ABSTRACT

Background: Evidence-based pharmacologic and behavioral interventions are often underused or inaccessible to persons with multiple sclerosis (MS) who have chronic pain and/or depression. Collaborative care is an evidence-based, patient-centered, integrated, system-level approach to improving the quality and outcomes of care for behavioral health and other chronic conditions. We describe the development and randomized controlled trial testing of a novel intervention, MS Care, which uses a collaborative care model to improve the care of depression and chronic pain in an MS specialty care setting.

Objectives: The specific aims were as follows: (1) to test the effectiveness of MS Care, a patient-centered collaborative care approach to treating depression and pain in individuals with MS, relative to usual care, in reducing pain and depression posttreatment (primary end point), and at the 6-month follow-up; and (2) to examine the impact of MS Care on secondary outcomes including quality of depression and pain care, disability, patient satisfaction, and quality of life posttreatment and at the 6-month follow-up.

Methods: We conducted a 2-group randomized (1:1) effectiveness trial comparing MS Care with usual care in an outpatient MS specialty care center. Eligible participants (N = 195) with chronic pain of at least moderate intensity ($\geq$ 3/10) and/or major depressive disorder were randomly assigned to MS Care or usual care. MS Care used a care manager to deliver and coordinate guideline-based medical and behavioral treatments in collaboration with the patient, specialty clinic providers, and pain/depression treatment experts. To facilitate treatment engagement, the care manager offered participants the choice to receive care-management sessions in person, by telephone, or via a combination. Those randomly assigned to usual care received treatment as usual through the clinic. Research staff unaware of intervention allocation obtained all outcome measurements via telephone interview pretreatment (baseline), posttreatment (4 months postrandomization: primary end point), and at the 6-month follow-up (10 months postrandomization). The primary outcome was control of pain and depression (ie, pain and depression were below clinically meaningful cutoffs posttreatment). Secondary outcomes included pain interference with normal activities, depressive symptom severity, quality of life, disability, fatigue, patient satisfaction, health care utilization, and quality of care posttreatment and at the 6-month follow-up. For the primary analysis, we compared the proportion of individuals who had control of depression and pain symptoms between the 2 groups at the end of the treatment period. Attrition and missing data were very low; imputation was not needed. Secondary outcomes were analyzed posttreatment and at the 6-month follow-up using t tests, chi-square tests, and Fisher tests.

Results: Participants in both groups were generally middle-aged, female, and diagnosed with MS for $\geq$ 10 years. The majority of participants met inclusion criteria for moderate or severe pain (72%) or pain and depression (23%); only a few individuals met inclusion criteria for depression alone (5%). There was no statistical difference (using an α level of 0.05 for all statistical tests) between the MS Care and usual care groups in the proportion of individuals whose pain and depression were both under control immediately posttreatment, the primary

end point being 18.8% (95% CI, 10.5-27.1) in MS Care vs 12.2% (95% CI, 5.1-19.3) in usual care (p = 0.24). At the 6-month posttreatment follow-up, the MS Care group was statistically different from the usual care group, with more individuals having depression and pain under control (17.9% in MS Care vs 7.4% in usual care; p = 0.04). Secondary outcomes were as follows: immediately posttreatment, the MS Care group showed statistically significant lower pain intensity, pain interference, depression severity, disability, and fatigue than usual care (p = 0.001 vs p = 0.04, respectively). Treatment satisfaction was also higher for the MS Care group (p < 0.001). At the 6-month follow-up, the MS Care group maintained statistically lower pain interference, disability, and fatigue (p = 0.004 vs p = 0.03, respectively). In analyses examining pain and depression outcomes separately, the MS Care group had significantly more pain responders than the usual care group posttreatment (p = 0.01) and at the 6-month follow-up (p = 0.03). For the depression outcome, the MS Care group had significantly more depression responders than the usual care group posttreatment (p = 0.04); this difference was not maintained at follow-up, however (p = 0.36).

Conclusions: Although MS Care was not superior to usual care in controlling pain and depression posttreatment, MS Care was effective in other outcomes of importance to people with MS and resulted in high rates of satisfaction.

Study Limitations: These included underrepresentation of patients with depression in the sample, being a single-center study, the restriction of the MS Care intervention to 16 weeks (relative to flexible duration in clinical practice), use of 2 care managers (vs multiple), and insufficient power to measure subgroup effects.

BACKGROUND

Multiple sclerosis (MS) is a chronic, progressive neurologic condition affecting approximately 2.3 million people worldwide.[1] As MS is typically diagnosed between the ages of 20 and 50, most people with MS live many years managing this chronic disease. Individuals with MS experience a constellation of symptoms and co-occurring conditions, including sensory problems, cognitive difficulties, weakness, spasticity, paresthesias, pain, visual disturbance, heat intolerance, fatigue, bowel/bladder dysfunction, and emotional changes.[2] Nearly all daily activities can be affected by MS, including physical functioning, activities of daily living, vocational functioning, role functioning, and leisure pursuits. The course, specific symptoms, and severity of disease progression vary considerably between and within individuals. As there is no cure for MS, current treatments focus on minimizing disease activity and progression, managing symptoms, and improving health-related quality of life.[3]

Chronic pain and major depressive disorder (MDD) are 2 of the most prevalent problems experienced by people with MS. Nearly 25% of adults with MS have MDD,[4] and > 50% experience moderate or severe chronic pain.[5-7] Approximately 20% to 25% of people with MS have depression and chronic pain.[8] Both are associated with poorer MS outcomes, worse functioning and health-related quality of life, and greater health care use.[6,9-11] In other medical populations, the occurrence of both conditions has been found to amplify health care use and costs[12] and reduce the effectiveness of treatments for the other condition.[13,14] In a study of MS patients with pain, those who were depressed tried more treatments and made more visits to providers for pain treatment relative to those who were not depressed.[15]

Depression and chronic pain are often undertreated in MS patients,[16] despite the availability of effective treatments.[6,7,17,18] An estimated 50% to 66% of people with MS and MDD are undertreated.[19-22] Multiple reasons are believed to account for this undertreatment, including poor utilization of depression screening information to improve treatment.[18] Although behavioral interventions specifically targeting depression have been found to be effective in samples of people with MS,[21] barriers such as stigma, unavailability of services, time constraints, and cost impact follow-through on recommendations for depression care.[23,24]

Given that chronic pain is inadequately treated in the general population,[25] it is not surprising that it is undertreated in the MS population. Pain treatments that patients prefer, including evidence-based nonpharmacologic pain-management strategies, are seldom prescribed or used.[26] Common barriers to pain care include a lack of providers with expertise in MS and multimodal pain-management approaches, transportation or geographic barriers, and system barriers such as the medical system's overreliance on biomedical pain treatments.[25,27] Systematic reviews[6,16] have highlighted the need to bridge the gap between patients and evidence-based treatments, ultimately in service to improving pain and depression care in patients with MS.

In other patient populations, the collaborative care model has revolutionized how behavioral health care is effectively delivered and thus provides a template for improving pain and depression care in people with MS. Collaborative care is a patient-centered, systematic, population-based approach to integrated care[28] that has improved outcomes for depression and more recently pain, within primary and specialty care settings.[29-33] Collaborative care aims to address undertreatment of behavioral health conditions by reorganizing the care system through (1) care managers who engage patients in treatment, deliver brief evidence-based treatments, and coordinate patients, providers, and community resources in the care plan; (2) clinical information systems to facilitate and track patients and outcomes; (3) measurement-based treatment to target care; (4) weekly case consultation in which experts review cases, supervise the care manager, and adjust treatment for a panel of patients; and (5) stepped care in which treatments are intensified or adjusted as indicated.[34] More than merely co-locating health providers in a clinic, collaborative care implements established principles of chronic care and interdisciplinary teams with complementary skills to collaborate closely in caring for a population of patients with complex medical conditions. At least 2 meta-analytic systematic reviews of > 80 randomized controlled trials (RCTs) showed that collaborative care is more effective than usual care in improving short- and long-term (up to 5 years) depression outcomes in primary care settings.[35,36] Several RCTs have also demonstrated that collaborative care was superior to usual care in improving pain, depression, and functional outcomes in patients with chronic pain but no known neurologic condition.[37-42]

Only one small (N = 83), nonrandomized trial using a collaborative care approach for depression care has been published on MS.[43] The trial emphasized depression screening, referral to a psychiatric nurse care manager, choice of guideline-based antidepressant or problem-solving therapies, outcome monitoring, and relapse prevention. About one-third (n = 28) of the subjects participated in the depression-management intervention for a median of 7 sessions with the care manager. The authors found that the frequency of major depression at the 6-month follow-up was lower in the intervention group relative to usual care, suggesting that it is worthwhile to further investigate this approach. Thus far, no studies have evaluated collaborative care for pain in patients with MS or other neurologic conditions.

This study is the first application of collaborative care to depression and pain in patients with MS or other neurologic conditions. The literature and the Patten[43] study suggest that collaborative care has considerable potential to improve outcomes and quality of care in MS patients with pain and/or depression. Our trial sought to build on the existing collaborative care evidence base and increase the potential benefits to people with MS via several innovations, including the following: (1) tailoring the intervention to the unique needs of the MS population (eg, complex symptoms, cognitive dysfunction, and varying levels of disability); (2) adapting collaborative care to address pain, depression, or both, thus ensuring relevance to a larger proportion of the MS population; (3) using telehealth as the primary means of delivering care to reach MS patients who live in rural areas or are otherwise unable to access regular in-person care; and (4) refining the intervention and research design via stakeholder engagement.

The current study's objective was to improve depression and pain care by implementing and evaluating a novel system of care in the context of the MS health care delivery system. Specifically, the study was designed to answer whether a patient-centered collaborative care model for pain and depression tailored to the needs and preferences of patients with MS (MS Care), compared with usual care, was effective at improving pain and depression outcomes. This trial is a single-center, 2-group randomized (1:1) effectiveness trial comparing MS Care, a 16-week collaborative care intervention for treating depression and/or pain in patients with MS, with usual care. The specific aims and related hypotheses were as follows:

- Aim 1: Test the effectiveness of MS Care, a patient-centered collaborative care approach to treating depression and pain in individuals with MS, relative to usual care, in reducing pain and depression posttreatment (primary end point) and at the 6-month follow-up.
- Hypothesis 1: Compared with those in usual care, patients randomly assigned to MS Care will demonstrate significantly greater control of pain and depression posttreatment (primary end point) and at the 6-month follow-up.
- Aim 2: Examine the impact of MS Care on secondary outcomes including quality of depression and pain care, disability, patient satisfaction, and quality of life posttreatment (primary end point) and at the 6-month follow-up.
- Hypothesis 2: Patients randomly assigned to MS Care will show significantly better quality of life, patient satisfaction, and quality of care, as well as reduced disability and fatigue, posttreatment and at the 6-month follow-up.

The findings will inform patients, clinicians, and the MS health care delivery systems about the benefits of collaborative care in addressing 2 of the most common, disabling co-occurring conditions in MS—pain and depression.

PARTICIPATION OF PATIENTS AND OTHER STAKEHOLDERS

Types and Numbers of Stakeholders Involved

Our stakeholders included 7 individuals living with MS; 6 clinicians (2 physicians, 2 nurses, 1 psychologist, and 1 medical assistant) at the University of Washington (UW) Medicine MS Center; 2 UW MS Center administrators (1 clinic coordinator and 1 clinic manager); and staff of the National Multiple Sclerosis Society (NMSS), including the Greater Northwest Chapter's director of services, the volunteer engagement manager, and a social worker who provides care-management services to individuals living with MS in the community.

How the Balance of Stakeholder Perspectives was Conceived and Achieved

Our research is built on a community-based participatory research (CBPR) intervention model (known as participatory action research in the rehabilitation field).[44] We have used this model to conduct other clinical trials in partnership with MS stakeholders, including several of the patient partners who collaborated with us on this study. This approach emphasizes co-learning between stakeholders and scientists, shared decision-making, transparency, and meaningful stakeholder involvement throughout all phases of the research process. We sought to involve all the various communities affected by the issues we were studying. To ensure sufficient representation, we aimed to have about half of our stakeholders be individuals living with MS.

