diagnosis, or presence of fatigue, pain or depression. There was a significant difference between groups in employment and level of depression. More participants in the T-ED group worked < 20h/w ($p = 0.026$) and more participants in T-ED also had a higher level of depression based on the Patient Health

Questionnaire – 9 (PHQ-9, p=0.022). These variables were controlled for when performing statistical analyses. Outcome measures were assessed at baseline prior to randomization, following the treatment course, and at 6 and 12 months after baseline to assess the long-term effects. Only change in pain, assessed by the NRS, will be discussed in detail here (Ehde et al., 2015).

Both T-ED and T-SM experienced withdrawal from study for various reasons, but retention rate remained >80% for both groups. More than 90% of total participants received at least the minimally effective dose of four sessions. There was a difference between T-SM and T-ED distribution for this statistic, but it was not significant ($p = 0.52$). The median number of sessions received was not significantly different between groups ($p > 0.05$). More time was spent in T-SM treatment (mean 61.5 min) than T-ED treatment (mean 45.8 min) sessions ($p < 0.001$) (Ehde et al., 2015).

Results of the study showed that following treatment, both T-SM (58%) and T-ED (46%) groups improved ≥ 50% in ≥ 1 measured symptom, though the difference between groups was not statistically significant ($p = 0.238$). Insignificance remained at 6 and 12-month follow-up surveys. Within each group, significant reduction in pain interference (≥30% improvement) was demonstrated post-treatment and was maintained with long-term follow-up. T-SM members did also report a greater positive affect ($p < 0.05$) at post-treatment than T-ED members, which was retained through 6-month follow up but not at 12-month follow up. The authors report that these results were contrary to their hypothesis; they predicted T-SM would show superior results to T-ED. Nonetheless, findings suggest multiple approaches for telephone self-management can help improve symptoms of MS. This study lacked comparison of commonalities between treatment interventions, those of which could partially explain the similar efficacy of T-ED and T-SM.

Additionally, the baseline qualities of participants could influence the results; it does take a certain kind of existing resilience to be willing/able to complete this intensive treatment for research, and high treatment response in both interventions could be secondary to the characteristics of individuals participating on a voluntary basis. Analysis of secondary outcomes did suggest that T-SM is favorable to T-ED in some ways. No adverse events were reported in this study (Ehde et al., 2015).

The secondary analysis of this study (Ehde, Arewasikporn, et al., 2018) evaluated factors that could have potentially moderated treatment effects including demographic information, clinical characteristics, symptoms, baseline levels of treatment outcomes and cognitive behavioral factors. Moderation analyses were completing using separate regression models and found that baseline patient activation - a cognitive behavioral factor, described as "an individual's knowledge, confidence, and skills for managing their health and health care" (Ehde, Arewasikporn, et al., 2018, p. 1269) - interacts with treatment group to predict change in fatigue following treatment (b = -1.022, p = .049). More specifically, patients exhibiting high levels of patient activation at baseline were more likely to experience decreased impact of fatigue when receiving T-SM vs T-ED (b= -7.415, p = .019) and patients with low levels of patient activation prior to treatment had no significant difference whether they were in the T-SM or T-ED groups (b = 1.932, p = .566). Despite the identification if moderators of treatment effects regarding fatigue, no significant moderators were found when considering pain intensity, which reduces the likelihood that baseline patient characteristics retract from the results founding the 2015 Ehde et al. study.

Alschuler et al. (2021) acknowledged that there is underutilization of effective behavioral and interpersonal pain interventions in pwMS, often due to barriers such as transportation burden

or lack of referral, and that such pain treatments are commonly implemented only after MS-related pain has become chronic or severe. A more advanced version of telephone self-management discussed above, Alschuler et al. (2021) orchestrated a single-blind pilot RCT that delivered a single videoconference session of pain intervention to individuals with a "new" (within the past 36 months) diagnosis of MS. The study population was comprised of persons that experienced moderate or worse chronic pain or moderately severe or worse pain catastrophizing within the past week. These criteria were addressed using the NRS (≥3) and Pain Catastrophizing Scale (PCS, ≥16) respectively. Given the pilot nature of this study, a small sample size was recruited (n = 30) to identify feasibility and acceptability of a large-scale study using this intervention. Fifteen individuals were assigned to each arm of the study, and 27 individuals completed the entire study. Interestingly, the demographic makeup of this study contrasts typical disease prevalence when considering two components: more than half of participants were male and the average time since MS diagnosis was relatively short at just over two years. The other metrics considered - MS subtype, race, marital and educational statuses - are consistent with prevalence and other study populations encountered in this research (Alschuler et al.).