Methods Used to Identify and Recruit Stakeholder Partners

Given our history of CBPR, our team already had established stakeholders with whom to partner on this study. These included several members of the UW Medicine MS Rehabilitation Research and Training Center Advisory Board (composed of people with MS, their families, and the NMSS) and the Greater Northwest Chapter of the NMSS. Relevant clinical stakeholders included the UW Medicine MS Center's medical director, who oversees and provides medical care to all MS patients at the clinic, and the clinic's administrator. Allison Krehbiel, director of services for the Greater Northwest Chapter of the NMSS, was a member of our stakeholder team from past studies and assisted us in identifying stakeholders.

Because MS Care was the first study to change the system of care for pain and depression in the MS clinic setting, it was important to have patient partners involved in all phases of our research. At the beginning of our project, we assembled a team of 7 patient partners who had experienced pain, depression, or both (representing varying subtypes of MS and demographic characteristics such as sex, age, and education) to collaborate with us across all study phases. They were part of our larger MS Care stakeholder team. We identified them with the help of our UW Rehabilitation Medicine Patient and Family Council, which includes people affected by MS; our MS Rehabilitation Research and Training Center Advisory Board; clinical staff; and Ms. Krehbiel, our stakeholder representing the NMSS. We also included other stakeholders such as clinic nurses and a family member (who also has MS) based on input from the other stakeholders.

Methods, Modes, and Intensity of Engagement

Our original PCORI proposal (study questions, design, and comparators) was informed by engagement with several stakeholders, including patient partners, who became members of our study's stakeholder team. We engaged our stakeholders throughout the study across all important aspects of the research enterprise, including study design, study monitoring, data interpretation, planning dissemination activities, and generating future research questions.

During the initial start-up phase we conducted multiple small group discussions, one-on-one communications, and email communications with our stakeholders, including MS providers, clinic staff, our patient partners, and our other stakeholders. We also consulted with collaborative care experts implementing similar systems for other chronic conditions in other health care systems. The purpose of these discussions was to obtain input on (1) the study aims, questions, design, and outcome domains; (2) perceived barriers to high-quality treatment of pain and depression in the clinic setting; (3) the structure, length, content, and format of the intervention; (4) inclusion/exclusion criteria; (5) choice of comparative condition; and (6) potential barriers and facilitators of participation in the intervention and study.

During the study implementation phase (enrollment, treatment, and data-collection activities), we held 4 MS Care study stakeholder monitoring meetings approximately 6 months

apart during which we reviewed implementation of the recruitment, enrollment, outcome assessment, and intervention procedures. Participant enrollment and retention reports were reviewed. Stakeholders helped troubleshoot any difficulties with enrollment or retention in addition to troubleshooting other challenges that arose during implementation. As needed, stakeholders were also asked to advise the research team on other study issues and tasks; examples include providing feedback on recruitment materials (eg, study-brochure revisions), enrollment challenges, and intervention materials. These collaborations were conducted electronically and in person.

During the dissemination planning phase, we held our final 2 stakeholder meetings on November 8, 2016, and April 25, 2017. At the November meeting, we reviewed the primary end point study findings (primary and secondary outcomes plus process measures). Stakeholders discussed their interpretations of these findings and the implications for dissemination and treatment of pain and depression. At the April meeting we reviewed the follow-up findings (primary and secondary outcomes) and feedback from the focus groups conducted with study participants. A robust discussion of what was learned from the entire project ensued, which primarily involved stakeholders discussing implications for care of pain and depression, implementation of the MS Care intervention in other settings, and potential avenues for improving the MS Care program. The stakeholders, particularly the patient partners, also generated several new research questions stemming from the present study's findings and focus-group feedback. In addition to the meetings, we engaged individual stakeholders via email and individual meetings for input on specific issues (eg, our website content and dissemination).

Impact of Engagement

Engagement positively impacted the study in numerous ways. Our patient partners were instrumental in identifying potential barriers to study implementation and ways to ensure that the value of the study was translated appropriately for patients and providers. For example, they refined our study brochure to make it more appealing to patients and provided ideas for how to describe the study to potential participants. Patient partners devised new

recruitment strategies that increased enrollment, ultimately helping us meet our enrollment goal. For example, at their suggestion, we started mailing recruitment letters to UW MS Center patients who did not have any upcoming clinic appointments. This approach aimed to capture those who might not have had an appointment scheduled but still received care at the center. We recruited additional study participants using this method. Our clinical stakeholders (providers, administrator, and staff) guided us in integrating the study procedures, staff, and intervention successfully into the clinic operation. Patient partners directed us to conduct focus groups not only with participants assigned to the MS Care intervention but also with those assigned to usual care. As described later in this report, these additional groups generated new information we would not have otherwise obtained and aided our interpretation of the study findings. Overall, our stakeholders' involvement in refining procedures, problem-solving obstacles, and monitoring study progress likely contributed to not only our high participant retention rate but also to our overall high study quality.

Our stakeholder team also positively impacted our data analyses and interpretation. Their input led to new interpretations of findings that the investigative team had not considered as well as helpful language for describing findings. The stakeholders also play an important role in our ongoing dissemination efforts that will, in turn, be used to promote adoption of the study evidence into practice. For example, the patient partners participated in decision-making about our MS Care website content. They generated additional website content and reviewed it as it was being built. As the MS Care approach is difficult to describe to individuals who do not have a foundation in collaborative care, it has been critical to involve the stakeholders in translating key concepts and language. The products of this collaboration, including the website, will improve our communications about the approach and evidence in future implementation efforts.

Our engagement also impacted future MS research. Stakeholders, particularly our patient partners, generated many compelling research questions based on this study's findings. They were enthusiastic about a few of the ideas, in particular, which led to some preliminary discussion for a future research study. Our stakeholders have also reported enthusiasm for

participating in future research with us and are eager to collaborate on disseminating results. They describe benefiting from their participation in the project; we plan to share some of these benefits in a manuscript we are developing on lessons learned from stakeholder engagement.

METHODS

Study Overview

This study's objective was to improve depression and pain care by implementing and evaluating a novel system of care in the context of the MS health care delivery system. The specific aims were as follows: (1) to test the effectiveness of MS Care, a patient-centered collaborative care approach to treating depression and pain in individuals with MS, relative to usual care, in reducing pain and depression posttreatment (primary end point) and at the 6-month follow-up; and (2) to examine the impact of MS Care on secondary outcomes including quality of depression and pain care, disability, patient satisfaction, and quality of life posttreatment and at the 6-month follow-up. To address these aims, we conducted a 2-group randomized (1:1) effectiveness trial comparing MS Care with usual care at an outpatient MS specialty care center. Eligible participants with chronic pain of at least moderate intensity ($\geq$ 3/10) and/or MDD were randomly assigned to MS Care or usual care.

Study Design

This study was a single-center, 2-group parallel randomized (1:1) effectiveness trial comparing 2 alternative approaches to pain and depression care in which outcome assessors were unaware of intervention allocation. We were interested in evaluating the effectiveness of collaborative care in the context of a real-world setting, allowing patients to choose components of their care, and comparing the intervention relative to usual care rather than no-treatment, placebo, or waitlist control condition.

Participants

Target Population and Sample Size

The study setting, recruitment methods, and eligibility criteria were selected to maximize the generalizability of the study findings to the population of patients with pain and/or depression who obtain care at MS specialty centers in the United States. Our target sample size was based on the proportion of individuals who achieved pain and depression control in the 2 large published studies of collaborative care for pain and depression[37,39] that

were similar in design to our study but conducted in different populations—primary care patients[37] and cancer patients.[39] In those studies, the proportions of individuals with pain control were 0.42[37] and 0.49[39] in the intervention groups and 0.17[37] and 0.26[39] in the control groups; the proportions for major depression control were 0.37[37] and 0.38[39] for the intervention groups and 0.17[37] and 0.24[39] for the control groups. Using a test of proportion, with a significance level of 0.05, to detect an increase of at least 0.20 in the proportion of pain control in the collaborative care group relative to the usual care group, with a power of 80%, the study required 90 participants per group. Similarly, for control of depression, the study required 87 participants per group. We aimed to enroll 95 to 100 cases per group to have sufficient power to detect differences if they exist.

Participant Recruitment Strategies

Participants (N = 195) were recruited from the UW Medicine MS Center (described under Study Setting). The UW Medicine MS Center employs a research recruitment system in which consecutive clinic patients are asked to indicate whether they are interested in learning about research opportunities when they check in for clinic appointments. The medical records of patients who indicate interest in research are then prescreened by a research staff member ("staff") to confirm the initial inclusion criterion of an existing MS diagnosis. Those with a confirmed diagnosis of MS were approached specifically about the MS Care study. If direct contact was not made, staff attempted to reach the patient by telephone outside of the clinic appointment. In addition, clinic health care providers also made direct referrals to the study, and individual clinic patients could self-refer to the study on reviewing a study brochure or flyer posted at the MS Center. At the suggestion of our stakeholders, staff sent recruitment letters to patients with upcoming appointments at the UW Medicine MS Center as well as to patients who did not have scheduled appointments in the immediate future.

Using a case-report form, staff asked interested patients with a confirmed MS diagnosis a set of standardized questions and measures to ascertain eligibility based on the inclusion/exclusion criteria. The screening occurred via telephone or in person during a clinic visit. Eligible individuals provided informed consent before any further study procedures. Staff

tracked the recruitment outcomes for all patients deemed ineligible or who declined participation, including the reasons for ineligibility or declining participation. In addition, basic demographic information without identification was requested from those patients considered eligible to participate but who declined to enroll; we used this information to compare these patients with study participants in order to assess the representativeness of the sample to the clinic population.

Inclusion and Exclusion Criteria

Inclusion criteria were as follows: The patient (1) had a definitive diagnosis of MS confirmed by his or her MS physician at the UW Medicine MS Center using McDonald 2010 criteria[46]; (2) planned to continue receiving care at the UW Medicine MS Center during the enrollment period to ensure integration of services; (3) had access to and was able to communicate by telephone to facilitate the telehealth components of the intervention and outcome assessments; (4) read, spoke, and understood English; (5) was 18 years or older; and (6) reported a clinically significant problem in pain or depression. This problem was specifically either (a) chronic pain (ie, average pain intensity in the past week of at least moderate severity, defined as a 3 or greater on a 0–10 numeric rating scale)[47] of at least 6 months' duration, with pain reportedly present greater than or equal to half of the days in the past 6 months; or (b) depression (ie, depressive symptoms over the past 2 weeks in the range of probable major depression on the Patient Health Questionnaire-9 [PHQ-9; total score of 10 or higher])[48] and endorsement of depressed mood and/or anhedonia (ie, one of the cardinal symptoms of depression) present more than half of the days in the past 2 weeks.

Exclusion criteria were as follows: (1) presence of a severe psychiatric disorder as demonstrated by (a) high suicide risk (ie, current intent or plan, or thoughts of suicide in the past month with at least 1 suicide attempt in the past); (b) diagnosis of bipolar disorder with current psychotic features; or (c) symptoms of a current psychotic disorder[49] at the time of screening; (2) severe cognitive impairment, resulting in inability to provide informed consent, defined as 2 or more errors on the 6-item screener[50]; (3) self-reported active substance abuse within the past month[51]; (4) reporting of a planned major surgery scheduled in the next 10

months; or (5) ongoing psychiatric care of depression provided by a psychiatrist (more than once a month).

Many individuals with MS are prescribed antidepressants and/or analgesics for a variety of reasons, although often at subtherapeutic doses,[22] so patients taking antidepressants and/or analgesics were eligible for the study. Women who were pregnant, breast-feeding, or planning pregnancy during the study were also eligible to participate given that they could use the behavioral treatment components of MS Care. We decided to exclude people who failed the cognitive screen (an extremely rare event in MS) out of concern that such severe impairment might have interfered with their ability to provide informed consent. We also decided to exclude people who were currently receiving frequent psychiatric care in order to avoid interference with existing medication management of depression, although we anticipated that this would not exclude many individuals given that few patients with MS have ready access to psychiatric care. Given that nearly all patients with MS receiving care at the UW Medicine MS Center have telephones and speak and read English, very few patients, if any, were excluded due to these constraints.

Average pain intensity (in the past week) was assessed using an 11-point numeric rating scale, for which 0 means “no pain” and 10 means “pain as bad as you can imagine.” The 0 to 10 numeric rating scale has consistently shown its validity as a measure of pain intensity through its strong association with other measures of pain intensity as well as its sensitivity to detect changes in pain associated with pain treatment.[52] The PHQ-9,[48] a 9-item measure of depressive symptoms, was used to assess for a probable major depressive episode (MDE). A score of ≥ 10 has high sensitivity and specificity for major depression in MS.[53] To screen for psychiatric exclusion criteria, we used the Mini-International Neuropsychiatric Interview (MINI) screener[49] to determine the presence of high suicide risk (MINI screener module C) or a diagnosis of a current psychotic disorder or bipolar disorder with current psychotic features (MINI screener section L). The CAGE-AID[51] was used to assess alcohol or psychoactive substance dependence within the past month, and the 6-item screener was used to assess cognitive impairment.[50]

Randomization, Allocation Concealment, and Procedures to Minimize Bias

Participants who completed the pretreatment baseline assessment were randomly assigned on a 1:1 ratio to either MS Care or usual care using blocked randomization stratified by the presence of pain, depression, or both, for a total of 3 groups. A staff member not involved in data collection managed the random assignment protocol. Care managers called participants to notify them of their assignment to allocation and, for those allocated to MS Care, to schedule the first treatment session.

In this single-blinded study, participants, care managers, treating MS physicians, and the consultant panel were aware of allocation but made significant efforts to ensure that staff collecting outcome assessments remained unaware of participants' group assignments. Data-collection staff were uninvolved in participants' care and trained in the importance of remaining unaware of group assignment. Staff were instructed to explicitly inform participants that they (the staff) were to remain unaware of participants' allocation and to stop any participant who began to discuss information that could lead to disclosure of allocation.

Interventions

MS Care

The collaborative care intervention, MS Care, is a systematic and integrated approach to improving the delivery and use of evidence-based treatments for chronic pain and depression in adults with MS. The MS Care intervention was built on substantial evidence for the effectiveness of collaborative care in treating depression in primary care,[54-57] evidence-based cognitive-behavioral interventions for pain and depression in patients with MS,[21,58-60] and pharmacotherapy recommendations for pain and depression specific to MS.[7,17] Studies of collaborative care targeting pain and depression in other medical populations, including primary care[37,38] and cancer,[39] also informed our adaptation of collaborative care for this study.

Built on principles of effective collaborative care,[34] the MS Care intervention was designed to enhance the existing comprehensive care found at the typical MS specialty care center. It is built around a care manager who directly interfaces with patients while

representing the treatment recommendations of an interdisciplinary team that includes not only the patient's MS providers (including neurologists, physiatrists, nurse practitioners, and nurses) but also specialists, specifically psychologists and psychiatrists with expertise in depression and/or chronic pain. MS Care also places great importance on the patient being an integral team member. The care team teaches patients about their central role in self-managing many aspects of their depression and/or pain so that they can participate in decision-making about treatment options. More information about the specific roles of the MS Care team members and how team members interact within the redesigned system of care can be found in our previously published methods paper.[61]

MS Care also enhances usual care in that it systematizes many aspects of pain and depression care (eg, weekly treatment response monitoring and weekly review of all patients not responding to treatment) and uses technology to support patient tracking, consultation, and outreach efforts. These features cue the team to rapidly intensify or modify care for patients whose pain and depression are not responding to treatment. They also allow the team to quickly identify those who are not adhering to treatment so that efforts to reengage the patient can be promptly deployed. The care manager provides the critical link for implementing these "rapid-response" strategies for delivering evidence-based care. Whereas usual care typically requires that pain and depression treatments be delivered in person in a clinic setting, MS Care offers patients the choice of receiving care-management sessions in person at the clinic, by telephone, or via a combination. For further information on how MS Care compares with and enhances usual care, see our methods paper.[61]

Once a patient was randomly assigned to MS Care, the MS Care manager contacted that patient to set up a patient-centered assessment and treatment planning session (session 1), which was followed by up to 11 additional 30- to 60-minute care-management sessions over 16 weeks, depending on treatment response and patient preference. In these sessions the care manager reviewed the patient's adherence to pharmacologic and nonpharmacologic treatments over the past week and collaboratively addressed barriers to adherence, using problem-solving and motivational enhancement strategies. The care manager also discussed

any new treatment recommendations from the care team. Each session then included instruction in and rehearsal of a behavioral self-management skill (eg, goal-setting, mindfulness meditation, relaxation), which the participants were encouraged to practice between sessions. Time was also spent reviewing the patient's homework from the past session, including practice and application of self-management skills for pain and mood. A summary of each session was documented in the electronic medical record, and the patient's scores on the pain and depression measures were recorded in the electronic caseload registry for review in the weekly team caseload review meetings. The care-management sessions were delivered by the care manager in person or by phone, based on patient preference. As MS Care is patient centered and thus intentionally flexible, each patient's care varied depending on individual needs, treatment goals, and preferences.

The care managers used a manual that was developed specifically for MS Care to guide them in delivering collaborative care for pain and depression in the context of MS. The manual provided an outline of the essential elements of a typical care-management session. It also included information about and modules for other evidence-based components of MS Care. A patient workbook (paper and/or electronic copy) was provided to MS Care participants; the workbook was tailored to each patient based on his or her specific symptoms, needs, and treatment plan. The workbook was used to facilitate review of information in session, particularly for those participating by phone, and to facilitate retention of educational content and practice of specific self-management skills outside of the care-management sessions. A follow-up call was conducted at week 24 to maximize maintenance of treatment gains; it included reviewing the patient's current symptoms, relapse prevention plan, and recommendations for further treatment and self-management strategies. This follow-up occurred approximately 8 weeks after the last regular care-management session, a time frame that might occur in clinical practice and that was feasible given the study time frame.

In addition to the care-management sessions, MS Care included weekly team caseload review (ie, expert consultation), treatment monitoring/intensification, care coordination, and relapse prevention. In the caseload review meetings the pharmacologic, behavioral, and

rehabilitation treatments were reviewed by experts in psychiatry, psychology, and pain management. Medications for pain and/or depression were reviewed; medication recommendations from the expert consultants followed established evidence-based treatment algorithms. Optimized management also included recommendations for other interventions such as physical therapy to address pain and/or to safely increase physical activity. Recommendations from these meetings were communicated by the care manager to the MS clinic providers via providers' preferred methods (eg, electronic medical record, in person, secure email, or telephone). If medication adjustments were approved, the treating MS physician provided an updated prescription. In occasional complex medication-management cases, direct communication between the treating MS physician and the content expert in that domain (eg, psychiatrist) occurred.

For specific details about the content of the care-management sessions and the other collaborative care components, see Appendix A.

Usual Care

The care manager called participants assigned to the usual care group to notify them of their group assignment and told them that they could continue to receive or seek care as they normally would, including at the MS Center. We recommended that they speak to their health care provider about possible options for addressing pain and/or depression. Participants also received a resource list of community and web-based resources for pain, depression, and MS. We reminded participants of the outcome-assessment timeline and the importance of completing the outcome assessments.

As patients of the UW Medicine MS Center, usual care participants typically receive medical care from a neurologist and/or rehabilitation medicine physician. Additional services available at the MS Center include rehabilitation psychology, vocational counseling, infusion services, and consultation with an on-site pharmacist. Patients also often receive services that are external to the MS Center. Common services include physical therapy, occupational therapy, speech therapy, and urology. On an individual basis, patients may be prescribed any of

a number of other external specialty services of relevance to this study; these may include treatment in a specialty pain center or care provided by an outside psychiatrist. The methods article[61] provides additional information about usual care at the UW Medicine MS Center.

Care Manager Training, Supervision, and Fidelity Monitoring

Two master's-level social workers acted as care managers in the MS Care study. Both care managers had expertise in behavioral interventions and care coordination before the study. Formal training in the collaborative care approach, treatment of pain and depression in MS, and study procedures was provided by co-investigators with relevant expertise. Didactic training was provided via lecture, experiential training, and an online training system. Given the breadth of treatment and the unique element of using a treatment model tailored to individual participants, the study included ongoing training via individual and group consultation as well as supervision on a weekly basis.

Although collaborative care is inherently flexible in its delivery of evidence-based interventions, the care-management sessions did have key components, including (1) use of valid measures to assess and monitor pain and depression severity and outcomes; (2) a shared care plan built around patient-centered goals and treatment targets; (3) provision of evidence-based treatments (medical and behavioral); (4) use of a registry to systematically track all patients, treatments, and outcomes; (5) 1 patient contact per week until treatment targets were attained and a relapse prevention plan in place; (6) monitoring of treatment response, adverse effects, and complications at each contact using valid measures; (7) discussion of cases that were new or not improving at weekly caseload consultation meetings; (8) proactive outreach to patients who did not follow up with care; and (9) facilitation of care coordination and communication among MS Care team, other health care providers, specialty care, social services, and community resources. To assess the care managers' fidelity to these key components, we audio-recorded care-management sessions, which we assessed through an independent review of randomly selected digital recordings from 10% of all sessions across both care managers.

Study Outcomes

Primary Outcome

We chose the primary outcome—control of pain and depression—and the measures used to determine control because they are considered the gold standards for assessing pain and depression outcomes in clinical and collaborative care research. Control of pain is defined as an average pain intensity score of < 3 in the past week or obtaining a ≥ 30% reduction in pain intensity from baseline. Pain intensity was assessed using the 10-point numerical rating scale for average pain intensity in the past week from the Brief Pain Inventory (BPI).[62,63] This measure has been validated in MS samples.[64] The 30% criterion is based on research in MS[65] and on the recommendations of a consensus panel[52] whose members defined this reduction as a clinically meaningful outcome. Control of depression is defined as a reduction of at least 50% depression severity or a score of < 0.5 on the Hopkins Symptom Checklist-20 version B (HSCL-20vB).[66,67] The HSCL-20vB is a brief self-report measure of cognitive, emotional, and somatic symptoms of depression commonly used in treatment outcome studies. The measure has excellent psychometric properties and is highly sensitive to change, particularly in medical populations. It contains the 13-item depression subscale and 7 additional items that reflect the somatic component of depression, all on a 5-point scale (0 = not at all, 4 = extremely). It has been shown to have high validity and reliability, including in people with MS.[68] The depression control cutoff is considered a clinically significant improvement in depression trials.[69] We selected the HSCL-20vB as our primary depression outcome measure over the PHQ-9 because the HSCL-20vB has been used as a primary outcome in many of the previous depression trials in MS, whereas the PHQ-9 has not.

The primary outcome—control of pain and depression—is a binary variable, scored as positive if the participant meets the criteria for both control of pain and control of depression at the posttreatment assessment. Those who only have one problem (ie, have pain *or* depression but not both) automatically met the control criteria for that domain at that time point. For example, if someone was identified as having depression but not pain, this person was defined as having “control of pain.” Thus, our prespecified primary outcome required

participants to have control of both pain and depression, regardless of their pain or depression status at the time of enrollment.