The specific intervention tested, "ENGAGE", is a 120-minute group encounter with up to four participants that is accessed via encrypted Zoom link. The group session focuses on education and modification of pain-related behaviors and attitude, as well as providing resources to participants (Alschuler et al., 2021). In some ways, the strategies used in this group encounter summarize and combine the efforts of the telephone-delivered strategies (T-SM, T-ED) as discussed above (Ehde et al., 2015). ENGAGE was tested against a passive control group in which patients received usual MS care. PCS, NRS and other outcome measures were assessed at

baseline/pretreatment (one to two weeks prior to session,) posttreatment (one to two weeks following session) and at a three-month follow-up (Alschuler et al.).

This pilot study showed that videoconference-delivered pain interventions are feasible and acceptable to pwMS based on recruitment, satisfaction, and retention data. Over half of ENGAGE participants sought additional information regarding chronic pain management, and all reported utilization of one or more techniques/skills discussed or reviewed in the videoconference session. However, statistical analysis of the outcome results showed no significant difference in any measures between the treatment or passive control study arms. While pain catastrophizing did decrease in the ENGAGE group at the initial post-treatment analysis, this metric had returned to baseline at follow-up analysis (Alschuler et al., 2021).

The new population ("newly-diagnosed pwMS") target of this pilot study can be considered both an advantage and a limitation: while it addresses a gap in knowledge and results could provide valuable information to guide future directions for research, there are also no studies to which these findings can be interpreted against. The lack of severe pain may also have unexpectedly influenced results, as those with less pain are less likely to seek intense efforts to change the symptom. The small sample size is certainly a limitation of this study, which is expected in trials assessing feasibility and acceptability of new interventions (Alschuler et al., 2021).

As discussed previously, comprehension of MS itself as well as etiology of its symptoms such as pain are still in beginning stages. To effectively treat pain, the correct phenotype and mechanisms of the symptom must be identified and understood. Thus, if accurate characterization of MS pain types is lacking, this can undermine treatment efficacy. In an interesting new approach to treatment of chronic pain in pwMS, experts in the field recognized

the therapeutic advantage thorough pain assessment could have on future chronic pain management in this population and subsequently directed research efforts to addressing the knowledge gap in this topic (Kratz, Whibley, et al., 2021). This nationwide survey study aimed to delineate types of pain present in pwMS including NP, nociceptive pain, nociplastic pain, and mixed neuropathic/nociplastic pain. These three phenotypes of pain are mechanistically based and defined by the International Association for the Study of Pain (IASP). Pain in MS is commonly assumed to be NP (originating from somatosensory nervous system dysfunction) given the CNS damage present in MS. Nociceptive pain is peripheral in nature and results from stimulation of pain receptors, which has not been well-identified in pwMS. Nociplastic pain is new concept in MS- this type of pain is idiopathic and is thought to occur from pain processing alterations or "central sensitization" - but has been previously recognized as the cause of symptoms in other functional syndromes such as fibromyalgia (Kratz, Whibley, et al., 2021).

Initially, 1220 pwMS completed the study survey, 842 of which were analyzed due to endorsement of chronic pain (69%). Age was found to be statistically significant when considering age of included vs. excluded individuals ($p = 0.007$) but not for any other demographic distribution. Pain was described and subtyped using the following questionnaires: painDETECT (PD-Q, neuropathic pain); American College of Rheumatology Fibromyalgia Survey Criteria (ACR FM Survey, nociplastic pain); and PROMIS Pain intensity 3a (pain intensity). Pain medication utilization and associated pain relief were also quantified. Nociceptive pain was considered the cause of pain as a diagnosis of exclusion (i.e., the presence of pain was not explained by neuropathic or nociplastic origin) (Kratz, Whibley, et al., 2021).

The results of pain distribution found in this study differ from any other previously published data on chronic pain characterization in pwMS. Results of Kratz, Whibley, et al.