Secondary Outcomes

A modified 7-item version[70] of the BPI[71] was used to assess pain interference using a 0 to 10 numeric rating scale (0 = "does not interfere" to 10 = "completely interferes"). The modified BPI changed the item "walking ability" to "mobility ability to get around" to accommodate wheelchair or power-mobility users and has been validated for use in the MS population.[64] Self-reported depression severity was computed from the HSCL-20vB (total score). Depression diagnosis status was collected via a structured diagnostic assessment, the MDE and dysthymia modules of the MINI, which can be administered reliably and validly by trained staff who are not clinicians.[49]

Our other secondary outcomes included those that our stakeholders identified as important ones impacted by pain and depression or those that the literature identified as commonly affected by depression and/or pain. Several measures, including pain interference (0–10 numeric rating scale, with 10 indicating greater interference) and treatment satisfaction ratings (ordinal scale), are also core outcome measures in clinical trials of pain treatments. The secondary outcomes, with their supporting references, are listed in Table 1 and include assessment of disability, fatigue, perceived self-efficacy for managing MS, and health-related quality of life. The Sheehan Disability Scale (SDS) was used to assess how much participants' symptoms impaired their functioning in the domains of work/school, social/leisure activities, and family/home responsibilities; scores can range from 0 (unimpaired) to 30 (highly impaired). Both the fatigue and self-efficacy scales are converted to T scores with a mean of 50 and standard deviation of 10; higher scores represent more fatigue and more self-efficacy. The Euro-QoL-5D Visual Analogue Scale (EQ-5D VAS) reports health status on a 0 (worst imaginable health state) to 10 (best imaginable health state) scale. Treatment satisfaction with 3 types of care—pain/depression care, MS Care, and overall health care—was assessed posttreatment and at the 6-month assessment, as was the global impression of change for pain and depression (ordinal scale for each). For those assigned to MS Care, the care managers tracked the nature

and number of treatment components delivered during treatment (eg, relaxation training , medication coordination) so that we could describe in detail the treatment components delivered as part of the MS Care intervention.

Table 1. Primary and Secondary Outcome Measures

Outcome or variable	Measure (no. of items)
Primary outcomes	
Control of pain	BPI pain-intensity scale[62,63] (4 items)
Control of depression	HSCL-20vB[67] (20 items)
Pain and depression secondary outcomes	
Pain interference	BPI[62,63] (4 items)
Quality of depression and pain care	Composite of medical services utilization from Cornell Services Index and self-reported medication data (composite measure)
Depressive disorder diagnosis	MDE and dysthymia modules of the MINI (18 items)
Other secondary outcomes	
Disability	SDS (3 items)
Health-related quality of life	EQ-5D[5] VAS (5 items)
Patient ratings of improvement and satisfaction with care	PGIC Scale (5 items) and PGATS (3 items)
Fatigue	PROMIS-Fatigue-MS (short-form)[6] (8 items)
Medical services use—past 3 months	Cornell Services Index (8 items)
Self-efficacy for managing MS	Self-Efficacy Scale for Multiple Sclerosis (4 items)
Medications	Self-reported medications, dose, and indication

Abbreviations: BPI, Brief Pain Inventory; EQ-5D VAS, Euro-QoL-5D Visual Analogue Scale; HSCL-20vB, Hopkins Symptom Checklist-20 version B; MDE, major depressive episode; MINI, Mini-International Neuropsychiatric Interview; PGATS, Patient Global Assessment of Treatment Satisfaction; PGIC, Patient Global Impression of Change; PROMIS, Patient-Reported Outcomes Measurement Information System; SDS, Sheehan Disability Scale.

Study Setting

We recruited participants and conducted the study from the UW Medicine MS Center in Seattle, a multidisciplinary center with in-house neurology, rehabilitation medicine, rehabilitation psychology, social work, rehabilitation counseling, infusion, and nursing services, as well as co-located physical therapy, occupational therapy, and speech therapy services. Each year the MS Center provides comprehensive care to more than 1800 patients representing a diverse payer mix (40% Medicare/Medicaid, 10% self-pay/charity care, and 50% commercial insurance). Approximately 35% to 40% of the center's patients live in rural areas within a 5-state region (Washington, Wyoming, Alaska, Montana, and Idaho). We chose this setting to compare 2 systems of care delivery—MS Care and usual care—within a health care system that is representative of the comprehensive care common in MS specialty settings.

Time Frame for the Study

In primary care studies and settings, the time frame for collaborative care interventions varies considerably depending on the context and treatment targets. For this study, we chose an intervention period of 16 weeks; up to 12 care-management sessions occurred within this time frame, depending on treatment response and patient preference. We selected 16 weeks because this time frame allows for an adequate dose of MS Care's behavioral and pharmacotherapy treatments while remaining feasible in the context of a 3-year study. Study outcomes were assessed at baseline (pretreatment), posttreatment (4-months postrandomization: primary end point), and at the 6-month follow-up (10 months postrandomization). This time frame permitted assessment of the 6-month maintenance of any treatment effects beyond the immediate posttreatment period. Recruitment commenced on May 1, 2014; the last participant was enrolled on May 20, 2016.

Data Collection and Sources

Research staff unaware of intervention allocation administered all outcomes via telephone interview at baseline, posttreatment, and the 6-month follow-up. At baseline, staff obtained descriptive variables from the medical record, in addition to the telephone interview. Baseline data included demographic variables (sex, age, race, ethnicity, education level,

employment status, postal zip code, and marital status) and MS variables, including MS first symptom and diagnosis dates (to compute disease duration), course of MS (relapsing remitting, primary progressive, secondary progressive, or progressive relapsing), and use of disease-modifying therapies. Staff administered an Expanded Disability Status Scale self-report, as it is a core measure of MS disease progression in clinical trials.[72] Baseline descriptive measures also included participants' pain and depression histories, including number of pain sites and pain duration. The baseline interview assessment was conducted over 2 phone interviews within 1 week. The posttreatment and 6-month follow-up outcome assessments were typically administered in 1 interview of approximately 45 minutes' duration. To decrease participant fatigue and burden, we offered participants the opportunity to take breaks as needed and to schedule assessments at their convenience.

We tracked recruitment outcomes for all clinic patients approached about the study, including for those who were ineligible or declined participation, and the reasons for ineligibility or declination. To minimize attrition among those enrolled in the study, we did the following: (1) provided the study intervention and assessments at times that were convenient to participants; (2) obtained outcome data via telephone assessments rather than paper-and-pencil questionnaires; (3) called in advance of telephone assessments to schedule the assessments and problem-solve scheduling conflicts as needed; (4) used the same trained assessors to complete all of a patient's telephone assessments whenever possible; (5) obtained contact information for 3 alternative contacts (eg, parents) and permission to reach out to these contacts if the participant could not be located; (6) offered financial compensation for the time and effort it took participants to complete the telephone assessments ($30 for each outcome assessment plus an additional $40 if all 3 assessments were completed, for a total of up to $130); and (7) implemented a database and assessment monitoring system that reminded staff to call participants at designated times for assessments.

We also obtained feedback on the MS Care intervention and study from participants via 4 focus groups conducted in March 2017. Our stakeholders encouraged us to obtain feedback via focus groups and helped develop the focus-group questions and discussion prompts. We

originally intended to seek input only from those who were allocated to the MS Care group, but we included those allocated to usual care at the direction of our stakeholder advisors. Via postal mail and telephone, we approached 40 randomly selected study participants (20 from each group) about participating in the focus groups. Of the 25 participants who expressed interest in participating when we contacted them, 16 attended the focus groups: 9 from the usual care group and 7 from the MS Care group (divided into 2 sessions each for a total of 4 sessions). At the request of the participants, the focus groups were conducted by teleconference with 3 to 5 participants per call. The discussions were semistructured with a guide. Focus-group participants in the MS Care group were asked questions such as the following: "What were the benefits of MS Care?" "Did MS Care impact the care you got at the MS Center in general?" "What changes should we make to improve the MS Care program?" Focus-group participants in the usual care group were asked questions such as the following: "What were your thoughts about being assigned to usual care?" "What was being in the study like for you?" "What could we do better as a health care system to improve care for people with MS who also have pain and/or depression?" Participants in both groups were asked, "How could we better engage people with depression in MS Care or depression care in general?" The focus groups were recorded, transcribed, and coded for content.

Analytical and Statistical Approaches

Patient demographic and clinical characteristics at baseline were compared between the 2 groups using t test for age and years of education, and chi-square test for sex, race, ethnicity, marital status, and employment. Our a priori analysis plan conformed to the intent-to-treat principle: all randomly assigned participants were to be included based on their assigned treatment group regardless of actual treatment received. For the primary analysis, we compared the proportion of individuals (MS Care vs usual care) who had control of depression and pain symptoms posttreatment, with a 2-sided significance level of 0.05. Initially, we had suggested that if necessary we would use imputation for missing values and sensitivity analysis comparing the results from complete data with the imputed data. Fortunately, attrition was very low in our study (1 person in MS Care and 2 in usual care posttreatment, and 3 in MS Care and 4 in usual care at the 6-month follow-up). Details are shown in Figure 1. Therefore, data

analyses were carried out using complete data. The secondary outcomes for the 2 groups were compared posttreatment and at the 6-month follow-up using t tests for continuous variables and Fisher tests for categorical variables.

Changes to the Original Study Protocol

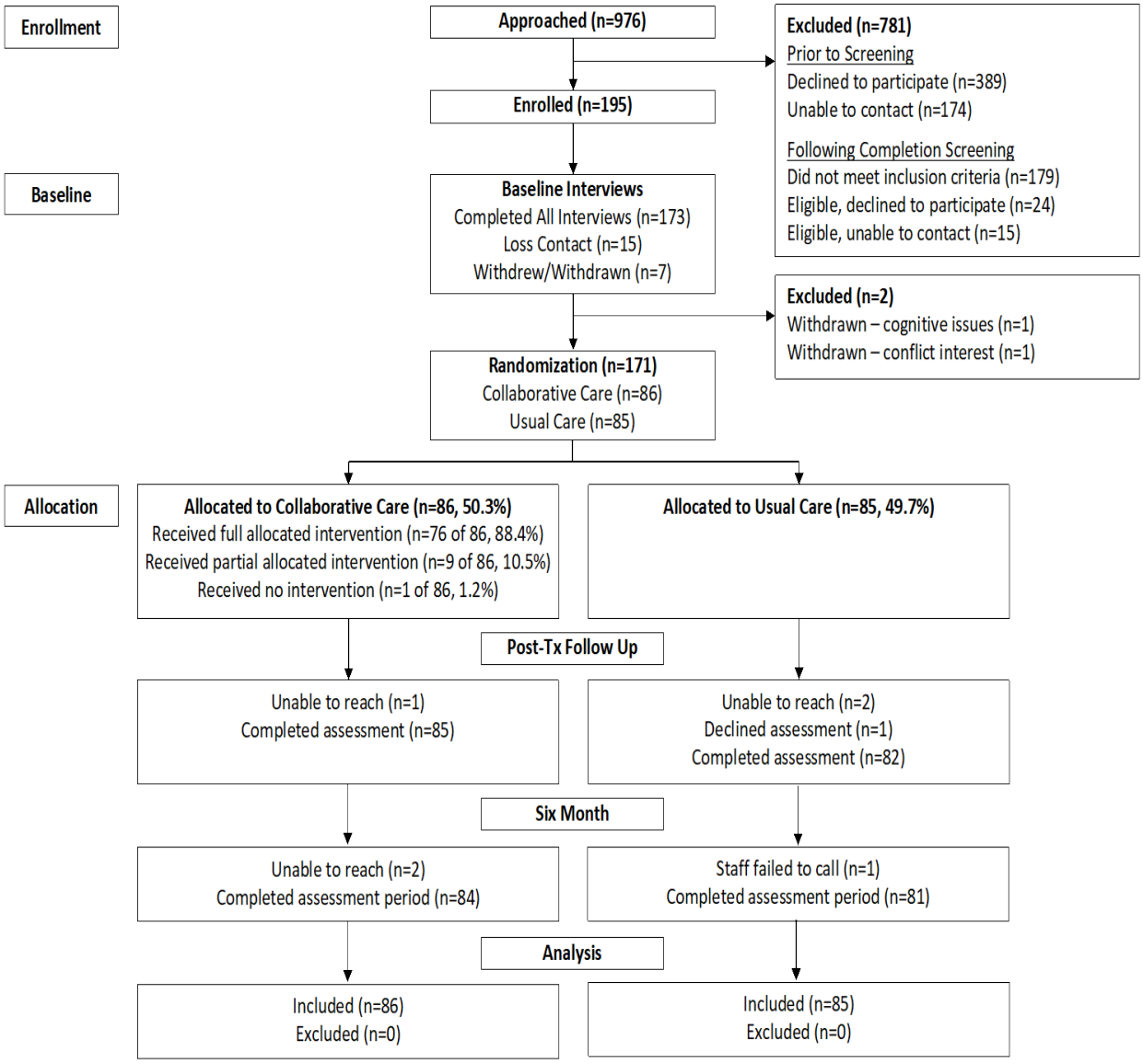
We did not make any major changes to the study protocol. We made several minor changes to facilitate participant recruitment procedures. For example, we obtained IRB approval on February 2, 2015, for several minor changes to our consent process, including for the following: (1) obtaining verbal consent to participate in the study instead of written consent (this allowed us to recruit individuals by telephone instead of by postal mail); and (2) allowing participants to send completed medical release information forms via fax rather than mail. At our patient partners' suggestion, we added an additional recruitment strategy: We mailed recruitment letters to MS Center patients who did not have any upcoming scheduled clinic appointments. This approach (approved by the IRB) aimed to capture those who might not have a scheduled appointment (and therefore would not be captured in our clinic-based recruitment approach) but who still received care at the center and might have chronic pain or depression.

RESULTS

Participant Enrollment and Baseline Characteristics

Figure 1 summarizes the participant flow through the study. Among the 976 patients approached about the study during the enrollment period, a total of 389 patients declined to participate before completion of the screening process. In addition, research staff were unable to contact 174 patients for purposes of screening. A total of 413 patients completed the eligibility screening, 234 (56.7%) were eligible, and 195 (83.4% of those screened and eligible) consented and were thus enrolled. Patients could decline study participation before or after completion of the screening process. Of the 413 patients who declined participation, 74% (306) were not interested in participating. An additional 12% (50) reported that they did not have problems with pain or depression. Other reasons for declination included too much time involved in participation (33; 8%), acute medical issues prohibiting participation (11; 3%), believing treatment would not help (3; < 1%), declining to answer depression/psychiatric screening questions (3; < 1%), living too far away (2; <1%), and other (5; < 1%). The most common reasons patients were ineligible were that they did not meet the pain or depression severity criteria (71; 40%) or did not have a definitive MS diagnosis (68: 38%) at screening (eg, a consecutive clinic patient who was seen at the MS Center but not diagnosed with MS at that clinic visit). The remaining reasons for ineligibility included the following: no plan to receive continued care at the UW Medicine MS Center for at least the next 6 months (11), being at high suicide risk (7), inability to provide informed consent/failure of cognitive screener (7), current psychotic episode (5), active substance abuse (4), inability to communicate in English (3), no access to phone/inability to communicate by phone (1), receiving depression care from a psychiatrist more than once per month (1), and declining to provide a current address during screening (1).

Figure 1. Participant flow



Of the 195 enrolled participants, 173 participants completed the baseline assessment, 7 participants withdrew, and 15 were lost to contact before randomization. Another 2 participants were excluded at this point, resulting in 171 randomly assigned participants. Of those, 168 (98%) completed the primary end point outcome assessments, and 165 (96%) completed the 6-month follow-up outcome assessments.

At baseline the treatment groups were similar across sociodemographic and clinical characteristics except that usual care participants were more highly educated (Table 2).

Participants in both groups were generally middle-aged, female, and white. Most had lived with MS for ≥ 10 years. Nearly two-thirds of the sample were not working, due to being retired or disabled. We enrolled participants from 20 different counties in Washington state and from 4 other states (Wyoming, Alaska, Montana, and Idaho). At the time of the screening, the majority of participants met inclusion criteria for moderate or severe pain (72%) or pain and depression (23%); only a few individuals met inclusion criteria for depression alone (5%).

Table 2. Patients' Demographic and Clinical Characteristics at Baseline

Characteristic	Group		*P* value[a]
	MS Care	Usual care	
Sample size	86	85	
Age, in years			
Mean (SD)	50.9 (12.6)	50.0 (12.9)	
Median (min, max)	52.5 (24.0, 80.0)	52.0 (24.0, 72.0)	
Sex, % females (n)	80.2 (69)	76.5 (65)	0.55
Race, % white (n)[b]	87.2 (75)	81.2 (69)	0.28
Ethnicity, % Hispanic (n) (1 missing in usual care)	9.3 (8)	10.7 (9)	0.76
Years of education			
Mean (SD)	14.5 (2.4)	15.2 (2.3)	0.04
Median (min, max) (1 missing in MS Care)	14.0 (8.0, 20.0)	16.0 (9.0, 20.0)	
Married or with partner, % (n)	50.0 (43)	57.6 (49)	0.32
Employment, % (n)			
Working now	27.9 (24)	34.1 (29)	0.27
Retired	20.9 (18)	16.5 (14)	
Disabled	47.7 (41)	40.0 (34)	
Other	3.5 (3)	9.4 (8)	
Screening group, % (n)			
Pain	72.1 (62)	71.8 (61)	0.93
Depression	5.8 (5)	4.7 (4)	
Pain and depression	22.1 (19)	23.5 (20)	
Years since diagnosis			
Mean (SD)	12.1 (10.5)	11.6 (8.9)	0.74
Median (min, max)	10 (0, 52)	11 (0, 33)	

Abbreviation: MS, multiple sclerosis.

[a] *P* value from t test for age and years of education, and from chi-square test for sex, race, ethnicity, marital status, and employment.

[b] Nonwhite racial categories were grouped together due to few people being in each category.

Treatment Adherence, Dose, Fidelity, and Adverse Events

Among the 86 participants allocated to MS Care, 40% (n = 34) had sessions exclusively by phone, 8% (n = 7) had sessions exclusively in person, and 52% (n = 44) had sessions by phone and in person. Nearly 70% (n = 59) had at least three-fourths of their sessions by phone. Across participants, nearly 75% of the total MS Care sessions took place by phone, with just over 25% occurring in person. The median number of care-management sessions was 11 (interquartile range, 10–12); 67% of the MS Care participants participated in 12 sessions and 90% participated in 10 to 12 sessions. A small percentage (9%) of participants had fewer than 12 sessions because they reached their treatment goals in fewer sessions and preferred to terminate treatment.

Although collaborative care is inherently flexible and thus varies in the specific treatment content, each care-management session had a prescribed structure and elements to guide the tailoring of evidence-based treatments to each patient. To determine if the care managers adhered to the required elements of the session content, an independent reviewer rated 120 session recordings from 10 randomly selected cases across both care managers. We found that the reviewed sessions were delivered with > 90% fidelity.

In line with the design of the study, a core set of components was delivered to virtually all participants: pain/depression psychoeducation (delivered to 100% of participants), self-monitoring (100%), values exploration (98.8%), goal-setting/activation (98.8%), and relaxation training (97.6%). Additional components were distributed among participants: problem-solving (92.9%), relapse prevention (85.9%), cognitive-behavioral therapy (84.7%), energy management (71.8%), and distress tolerance and managing strong emotions (69.4%). Slightly more than half of the participants received modules on cultivating social support (58.8%) and mindfulness-based strategies (51.8%).

There were no adverse events related to study procedures.

Control of Pain and Depression (primary outcome)

The primary aim was to compare MS Care with usual care in reducing depression and pain in MS patients receiving care at an MS specialty center. We hypothesized that compared with those in usual care, participants allocated to MS Care would demonstrate significantly greater control of pain and depression posttreatment. When designing the study, we defined control of pain as either average pain severity < 3 in the past week on a 0 to 10 numeric rating scale or obtaining ≥ 30% reduction in pain severity from baseline. Control of depression was defined as a reduction of at least 50% in depression severity or a score of < 0.5 on the HSCL-20vB. The reason for entry into the study (lack of control of pain, of depression, or of both) was not considered in the outcome definition.

As shown in Table 3, there was no statistical difference between the 2 groups in the proportion of individuals whose pain and depression were under control at the primary end point (posttreatment), although the MS Care group had a slightly higher proportion (18.8% vs 12.2% in usual care, $p = 0.24$). At the 6-month follow-up, the MS Care group was statistically different from the usual care group (17.9% in MS Care vs 7.4% in usual care, $p = 0.04$), with 10.5% more individuals with depression and pain under control.

Table 3. Binary Primary Outcome Results for Pain and Depression Control

Pain and depression control	Posttreatment[a]			6-month follow-up[b]		
	MS Care	Usual care	*P* value[c]	MS Care	Usual care	*P* value[c]
Yes, % (n)	18.8 (16)	12.2 (10)	0.24	17.9 (15)	7.4 (6)	0.04
95% CI	10.5-27.1	5.1-19.3		9.7-26.0	(1.7-13.12)	
No, % (n)	81.2 (69)	87.8 (72)		82.1 (69)	92.6 (75)	
95% CI	72.9-89.5	80.7-94.9		74.0-90.3	(86.9-98.3)	
Total	100 (85)	100 (82)		100 (84)	100 (81)	

Abbreviations: MS, multiple sclerosis.
[a] 1 missing value in the MS Care group and 3 missing values in the usual care group.
[b] 2 missing values in the MS Care group and 4 missing values in the usual care group.
[c] From chi-square test of homogeneity.

the lack of statistical significance is due to the small sample size. Regarding satisfaction with health care (Table 5), both groups reported generally high satisfaction overall, regardless of the time point. However, the MS Care group tended to have a higher proportion endorsing “very satisfied” than the usual care group, with statistically significant differences for all 3 types of care assessed—pain/depression care, MS Center care, and overall health care—posttreatment. These differences were not maintained at the 6-month follow-up, however. Although declining slightly, satisfaction remained high overall at the follow-up.

Table 4. Secondary Outcome Measures: Baseline, Posttreatment, and 6-Month Follow-up

Secondary outcome measures	Baseline			Posttreatment			6-mo follow-up		
	MS Care	Usual care	*p*[a]	MS Care	Usual care	*p*[a]	MS Care	Usual care	*p*[a]
Sample size	86	85		85	82		86	85	
Pain measures									
BPI score									
Mean (SD)	4.8 (2.3)	4.7 (2.5)	0.94	3.4 (2.3)	4.7 (2.6)	0.001	3.7 (2.3)	4.7 (2.4)	0.006
Median (min, max)	5.1 (0.4, 9.6)	4.3 (0.0, 9.4)		3.4 (0.0, 10.0)	4.7 (0.0, 10.0)		3.5 (0.0, 9.4)	5.2 (0.0, 8.9)	
Missing	1	0		0	0		2	4	
Average pain intensity									
Mean (SD)	4.9 (2.1)	4.9 (1.9)	0.97	4.1 (2.2)	4.9 (2.1)	0.02	4.3 (2.2)	4.8 (2.2)	0.09
Median (min, max)	5.0 (0.0, 10.0)	5.0 (0.0, 9.0)		4.0 (0.0, 8.0)	5.0 (0.0, 10.0)		4.0 (0.0, 10.0)	5.0 (0,0. 9.0)	
Missing	1	0		0	0		2	4	
Other measures									
Depression severity (HSCL-20vB)									
Mean (SD)	1.6 (0.8)	1.5 (0.7)	0.61	1.1 (0.7)	1.3 (0.8)	0.01	1.2 (0.7)	1.3 (0.7)	0.59
Median (min, max)	1.5 (0.1, 3.4)	1.4 (0.1, 3.5)		0.8 (0.0, 3.2)	1.4 (0.0, 3.2)		1.0 (0.2, 3.2)	1.2 (0.1, 3.2)	
Missing	0	0		0	0		2	4	
Disability (SDS)									
Mean (SD)	15.1 (8.2)	16.1 (7.6)	0.42	10.0 (7.7)	13.4 (8.8)	0.02	12.1 (7.5)	15.6 (7.4)	0.004