(2021) demonstrated NP alone as the least common cause of pain (9% participants) and nociplastic pain alone as the second least common phenotype (23% of participants). Twenty-seven percent (27%) of patients were categorized as experiencing mixed-type pain with both neuropathic and nociplastic qualities present. Hence, overall 50% of patients experienced features of nociplastic pain and 36% of patients suffered from features of NP. Nociceptive pain was assumed in 41% of patients as their pain did not meet criteria for either neuropathic or nociplastic pain. Therefore, this study suggests that nociplastic pain either alone or in conjunction with other subtypes is the most common type of chronic pain in pwMS, whereas NP is the least common cause of pain (Kratz et al., 2021a).

Regarding pain intensity, this study found that each of the 4 pain subtypes discussed was significantly different from one another ($p < .0001$) with the exception being comparison of nociceptive and nociplastic pain to each other. Nociceptive pain exhibited the least intensity, nociplastic and neuropathic pain alone showed higher but nearly equal intensity, and mixed neuropathic/nociplastic pain was rated as the most intense. NSAIDs were the most frequently utilized medication for analgesia (66.5%) in the study cohort, but when considering frequency of medication use by pain subtype, each type of medication considered (cannabinoids, opioids, anticonvulsants, SNRIS, SSRIS, antispasmodics, steroids, benzodiazepines) showed statistical significance ($p <.001$ -.003) when using χ^2 tests. Full discussion of pain relief for each medication class and pain subtype is beyond the scope of this research which focuses on nonpharmacological modalities for treatment of chronic pain in pwMS, but it is relevant to mention that some medication classes proved to significantly (*f)* relieve pain in one subtype more than others. Cannabinoids were most effective in nociplastic and mixed type pain ($p =0.01$) and

NSAIDS were most effective in nociceptive pain ($p < .001$). No other drug classes provided significantly different pain relief in one subtype compared to others (Kratz et al. 2021a).

This study, the first to evaluate presence of nociplastic pain in pwMS, has several strengths, especially the large, diverse sample size and validated pain measures for pain intensity, nociplastic pain, and neuropathic pain. However, specific limitations are present as well. Nociceptive pain was not categorized via specific indicators (rather, a diagnosis of exclusion) which is a limitation in identifying its true presence either alone or concurrently with another type of pain. Secondly, since this is the first study to evaluate nociplastic pain in pwMS, other data for comparison are lacking. This is especially important to consider as the results of this study refute the commonly held belief that NP is the most prevalent chronic pain phenotype in pwMS.

Another recent study also aimed to quantify and correctly identify different types of pain in pwMS (Ferraro et al., 2018). This study, single-centered and cross-sectional in nature, utilized validated tools such as the Brief Pain Inventory (BPI,) Italian Pain Questionnaire (IPQ,) and Neuropathic Pain Symptom Inventory (NPSI) to categorize pain in 374 pwMS. Among the study population, prevalence of chronic pain (daily, >3 months) was 52.1%, 36.9% of which was reported as lower extremity. This is consistent with previously published data as discussed in preceding sections of this paper (Young et al., 2017). Interestingly, there were no demographic differences between PAIN+ and PAIN- groups, which opposes other publications citing age, biological sex, and disease duration as indicators of chronic pain presence. Nearly half of individuals reporting chronic pain described features of NP (23.7% overall prevalence,) which also was associated with higher pain intensity and disability. This is contrast to Kratz et. al, whose recent research (2021) showed that NP is the least common type of chronic pain in pwMS

when expanding the types of pain considered. However, Ferraro et al. did not consider nociplastic pain as a possible phenotype.

When disability was measured by the Expanded Disability Status Scale (EDSS,) the PAIN+ population experienced higher levels compared to PAIN- population ($p = 0.025$). Additionally, the presence of sensory functional system impairment was also significantly different between the two groups ($p = 0.016$) when analyzed with multivariate statistical regression. When comparing populations with NP and without NP, it was found that those with NP experience a significantly higher amount of disability and sensory functional system impairment ($p< 0.001$), as well as increased dysfunction in pyramidal and bowel/bladder functional systems ($p = 0.005$.) These numbers remained significant when dissecting the PAIN+ group into those experiencing NP qualities and those experiencing other types of chronic pain (Ferraro et al., 2018).

Future Directions/ Ongoing Research

Not only is it important to discuss and review previously published literature regarding chronic pain treatment in pwMS, but also it is relevant to introduce unpublished and ongoing research that will contribute to the vault of knowledge in this topic. Some topics of current research are investigating on-demand access to MS resources, improvement of psychological and emotional methods of pain management, and implementation of collaborative care for pwMS.

While in the past there have been significant barriers to pwMS' ability to access well-developed and tested psychological or educational resources for management of symptoms such as pain, current widespread technology has the potential to improve this disparity by making interventions portable and therefore more readily available. Much prior research has been done on use of self-management tools such as behavioral modification, but often these studies are

designed and interpreted primarily by researchers. Kratz et al. (2021b) created a web-based symptom management program, “My MS Toolkit,” that was developed alongside pwMS and subsequently tested by 20 participants with MS that experience high levels of chronic pain and other MS-related symptoms. The single-arm pilot trial allowed participants unguided access to My MS Toolkit for a period of 12 weeks, during which the participants on average accessed the program 5.4 times and spent about 7 minutes per visit on the site. The program has subsequently been published and is easily accessed online at https://mymstoolkit.com. The home page, accessed for the purpose of this research, indicated that some accessible material within My MS Toolkit includes education of symptoms, goal setting, relaxation skills, energy management, working with thoughts and emotions, sleep, communication, and physical activity (*My MSToolkit – A Toolkit for Those with MS*, n.d.). However, some of these topics may not have been present in the original pilot study, as specific information was not disclosed in the description of study design. Within the pilot study, NRS and other measures of symptoms were completed before and after the study period, as well as biweekly throughout. Despite lack of statistically significant improvement in outcome measures, 16/20 (80%) of pilot study participants stated that symptoms or other measures were “somewhat” or “moderately better” and 45.5% of pwMS experiencing chronic pain (n = 11) had a clinically significant reduction in its intensity (Kratz, Alschuler, et al., 2021).

Advantages of this study are the inclusion of MS stakeholder in development, ease of access to My MS Toolkit (smartphone, computer, tablet) and variety of material included on the toolkit. However, the preliminary nature and small study sample are limitations of the findings, as results can only be claimed as ‘promising’ regarding efficacy; nonetheless, further research

into My MS Toolkit as a management tool for MS symptoms may be a worthwhile investment and certainly is feasible and acceptable (Kratz, Alschuler, et al., 2021).

Additional ongoing research focuses on identifying the optimal approach for best preparing pwMS to mentally address chronic pain. Psychological interventions for pain such as cognitive behavioral therapy (CBT) and mindfulness-based cognitive therapy (MBCT) have successfully improved pain-related outcomes in pwMS, but little is known about outcome moderators between these two approaches. Ehde et al.(2019) created a three-arm RCT protocol (n =240) which is the first of its kind to compare usual care to CBT and MBCT in pwMS experiencing chronic pain. The treatment groups (n = 80, n =80) in this study will each receive eight video- conferenced group therapy sessions of CBT and MBCT, respectively. The usual care group (n =80) will receive no cognitive intervention or therapy. The outcome measure of interest (average pain intensity, measured via NRS) will be assessed pre-treatment, following four treatment sessions, following treatment, and six months following final treatment. The results have not yet been published but could provide insight into which method is superior in reducing average pain intensity in pwMS (Ehde et al., 2019).

Collaborative care is an encompassing approach to achieving optimal care (used for treatment of many conditions) and includes not a single intervention, but rather a coordinated and interdisciplinary effort by multiple team members. An MS-specific program, MS Care, is currently in the process of undergoing a 16-week RCT comparing collaborative care to usual care at an MS specialty center (Ehde, Alschuler, et al., 2018). The primary outcomes of this study are pain control and depression control. Care quality, patient satisfaction, compliance, and QoL are also being analyzed. Participants in the MS Care intervention are provided with a care manager to facilitate optimal treatments, both physical and psychological, based on guidelines.

Additional team members include previous members of each patient's treatment team, expert MS providers, and consulting psychologists/ psychiatrists (Ehde, Alschuler, et al., 2018). Outcome assessments for this study are/will be measured pre-treatment, post-treatment, 6 months following the completion of initial 16 weeks. Results have not been published from this study, but may suggest whether or not collaborative care improves pain control in pwMS.

Discussion

Chronic pain is a common symptom of MS, and is present in approximately 50% or more persons with this disease, though in many phenotypes, and can change quality and intensity over time (Cree & Hauser, 2018; Young et al., 2017). Although there is basic understanding of the types of pain present in pwMS, specific indicators of etiology are lacking. Plantone et al. (2021) successfully identified relationships between MS-related brain lesion location and presence or absence of pain, which is an exciting advancement. Repeat studies with larger sample sizes are necessary to corroborate the information found by Plantone et al. Quantification mapping of MS-related CNS lesions outside of the brain (i.e., within the spinal cord) are also necessary as lesiosn in these locations may also contribute to presence or phenotype of pain in pwMS. To comprehend clinical significance of these findings, further research is needed regarding treatment outcomes based on location of lesions.