Secondary outcome measures	Baseline			Posttreatment			6-mo follow-up		
	MS Care	Usual care	*p*[a]	MS Care	Usual care	*p*[a]	MS Care	Usual care	*p*[a]
Median (min, max)	16.0 (1.0, 30.0)	17.0 (0.0, 29.0)		9.0 (0.0, 28.0)	13.0 (0.0, 30.0)		11.0 (0.0, 29.0)	17.0 (0.0, 30.0)	
Missing	15	8		11	11		8	9	
PROMIS-Fatigue score									
Mean (SD)	61.0 (7.9)	61.2 (6.8)	0.83	57.5 (8.5)	60.2 (8.4)	0.04	57.9 (7.6)	60.5 (7.6)	0.03
Median (min, max)	62.0 (39.9, 81.3)	62.0(44.1, 77.9)		57.7 (34.7, 77.9)	62.0 (34.7, 81.3)		57.7 (34.7, 73.9)	60.9 (34.7, 72.4)	
Missing	1	3		0	0		2	4	
UWCORR Self-efficacy scale									
Mean (SD)	44.9 (8.1)	44.6 (7.0)	0.78	46.5 (9.9)	44.2 (8.3)	0.12	47.0 (9.3)	45.9 (8.7)	0.44
Median (min, max)	44.1 (23.8, 68.9)	44.1 (28.9, 61.3)		45.6 (26.5, 68.9)	43.4 (26.5, 68.9)		45.6 (20.0, 68.9)	45.6 (20.0, 68.9)	
Missing	6	0		5	0		5	4	
EQ-5D VAS									
Mean (SD)	58.9 (21.9)	58.2 (19.9)	0.82	58.5 (22.5)	58.7 (21.1)	0.96	62.6 (18.9)	63.2 (17.2)	0.84
Median (min, max)	60.0 (0, 95)	60.0 (0, 95)		60.0 (2, 95)	60.0 (0, 90)		65.0 (10, 97)	65.0 (15, 90)	
Missing	0	0		1	3		2	4	
PGIC									
Pain compared with baseline, % (n)[b]									
Very much better				11.1 (9)	2.6 (2)	<0.001	17.7 (14)	1.3 (1)	<0.001
Much better				28.4 (23)	16.7 (13)		22.8 (18)	13.0 (10)	
A little better				40.7 (33)	16.7 (13)		29.1 (23)	23.4 (18)	

Secondary outcome measures	Baseline			Posttreatment			6-mo follow-up		
	MS Care	Usual care	*p*[a]	MS Care	Usual care	*p*[a]	MS Care	Usual care	*p*[a]
No change				12.3 (10)	34.6 (27)		15.2 (12)	27.3 (21)	
A little worse				4.9 (4)	19.2 (15)		11.4 (9)	23.4 (18)	
Much worse				2.5 (2)	7.7 (6)		3.8 (3)	9.1 (7)	
Very much worse				0.0 (0)	2.6 (2)		0.0 (0)	2.6 (2)	
Depression compared with baseline, % (n)[c]									
Very much better				15.4 (4)	7.7 (2)	0.46	13.6 (3)	4.3 (1)	0.28
Much better				26.9 (7)	11.5 (3)		31.8 (7)	8.7 (2)	
A little better				26.9 (7)	19.2 (5)		22.7 (5)	21.7 (5)	
No change				19.2 (5)	30.8 (8)		22.7 (5)	34.8 (8)	
A little worse				7.7 (2)	19.2 (5)		4.5 (1)	17.4 (4)	
Much worse				3.8 (1)	7.7 (2)		4.5 (1)	8.7 (2)	
Very much worse				0.0 (0)	3.8 (1)		0.0 (0)	4.3 (1)	

Abbreviations: BPI, Brief Pain Inventory; EQ-5D VAS, Euro-QoL-5D Visual Analogue Scale; HSCL-20vB, Hopkins Symptom Checklist-20 version B; MS, multiple sclerosis; PGATS, Patient Global Assessment of Treatment Satisfaction; PGIC, Patient Global Impression of Change; SDS, Sheehan Disability Scale; UWCORR, University of Washington Center on Outcomes Research in Rehabilitation.

[a] From t test for BPI, average pain intensity, HSCL-20vB, SDS, PROMIS-Fatigue, and UWCORR Self-efficacy. *P* value from Fisher exact test for PGIC items.

[b] 81 individuals screened for pain in each group at baseline.

[c] 24 individuals screened for depression in each group at baseline.

Table 5. Treatment Satisfaction: Posttreatment and at 6-Month Follow-up

	Posttreatment			6-mo follow-up		
	MS Care	**Usual care**	***p*[a]**	**MS Care**	**Usual care**	***p*[a]**
Sample size	85	82		86	85	
PGATS: Satisfaction with any care for pain and/or depression, % (n)						
Very dissatisfied	0.0 (0)	0.0(0)	<0.001	1.2 (1)	1.3 (1)	0.14
Dissatisfied	3.5 (3)	9.9 (8)		4.8 (4)	3.8 (3)	
No preference	7.1 (6)	30.9 (25)		11.9 (10)	25.0 (20)	
Satisfied	30.6 (26)	40.7 (33)		32.1 (27)	35.0 (28)	
Very satisfied	58.8 (50)	18.5 (15)		50.0 (42)	35.0 (28)	
PGATS: Satisfaction with care at MS Center, % (n)						
Very dissatisfied	0.0 (0)	1.3 (1)	0.04	0.0 (0)	0.0(0)	0.40
Dissatisfied	1.2 (1)	1.3 (1)		2.5 (2)	2.6 (2)	
No preference	3.5 (3)	10.1 (8)		4.9 (4)	11.5 (9)	
Satisfied	23.5 (20)	35.4 (28)		22.2 (18)	25.6 (20)	
Very satisfied	71.8 (61)	51.9 (41)		70.4 (57)	60.3 (47)	
PGATS: Overall satisfaction with all health care, % (n)						
Very dissatisfied	1.2 (1)	0.0 (0)	0.007	0.0 (0)	0.0(0)	0.72
Dissatisfied	3.5 (3)	1.2 (1)		3.6 (3)	3.8 (3)	
No preference	2.4 (2)	9.8 (8)		4.8 (4)	6.3 (5)	
Satisfied	29.4 (25)	46.3 (38)		38.1 (32)	45.0 (36)	
Very satisfied	63.5 (54)	42.7 (35)		53.6 (45)	45.0 (36)	

Abbreviations: MS, multiple sclerosis; PGATS, Patient Global Assessment of Treatment Satisfaction.
[a] From t test for Brief Pain Inventory (BPI), average pain intensity, Hopkins Symptom Checklist-20 version B (HSCL-20vB), Sheehan Disability Scale (SDS), PROMIS-Fatigue, and UWCORR (University of Washington Center on Outcomes Research in Rehabilitation) Self-efficacy. *P* value from Fisher exact test for PGATS items.

Tables 6 and 7 show the findings from the Cornell Services Index, the measure of health care service utilization that we modified to capture rehabilitation services for this study, as well as depression treatment quality indicators. At baseline, MS Care participants reported

significantly more home health services utilization than usual care participants (p = 0.05); the 2 groups otherwise did not differ in utilization at baseline. The groups also did not differ significantly in their reported utilization of outpatient visits, rehabilitation services, alternative medicine services, total outpatient services, hospitalizations, or emergency department/urgent care visits posttreatment or at the 6-month follow up. Although the groups did not differ at baseline, posttreatment, and the 6-month follow-up, a significantly greater proportion of MS Care participants reported receiving psychotherapy (ie, counseling, therapy, or care management) than those in usual care (see Table 7). Table 7 also shows the proportions of participants, by group, that met criteria for an MDE, dysthymia, or both. At the 6-month follow-up, fewer MS Care participants met criteria for a current MDE, dysthymia, or both than usual care participants (p = 0.06).

Table 6. Health Care Services Utilization: Baseline, Posttreatment, and 6-Month Follow-up

	Baseline		Posttreatment		6-mo follow-up	
	MS Care	**Usual care**	**MS Care**	**Usual care**	**MS Care**	**Usual care**
Sample size	86 (0)	85 (0)	85 (1)	82(3)	83 (3)	81 (4)
Health care utilization (past 4 mo)						
Total no. outpatient visits						
Mean (SD)	5.7 (6.1)	6.4 (9.3)	4.8 (4.3)	5.6 (7.8)	4.0 (4.8)	5.4 (8.9)
Median (min, max)	4 (0, 33)	4 (0, 66)	4 (0, 21)	4 (0, 54)	3 90, 37)	3 (0, 72)
***p*[a]**	0.57		0.46		0.21	
Home health and aid services, % (n) receiving						
Total no. sessions[b]	26.7 (23)	12.9 (11)	11.8 (10)	14.6 (12)	16.7 (14)[c]	16.0 (13)
Mean (SD)	19.9 (130.9)	13.3 (69.8)	11.9 (51.4)	7.7 (34.1)	12.6 (41.2)	11.3 (51.4)
Median (min, max)	0 (0, 1200)	0 (0, 601)	0 (0, 400)	0 (0, 276)	0 (0, 228)	0 (0, 414)
***p*[d]**	0.05		0.67		0.85	
Rehab services, total sessions attended[b]						
Mean (SD)	6.8 (12.6)[e]	10.1 (34.7)	6.4 (10.5)	8.5 (20.2)	6.6 (8.7)[f]	7.3 (16.4)[g]
Median (min, max)	1 (0, 80)	1 (0, 283)	2 (0, 71)	0.5 (0, 130)	2 (0, 32)	1 (0, 110)
***p*[d]**	0.71		0.37		0.48	

	Baseline		Posttreatment		6-mo follow-up	
	MS Care	**Usual care**	**MS Care**	**Usual care**	**MS Care**	**Usual care**
Alternative medicine, total sessions attended[b]						
Mean (SD)	2.6 (6.0)[e]	9.0 (30.9)	2.3 (6.3)	3.6 (9.9)	5.0 (16.5)[h]	3.5 (9.9)[g]
Median (min, max)	0 (0, 33)	0 (0, 186)	0 (0, 48)	0 (0, 67)	0 (0, 120)	0 (0, 76)
p[d]	0.95		0.53		0.92	
Sessions total (home health, rehab, alternative)						
Mean (SD)	29.2 (130.8)	32.4 (85.0)	20.7 (52.1)	19.8 (46.9)	23.8 (43.8)[c]	21.9 (55.8)
Median (min, max)	5.5 (0, 1200)	4 (0, 608)	7 (0, 404)	5.5 (0, 281)	6 (0, 234)	4 (0, 420)
p[d]	0.62		0.74		0.59	
Hospital/ED						
How many hospital stays? % (n)[i]						
No hospital stays	96.5 (83)	94.1 (80)	91.8 (78)	97.6 (80)	98.8 (82)	98.8 (81)
1	0	1.2 (1)	3.5 (3)	2.4 (2)	0	0
2	3.5 (3)	3.5 (3)	3.5 (3)	0	1.2 (1)	0
3	0	0	1.2 (1)	0	0	0
4	0	0	0	0	0	1.2 (1)
6	0	1.2 (1)	0	0	0	0
Stayed overnight?						
Yes, % (n)	10.5 (9)	10.6 (9)	9.4 (8)	8.5 (7)	6.0 (5)	6.2 (5)

	Baseline		Posttreatment		6-mo follow-up	
	MS Care	Usual care	MS Care	Usual care	MS Care	Usual care
***p*[j]**	1.0		1.0		1.0	
Any visits ED/urgent care?						
Yes, % (n)	24.4 (21)	36.5 (31)	27.1 (23)	31.7 (26)	20.2 (17)	21.3 (17)
***p*[d]**	0.10		0.61		1.0	
How many ED/urgent care visits?[j]						
1	71.4 (15)	58.1 (18)	82.6 (19)	57.7 (15)	76.5 (13)	52.9 (1)
2	19.0 (4)	22.6 (7)	17.4 (4)	11.5 (3)	17.6 (3)	29.4 (5)
3	4.8 (1)	6.5 (2)	0 (0)	23.1 (6)	5.9 (1)	11.8 (2)
4	4.8 (1)	0 (0)	0 (0)	3.8 (1)	0 (0)	5.9 (1)
5	0 (0)	6.5 (2)	0 (0)	0 (0)	0 (0)	0 (0)
6 or 7	0 (0)	6.5 (2)	0 (0)	3.8 (1)	0 (0)	0 (0)

Abbreviations: ED, emergency department; MS, multiple sclerosis.
[a] From t test for difference on means.
[b] No. of sessions is set to 0 when a person did not receive any.
[c] No. of observations = 84.
[d] From Mann-Whitney test for differences in distribution.
[e] No. of observations = 85.
[f] No. of observations = 81.
[g] No. of observations = 80.
[h] No. of observations = 82.
[i] Distributions are too sparse to calculate a test of differences.
[j] From 2-sided Fisher exact test.