Pain in pwMS can impact afflicted persons in multiple ways, and can prove to be quite debilitating as it often leads increased disability (Ferraro et al., 2018) and decreased social interaction/activities outside of the home (Gromisch et al., 2020). Due to prevalence and pervasiveness of pain in pwMS, it is important for all providers - including general practitioners - to have a basic knowledge of the condition as well as avenues that can be pursued for treatment (Lin et al., 2021).

Accurate identification and proper classification are critical in determining the treatment approach for pain in general; chronic dysesthetic pain in pwMS is no exception to this statement. The disparity and discrepancies in categorization of pain may be contributing to the lack of treatment efficacy in pwMS when considering nonpharmacological approaches, and especially when considering pharmaceutical methods (Kratz, Whibley, et al., 2021). Most data evaluating pain prevalence in pwMS cite NP as the most common type of chronic pain present in pwMS (Duffy et al., 2018; Ferraro et al., 2018; Szok et al., 2019) either by assumption due to the presence of CNS lesions, or stratification of pain into limited categories. Therefore, most of the limited research on pharmacological treatment of chronic pain in pwMS has considered NP. New research published by Kratz, Whibley, et al. (2021) challenged this common finding by including a novel type of pain in pwMS- nociplastic pain. These newest results showed that isolated NP is actually the least common type of pain present in pwMS (9%) and when combined with nociplastic pain (27%) is still only estimated to be present 36% of the time, which could explain the lack of analgesia provided by medications that typically provide relief to this category of pain in other diseases. Kratz, Whibley, et al. demonstrated evidence that nociplastic pain either alone (23%) or combined with NP was the most common type of pain to be delineated in pwMS (50%.) As assigned by exclusion from other categories, nociceptive pain was assumed to be the mechanism behind the other 41% of chronic pain presentations. These new results must be interpreted with caution; subsequent, repeated studies are needed to confirm the findings. However, this study did include a relatively large sample size which makes results more reliable than some other studies of the same nature. It is difficult to compare the findings of Kratz, Whibley, et al. to other studies, as this was a novel use of certain pain scales in pwMS. It perhaps would have been more rooted if similar scales in other studies were available for comparison, for

example if Ferraro et al. had stratified pain using these measures rather than neuropathic vs. non-neuropathic categories. Nonetheless, there is evidence that nociplastic pain is likely present in pwMS, and pharmacologic agents that target this mechanism of pain may be more efficacious in providing analgesia in this population.

Further supporting the need for proper classification of pain, Kratz, Whibley, et al. (2021) demonstrated that efficacy of pharmaceutical analgesics differs based on pain category: NSAIDs are most effective at treating nociceptive pain, and cannabinoids best provide analgesia to pain that is nociplastic or mixed nociplastic/NP in nature. Therefore, the common agents utilized in treatment of chronic pain in pwMS (antiepileptics, gabapentinoids, antidepressants) (Cree & Hauser, 2018; Duffy et al., 2018; Szok et al., 2019) are less likely to be helpful in treating chronic pain in pwMS than other agents such as cannabinoids or NSAIDs (Duffy et al.; Szok et al.). Adjustment of current provider-accepted treatment guidelines of chronic pain in pwMS may increase treatment efficacy. Further discussion of pharmacological treatment is not pertinent to this research but was relevant to mention. Typical medication options used for pain treatment often fail to provide adequate relief and come with adverse effects, which is a primary driver of the need for nonpharmacologic interventions for chronic pain treatment in pwMS. Further research is needed to determine the impact reclassification of MS-related chronic pain has on efficacy of non-pharmacological interventions.