Table 7. Depression Outcomes and Care Quality: Baseline, Posttreatment, and 6-Month Follow-up

	Baseline		Posttreatment		6-mo follow-up	
	MS Care	**Usual care**	**MS Care**	**Usual care**	**MS Care**	**Usual care**
Sample size	86 (0)	85 (0)	85 (1)	82(3)	83 (3)	81 (4)
Quality of depression care						
Medication adherence						
Yes, % (n)	39.7 (29)	36.1 (26)	42.0 (29)	43.8 (28)	43.2 (35)	39.2 (29)
***p*[a]**	0.65		0.84		0.61	
Having psychotherapy[b]						
Yes, % (n)	32.9 (28)	34.1 (29)	67.1 (57)	30.5 (25)	52.4 (44)	33.3 (27)
***p*[c]**	1.0		<0.001		0.02	
Current MDE?						
Yes, % (n)	51.2 (44)	51.8 (44)	30.6 (26)	37.8 (31)	26.2 (22)	42.0 (34)
***p*[c]**	1.0		0.33		0.03	
Current dysthymia?						
Yes, % (n)	18.6 (16)	14.3 (12)	16.5 (14)	12.2 (10)	10.7 (9)	14.8 (12)
***p*[c]**	0.54		0.51		0.49	
Current MDE or dysthymia? % (n)						
Neither	45.3 (39)	45.2 (38)	64.7 (55)	62.2 (51)	66.7 (56)	58.0 (47)
MDE only	36.0 (31)	40.5 (34)	18.8 (16)	25.6 (21)	22.6 (19)	27.2 (22)
Dysthymia only	3.5 (3)	2.4 (2)	4.7 (4)	0 (0)	7.1 (6)	0 (0)
Both	15.1 (13)	11.9 (10)	11.8 (10)	12.2 (10)	3.6 (3)	14.8 (12)
***p*[a]**	0.87		0.19		0.06	

Abbreviations: MDE, major depressive episode; MS, multiple sclerosis.

[a] From chi-square test.

[b] Values refer to the past 6 months for baseline and 6-month follow-up and to the past 4 months for posttreatment.

[c] From 2-sided Fisher exact test.

Additional Analyses

Our prespecified primary outcome required participants to have control of both pain and depression, regardless of their pain or depression status at the time of enrollment. We therefore examined the 2 outcomes separately (Tables 8-11).

Table 8. Pain Control Only

	Randomization group, % (n)			
	MS Care	**Usual care**	**Total, % (n)**	***p***
Pain control posttreatment				
Yes	38.1 (32)	19.5 (16)	28.9 (48)	0.01
No	61.9 (52)	80.5 (66)	71.1 (118)	
Total	100 (84)	100 (82)	100 (166)	
Pain control at the 6-mo follow-up				
Yes	41.7 (35)	25.9 (21)	33.9 (56)	0.03
No	58.3 (49)	74.1 (60)	66.1 (109)	
Total	100 (84)	100 (81)	100 (165)	

Abbreviation: MS, multiple sclerosis.

Using the chi-square test of homogeneity, we reject the null hypothesis that the 2 groups had the same proportions of individuals with pain control at posttreatment ($p = 0.01$ for the Pearson chi-square test) and at the 6-month follow-up ($p = 0.03$ for the Pearson chi-square test). At posttreatment, the proportion of individuals with pain control in the MS Care group was almost twice as large as in the usual care group, with a difference of 18.6%. At the 6-month follow-up, the proportion of individuals with pain control in the MS Care group was 15.8% higher than in the usual care group. Table 9 describes how participants changed across each time point in terms of pain control.

Table 9. Pain Control Outcomes Over Time

Group	Pain control, % (n)			
	Neither time	Only posttreatment	Only at 6-mo follow-up	At both times
MS Care	50.0 (41)	8.5 (7)	12.2 (10)	29.3 (24)
Usual care	65.8 (52)	8.9 (7)	13.9 (11)	11.4 (9)

Abbreviation: MS, multiple sclerosis.

For depression control, using the chi-square test of homogeneity, we reject the null hypothesis that the 2 groups had the same proportions of individuals with depression control posttreatment (p = 0.04 for the Pearson chi-square test). The proportion of individuals with depression control was higher in the intervention group than in the usual care group, with a difference of 14.4%. However, using the chi-square test of homogeneity, we do not reject the null hypothesis that the 2 groups had the same proportions of individuals with depression control at the 6-month follow-up (p = 0.36 for the Pearson chi-square test). Table 11 describes how participants changed across each time point in terms of depression control.

Table 10. Depression Control Only

	Randomization group, % (n)		Total, % (n)	*p*
	MS Care	Usual care		
Depression control posttreatment				
Yes	38.8 (33)	24.4 (20)	31.7 (53)	0.04
No	61.2 (52)	75.6 (62)	68.3 (114)	
Total	100 (85)	100 (82)	100 (167)	
Depression control at the 6-mo follow-up				
Yes	29.8 (25)	23.5 (19)	26.7 (44)	0.36
No	70.2 (59)	76.5 (62)	73.3 (121)	
Total	100 (84)	100 (81)	100 (165)	

Abbreviation: MS, multiple sclerosis.

Table 11. Depression Control Outcomes Over Time

Group	Depression control, % (n)			
	Neither time	Only posttreatment	Only at 6-mo follow-up	At both times
MS Care	53.0 (44)	16.9 (14)	7.2 (6)	22.9 (19)
Usual care	68.4 (54)	10.1 (8)	8.9 (7)	12.7 (10)

Abbreviation: MS, multiple sclerosis.

Focus Group Results

MS Care Focus Groups

Focus-group participants who had received the MS Care intervention described numerous benefits from this treatment approach; several themes emerged. Participants described benefiting from instruction in specific strategies to manage pain and mood, including mindfulness exercises, relaxation techniques, and activity pacing. One participant said, “The collaborative care really helped me identify the resources that I already possess and put them together and use them…[I] have some tools.” Another noted, “It was empowering to have a backup plan to cope when that kind of stuff [pain] happened. It was comforting as well. I felt like I had more tools to deal with the difficulties I face and the uncertainty of all that.” Participants also described finding the MS Care workbook helpful; for example, one said, “This book [MS Care workbook] is like my way of life now, so I thought the book was really helpful—even now—I use it now.” Multiple participants described benefiting by having nonpharmacologic tools to manage pain. For example, one individual said, “I’m not a big fan of taking pain medications. My goal going into the study was to find other ways to deal with and cope with pain so I could take less. It was incredibly helpful for that.” Another stated, “Now I’ve got it really managed without medication, so that’s a really good thing.” Several participants reported being “accountable” to their care manager as beneficial, for example, “Having someone calling me and keeping account, and keeping me thinking about these issues was incredibly helpful.”

All MS Care focus-group participants highlighted the convenience and flexibility of the treatment sessions (ie, choice of in-person or telephone sessions) as a strength of the program. Many appreciated having the choice to do each session in person or by phone. Two participants noted that receiving treatment by phone took some "getting used to," but that the convenience outweighed this: "It was a little hard to get used to at first…I missed the visual cues you can get from someone. If I had lived closer, I absolutely would've been all in to do them all in person. The convenience of being able to do it by phone was great." Another said, "I did appreciate not having to come to the clinic, but I have a hard time communicating very well on the telephone. I would have preferred to be in person more often. It really wasn't possible and I think it's better than—I mean we achieved good things in spite of my telephone problem."

The structure of the collaborative care team, with the pain and depression experts consulting in the background and the care manager coordinating and communicating about care across providers, was also described as a strength. For example, one participant stated, "I'm a big fan of the team approach. I'm sure it also lightens the burden for the doctors and nurses." Another said, "The care manager was just the right mix of someone who took the time to get to know me but also was part of the medical team…she was like a bridge [to the medical team]." Multiple MS Care participants described improvements in or changes to their care as a result of participating: "The care manager helped to connect me with others [providers] in clinic" and "My doctor asked about and encouraged me to use my MS Care tools." Another described improved communication with their primary care provider: "Talking with the care manager gave me the lingo to talk with my primary care provider…she gave me more tools to be able to do that…to be able to advocate for myself when it came to pain management or other issues like that."

Focus-group participants were also asked what they would change to improve MS Care. All the participants initially said that they would not change it and recommended that MS Care be offered to others with MS within and outside UW Medicine. After further queries, several participants said that it would have been helpful to have care-management sessions available

after the 16-week window, perhaps with less intensity, to help stay on track with the tools they learned during the intervention phase.

On the topic of barriers to engaging potentially depressed patients in care for MS or depression in general, a prominent theme was that depression terminology may present barriers to care. One participant captured this by stating, “the word ‘depression’ is off-putting…maybe use the word ‘mood’ or ‘stress’ instead.” The term “depression” was viewed as “stigmatizing” by several participants. One recommended using the term “anxiety,” noting that anxiety may be more common and less stigmatizing than the term “depression.” Others described being labeled as “depressed” as stigmatizing and said that the label may be a barrier to care for some. Several pointed out that depressive symptoms, including feelings of apathy and hopelessness, are barriers to seeking care: “Depression itself gets in the way…it’s the nature of the disease.”

Usual Care Focus Groups

Participants’ reactions to being allocated to the usual care group centered around being disappointed about their allocation to usual care while also remaining in the study to benefit others (eg, to “give back and help others” and “I’ll give back any way I can”). One participant stated that they were “disappointed [to be assigned to usual care], as it is hard to get care in rural areas…but [I] decided to stay in [the] study to validate the research.” Participants also reported benefiting from participating in the study, despite their allocation to usual care, describing benefits from knowing that they would be assessed and thus feeling accountable for their health behaviors. To illustrate this, one participant said, “It was helpful to have the [outcome-assessment] calls, because it keeps the ball in front of you,” and another said, “I knew I would have to answer questions, so it forced me to think about how I was managing.” Overall, the usual care focus-group participants described their study experiences positively and did not indicate any concerns other than a few challenges answering some of the outcome rating scales. For example, one said that it was “hard to put your feelings into a scale.”

A robust discussion ensued among the usual care focus-group participants in response to the question about barriers to engaging potentially depressed patients in depression care. Similar to the MS Care focus-group participants, they described the terminology used in discussing depression as a potential barrier. As in the MS Care focus groups, usual care participants also pointed out that those who are depressed may be the least likely to seek help because of the nature of depression. They identified additional barriers, including having to manage multiple conditions and poor access to providers with expertise in MS and other comorbidities, particularly in rural areas. One participant captured both of these themes: "I do think that a lot of people with MS that I know have multiple chronic conditions…and dealing with the doctors in a rural area that aren't—don't have a lot of MS background [so] trying to go to a counselor or a psychiatrist is very difficult to the point where I feel like it's just not worth it." Multiple participants recommended utilizing more outreach via e-care messages or more frequent assessments: "Depression is periodic, so [I] may not have been depressed at the time [of clinic visit]."

When asked how the health care system could help patients with MS manage pain, several thematic recommendations emerged. These included having MS providers work more closely with pain management specialists as well as other providers such as physical therapists: "Make sure there's a good way for them [the MS provider and therapist] to have communication, not only at the end saying 'we went through this treatment and here's the report,' maybe something in the beginning…that is more individualized." Having alternatives or adjuvants to pain medications was also a common theme: "having or knowing more options that are available that can actually treat pain [such as] physical therapy, occupational therapy, strength training, and others." Another theme for improving care was to increase "telemedicine" options, especially for patients living rurally. For example, one individual who lives rurally said, "I think more access to the telemedicine option, if that could be incorporated…what I get here when I go see my primary care physician is they don't have a clue [how to help me]. So, better access via telephone or computer, I think, with like the MS Clinic, would be helpful." Another recommended a "virtual care clinic [for pain and depression] where you can talk to someone and see their face."