Previous research regarding non-pharmacological treatments of pain specifically in MS is lacking, but meta-analyses did suggest that some interventions may be helpful, particularly tai chi/hydrotherapy, telephone delivered education, hypnotic analgesia and tDCS. Previous studies provided mixed results regarding the efficacy of neurofeedback and did not support tRNS or reflexology as helpful in treating chronic pain in this population (Amatya et al., 2019). Even the

modalities with promising results in analyses cannot be recommended at this point due to low quality of evidence, high risk of bias, as well as very small sample sizes that comprise the analyzed studies. However, evidence does not indicate harm will come from these interventions, so they are safe to be implemented when a patient wishes to try an alternative or supplementary nonpharmacological approach. Some studies have suggested "clinically significant" reduction in chronic pain with the use of SCS (which is rather arbitrary, standardized results are preferred) (Provenzano et al., 2016). SCS must be approached more cautiously than other discussed nonpharmacological interventions given the invasive nature of placement (Sivanesan, n.d.) and consideration of possible adverse events with this modality (Provenzano et al.) Nonetheless, SCS remains a viable option - accessed through specialty care - for some MS patients with intractable pain. When considering referral for placement of an SCS, clinicians must consider if pain has been properly classified, as this device best treats central NP (Provenzano et al.). Therefore, it will likely be ineffective if utilized to treat nociplastic pain that is assumed to be NP as discussed above with Kratz, Whibley, et al. (2021).

New research regarding nonpharmacological interventions for treatment of chronic pain in pwMS have improved the strength of recommendation for some interventions, but overall evidence remains weak for most modalities. Inherent to many of the studies regarding treatment of chronic pain in pwMS is a selection bias - participants are often recruited from databases and must volunteer/agree to sign up. Additionally, the sample sizes are not sufficient to detect trends towards significance, in many cases.

The literature review for this research does suggest that both massage therapy (Salarvand et al., 2021) and exercise (Demaneuf et al., 2019) are able to provide analgesia to pwMS experiencing chronic pain, as most studies considered in meta-analyses for each respective

intervention demonstrate improvement. Like previously analyzed interventions, level of evidence for these treatments remains weak secondary to small sample size and high risk of bias. For each intervention, considered studies were vastly heterogenous and lack of standardization makes it impossible to recommend a specific regimen. It can be determined at this point that exercise and massage therapies are likely beneficial (if not for analgesia, then for overall health) to pwMS, but corroboration by sound research and statistics remains lacking.

As discussed, previous research has suggested tDCS is beneficial for pwMS experiencing chronic pain (Amatya et al., 2018). Preliminary results from the most recent study regarding a new tDCS protocol suggest beneficial analgesia following treatment in pwMS (Young et al., 2020.) Further research is needed to determine clinical significance of these findings. A larger sample size and extended period of study would be necessary to ascertain feasibility and extent of benefit for tDCS, as many questions are left unanswered: How long does the analgesia last? Do repeat treatments continue to provide benefit? How relevant is VAS reduction to satisfaction of the patients? Further research is warranted into this intervention, but with the questionable benefit and time commitment, it likely should not be considered first-line nonpharmacological treatment for chronic pain in pwMS.

The findings of Jensen et al. (2016, 2018) suggest that hypnotic analgesia with or without pre-treatment enhancers may be beneficial and reduce chronic pain in pwMS. The 2016 study provided a basis for validated design, but the relevant results were produced in the 2018 study. Although a moderate time effect was discovered in the study as whole, analyses found that there was also a significant Time x Treatment effect. Hypnotic analgesia alone improved pain in pwMS, but was enhanced by both pretreatment neurofeedback and meditation strategies (Jensen et al., 2018). Again, further research regarding this intervention must be completed before

hypnotic analgesia and treatment enhancers can be recommended without reserve but results thus far are promising.

Ehde et al.'s. 2016 study involving self-management (T-SM) and educational content (T-ED) delivered remotely though the medium of telephone calls provided interesting findings. As cognitive strategies are known to be successful in treating other types of chronic pain, the authors hypothesized that T-SM would provide superior improvement than T-ED. Surprisingly, following 8 weeks of treatment both groups noted significant decreases in NRS from baseline, but there was no significant difference between the groups. This suggests that both methods studied were beneficial in providing pain relief for pwMS. The significance of reduced NRS was retained through 6 months following treatment. The pain intensity at 12-month follow-up was not retained (Ehde et al., 2016.) A secondary analysis (Ehde, Arewasikporn, et al., 2018) showed that baseline qualities of participants did not predict the change in NRS. These results suggest that further research into this modality is warranted: commonalities should be considered, as well as a larger sample size. As the significant improvement remained through 6 months but not 12 months, implementation of repeat "refresher" sessions could occur to investigate whether the period of benefit could be extended.

Mindfulness (which requires trained techniques) may be a feasible moderator for chronic pain in MS given its negative association with pain presence (Senders et al., 2018). The results of Senders et al. are not surprising and are quite consistent with other research regarding pain associations; for example, Gromisch et al. (2020) detailed findings of emotional cognitive strategies as indirectly affecting pain interference among pwMS. This research solidifies the importance of cognitive efforts by pwMS experiencing chronic pain, as it may impact not only his or her pain, but also other life factors that can be affected by pain. Based on this study,

continued analysis, and research into effects of different cognitive strategies on pain improvement is warranted. In fact, given the concrete evidence provided by this data, it can be recommended as a generality that pwMS experiencing chronic pain could benefit from mindfulness, regardless of the method from which this is pursued. Results have not yet been posted from the 2019 study (Ehde et al.) comparing specific psychological approaches- CBT vs. MCBT - but this research will advance understanding of mindfulness and its benefits/pain association to pwMS.

Alschuler et al.'s feasibility and acceptability study (2021) of a videoconference group session suggested that this intervention can be of assistance to pwMS suffering from chronic pain. Although over the study period no significant reduction in pain scales was achieved, the sample size was very small, all participants reported utilization of reviewed skills, and most participants felt that their pain had improved following the meeting (Alschuler et al., 2021). Similarly, a different study showed that use of My MS Toolkit is feasible and acceptable given participant satisfaction and clinically significant improvement in pain over the study course (Kratz, Alschuler, et al., 2021). Both videoconference group sessions and on-demand access to educational and self-management content are feasible and acceptable interventions for chronic pain in pwMS, and therefore further investigation is justified to these modalities as well. Finally, if the results of the MS Care trial protocol are consistent with the authors' hypothesis of improved pain care in pwMS using collaborative care, this is an approach that may be implemented in a more widespread manner (Ehde, Alschuler, et al., 2018).

Conclusion

The literature review completed for this study suggests that chronic extremity pain is a common symptom in MS and its effects are often severe, but vary. MS-related chronic pain is

notoriously difficult to treat despite its prevalence, and current pharmacologic recommendations are based on guidelines for general NP, not specifically pwMS. Unsurprisingly, given the lack of MS-directed treatment guidelines, pharmaceutical regimens for chronic pain in pwMS often prove inefficacious. Medication failure and adverse effects commonly prevent pwMS experiencing chronic pain from seeking treatment. New research suggests that part of the difficulty in treating chronic pain in pwMS stems from improper and incomplete classification. While commonly assumed to be NP in nature, some pain should be categorized differently, as nociplastic pain or other types of pain. If reclassified, these types of pain would be best treated with different medications such as cannabinoids and NSAID, which are not typically used to treat NP.

Previous research has supported, with very weak evidence, nonpharmacologic treatments to be beneficial in chronic pain treatment for pwMS, either alone or as adjunct to medication regimens. The interventions that have previously demonstrated the most evidence for support include hydrotherapy, telephone-delivered education, hypnosis, and tDCS. Additionally, SCS has been used in specific persons, but is typically accessible only as a last resort for refractory pain. New evidence suggests that hypnotic analgesia with pre-treatment enhancers (neurofeedback and mindfulness medication) and telephone delivered self-management skills may be beneficial in improving pain within this population. Recently published meta-analyses suggest exercise and massage therapy are effective pain-treatment interventions in pwMS. However, this evidence is poor, and recommendation of these treatments is weak. Further research of all interventions discussed is needed in pwMS to created evidence-based guidelines. New research is in process, considering multiple treatment avenues such as optimization of cognitive approaches, MS-specific collaborative care, on-demand access to pain treatment resources, and videoconference

use. Clear evidence has emerged showing that mindfulness (an obtained skill) reduces the frequency of pain presence in pwMS, so it may be beneficial for all individuals in this category to pursue these cognitive abilities.

At this point, it can be concluded that nonpharmacologic interventions lack concrete evidence but may be safer and/or more preferred to pharmaceutical interventions as the possibility of inflicted adverse effects is limited. The selection of specific modalities, unfortunately, must be left to patient and provider preference until further evidence is obtained.

Applicability to Clinical Practice

With the information collected and discussed in this research, medical providers will have a good understanding of non-pharmacologic and alternative treatment options in pwMS and will be able to use this information to guide future clinical decisions and treatment recommendations. Furthermore, the brief summarization of pharmacological avenues that may be appropriate for chronic pain treatment in pwMS will provide practitioners a reference should they find this is a route they pursue with their future patients.

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