DISCUSSION

Context for Study Results

This study is the first RCT to evaluate the effectiveness of a collaborative care approach to the treatment of pain and depression in adults with MS. Despite robust evidence of its effectiveness in treating depression and other comorbid symptoms in other chronic health conditions, we are unaware of any other applications of the collaborative care model to pain and depression in patients with neurologic conditions. Contrary to our primary hypothesis, there was no statistical difference between the MS Care and usual care groups in the proportion of individuals whose pain and depression were both under control posttreatment, the primary end point. At the 6-month follow-up, however, the MS Care group was statistically different from the usual care group, with more individuals having depression and pain under control. This finding suggests that it may take longer than 16 weeks (the length of the study's intervention phase) for the benefits of collaborative care to take effect when treating chronic pain and/or depression. Other studies of collaborative care for pain and depression have had longer treatment windows (eg, 6 months in one primary care study[37]). In clinical settings collaborative care is not typically limited to a brief treatment window as was necessary in this study.

Our secondary hypothesis, that those assigned to MS Care would do better on the secondary outcomes, was generally supported posttreatment, with mixed results at the 6-month follow-up. Compared with usual care, the MS Care group showed statistically significant lower pain intensity, pain interference, depression severity, disability, and fatigue posttreatment. At the 6-month follow-up, the MS Care group again had statistically lower pain interference, disability, and fatigue but not average pain intensity or depression severity. As a group, the improvements in the secondary outcomes—particularly pain interference, pain intensity, and fatigue—were generally maintained over time. Furthermore, at the 6-month follow-up, fewer MS Care participants met criteria for a current MDE, dysthymia, or both than usual care participants. The groups did not differ in reported self-efficacy for managing MS at

any time point. The improvements seen in the MS Care group are particularly notable given the chronicity of pain and fatigue in the MS population.

To obtain perspective on the benefits of and satisfaction with care during the study period, we also examined participants' self-reported impressions of change and satisfaction with care. A greater number of participants with pain at baseline, with or without depression, reported improvements in pain both posttreatment and at the 6-month follow-up in the MS Care group relative to the usual care group. We did not find differences between the 2 groups for individuals who were screened for depression (with or without pain), however, although these individuals formed a much smaller group. In the context of a high level of patient satisfaction with care overall, posttreatment participants assigned to MS Care reported significantly greater levels of patient satisfaction with pain/depression care, MS disease care, and health care in general relative to those assigned to usual care. Although satisfaction remained high, these between-group differences were not maintained at the 6-month follow-up. A summary of these findings is presented in Table 12.

Table 12. Summary of Study Findings

Outcome	Summary of findings comparing MS Care and usual care[a]
Primary outcome	
% with control of pain and depression	No difference posttreatment. At the 6-month follow-up, 10.5% more of MS Care participants had pain and depression control than did usual care participants.
Pain and depression secondary outcomes	
Pain interference	MS Care was lower posttreatment and at the 6-month follow-up.
Pain intensity	MS Care was lower posttreatment.
% with pain control	More MS Care participants had pain control posttreatment and at the 6-month follow-up.
Depression severity	MS Care was lower posttreatment.
% with depression control	More MS Care participants had depression control posttreatment.
% with a current depressive disorder	Fewer MS Care participant had a current MDE, dysthymia, or both at the 6-month follow-up.
Other secondary outcomes	
Disability	MS Care was lower posttreatment and at the 6-month follow-up.
Health-related quality of life	No differences at either time point.
Fatigue	MS Care was lower posttreatment and at the 6-month follow-up.
Self-efficacy for managing MS	No differences at either time point.
Patient ratings of improvements	MS Care had higher ratings of improvements in pain posttreatment and at the 6-month follow-up.
Satisfaction with care	MS Care participants had greater satisfaction with pain/depression care, MS clinic care, and overall health care posttreatment than usual care participants.

Abbreviation: MDE, major depressive episode; MS, multiple sclerosis.
[a] If a difference is mentioned in the table, it is statistically significant.

This study's mixed findings merit thoughtful consideration. Only 19% of MS Care participants and 12% of usual care participants had control of pain and depression posttreatment, a difference that was not statistically significant. Even fewer—18% in MS Care and 7% in usual care—had control of both at the 6-month follow-up, which was statistically different. However, results from the secondary outcomes and patient-reported ratings of change and satisfaction indicate that the MS Care intervention was effective in improving outcomes relative to usual care. This discrepancy may be due, in part, to our selection of a binary, composite primary outcome. Our primary outcome—requiring participants to have control of pain (average pain intensity < 3 on a 0–10 scale in the past week *or* ≥30% reduction in pain severity from baseline) and depression (a reduction of at least 50% in depression severity *or* a score of < 0.5 on the HSCL-20vB)—was quite conservative and did not take into account the participants' reason for entry into the study. Most collaborative care studies in other populations, including the few that examine pain, assess outcomes separately; many also use continuous measures.

In analyses examining the proportion of treatment responders separately—that is, those who had control of pain *or* control of depression—both groups had higher proportions of control of the individual outcomes over the course of the study. The MS Care group had significantly more pain responders (38%) than the usual care group (20%) posttreatment. This statistically significant difference was maintained at the follow-up for the MS Care (42%) and usual care (26%) groups. For the depression outcome, the MS Care group had significantly more depression responders (39%) than the usual care group (24%) posttreatment. The 2 groups did not differ at follow-up, however (MS Care, 30%; usual care, 24%). These findings indicate that participants who had control in one domain did not necessarily have control in the other domain.

Despite the fact that chronic pain and depression are prevalent in not only MS but also in other neurologic conditions and chronic diseases treated in specialty care settings (eg, spinal cord injury, limb loss), this study is the first to evaluate collaborative care for pain and depression in a specialty clinic setting. To date, only 3 published studies have used a

collaborative care approach to managing pain; all were conducted in primary care. The improvements (decreased pain interference and intensity, including the continuous outcomes) found in this study are comparable to those found in these 3 comparative effectiveness trials of collaborative care relative to usual care for primarily musculoskeletal chronic pain.[29,33,37] For example, these primary care trials reported 6-month responder rates ranging from 38%[37] to 42%[33] for participants receiving collaborative care; we found 42% in the MS Care group at the 6-month follow-up. Our findings for pain intensity and interference are also comparable with these studies.

Our findings are also generally consistent with the one published effectiveness trial, the Standardized Clinical Assessment and Management Plan (SCAMP) trial, that compared collaborative care with usual care for primary care patients with pain and depression.[37] In the SCAMP trial, collaborative care consisted of 3 stepped phases of care. A nurse care manager, supervised by a psychiatrist, delivered 3 months of optimized antidepressant therapy (step 1); 6 sessions of a pain self-management program (step 2); and a continuation/relapse prevention phase consisting of 2 phone calls from the care manager 8 and 10 months later with adjustments or referrals as needed (step 3). Responder analyses at the 6-month follow-up showed that 38% of the collaborative care group and 17% of the usual care group had a clinically meaningful reduction in pain (ie, $\geq$ 30% reduction in BPI total score). For depression, 38% of the collaborative care group and 14% of the usual care group had a clinically meaningful reduction in depression (ie, ≥ 50% reduction in HSCL-20vB, a measure in the same family as our depression measure). Kroenke et al also reported findings for a composite outcome, which required a clinically meaningful reduction in pain and depression. As in our findings, fewer individuals in the SCAMP trial had meaningful reductions in pain and depression outcomes. Kroenke et al found that 24% of collaborative care participants and 8% of usual care participants had meaningful changes in both outcomes at the 6-month follow-up, rates comparable with our 6-month findings.

Our study differed from these existing collaborative care studies in several important ways beyond the patient population (MS patients vs musculoskeletal pain patients) and study

setting (specialty care vs primary care). The MS Care intervention emphasized instruction in cognitive-behavioral pain and depression self-management skills, whereas other studies appeared to use less intensive behavioral interventions. Given the emphasis on cognitive-behavioral interventions, licensed social workers with expertise in behavioral interventions served as the MS Care managers. In contrast, nurses were care managers in 2 of the studies,[33,37] and a psychologist in the other.[29] However, all these collaborative care approaches, including MS Care, had in common the health care system redesign believed to underlie collaborative care's effectiveness (described in Figure 1 and Appendix B).

Providing MS Care participants a choice to participate in treatment by phone was well received and might have contributed to the high rates of treatment adherence and treatment satisfaction found in this study. Nearly 75% of the care-management sessions occurred by phone. Previous studies have shown that behavioral interventions delivered by phone are effective in samples of adults with MS.[21,58,73,74] This study adds to the growing evidence that the telephone is an effective, simple method for increasing access to and uptake of behavioral health care in this population that may otherwise find in-person care inaccessible.

Generalizability of the Findings

The study sample reflects the general MS population, as in the United States MS disproportionately affects women (2:1 or 3:1) and white people of Northern European ancestry.[75] Given that we were interested in comparing the effects of 2 systems of care, we invited all UW Medicine MS Center patients who screened positive for depression, pain, or both to participate, regardless of age, sex, race, ethnicity, socioeconomic status, geography, or disability level. Because we did not exclude anyone on the basis of these factors, our findings are likely generalizable to the population of patients with MS who obtain care in specialty MS centers in the United States. Although our sample is reflective of the MS population, the results may be less generalizable to people with MS from underrepresented categories, including those who are not white or who are less educated. The results may also be less generalizable to subgroups with MS who are unable to access MS specialty care or who do not receive care from health care providers with MS expertise. The results are not generalizable to the subgroup of

individuals with MS who do not have access to a phone and/or do not speak English; future studies of the MS Care approach should adapt the intervention to include patients from such underrepresented groups.

Although the MS population lacks diversity in some domains (sex, race, and ethnicity) relative to the general US population, individuals with MS fit PCORI's definition of a vulnerable and/or underserved population by being inclusive of those with multiple chronic conditions and PCORI's interest in hard-to-reach populations or patients with multiple chronic conditions. We included participants from a hard-to-reach population, that is, a sample that reflects geographic diversity, including rural areas. The NMSS's fact sheet, Living With Multiple Sclerosis in Rural America,[76] summarizes research documenting that people with MS living in rural areas experience health disparities. They are older, less educated, more likely to be unemployed, and have lower incomes compared with those with MS in urban areas. Rural residents with MS are more likely to report poorer overall health, community participation, independence, and quality of life, in conjunction with poorer access to and satisfaction with mental health and rehabilitation services. By using telehealth to deliver care management, our study attempted to include rural people living with MS from UW Medicine's catchment region (Washington, Wyoming, Alaska, Montana, and Idaho).

Although 84% of fully eligible patients agreed to participate in the study, many clinic patients who might have been eligible did not participate in the full study screening. Thus, the extent to which our results would extend to those with MS who were not interested in screening or being in a trial is not known. Focus-group participants assigned to usual care reported that they benefited from the study because they knew that they would complete the outcome measures periodically and thus felt motivated and accountable for their health behaviors. Whether this accounts for some of the benefits seen in the usual care group is unknown but provides important information to consider.

Implementation of Study Results

Our study findings suggest that MS Care has benefits to MS patients with pain and/or depression, and also results in higher satisfaction with care than usual care. MS Care, the first

application of the collaborative care model to an MS specialty center, was well received, resulted in improvements in multiple outcomes, and has the potential to be implemented broadly. A number of elements were instrumental in implementing MS Care in the UW Medicine MS Center, including engaging stakeholders in all stages of MS Care development and roll-out and integrating the model into the clinical flow. The MS Care team routinely produced information flyers and updates for referring providers and clinic staff that emphasized actual benefits experienced by MS Care participants, including in the words of the patients.

Successful implementation of MS Care required integrating the care managers into the clinical team. To do this, we hired 2 highly trained clinical social workers with backgrounds in MS, depression, and/or pain management using evidence-based treatment and/or collaborative care. They were able to build relationships, work flexibly, and be visible in the clinic, and they were trained in strategies for communicating with the clinic providers. We also emphasized the importance of attending to factors that increase the integration of programs into clinical settings. Attending to the recommendations of Heath et al[79] for achieving the highest level of integration, we arranged to have the care managers located in the same physical space as the rest of the MS Center team. As the care manager role was new to this setting, efforts were made to clearly define the roles and responsibilities of the care managers. The roles of other collaborative care team members, including the expert consultants as well as the MS providers and staff, were also defined in a series of meetings and communications with clinic staff.

In our setting, the care managers spent an average of 1.5 hours per week on each case during the treatment phase of the study. This estimate includes their time spent directly with the patient in care-management sessions (often 45–60 minutes per session), as well as time spent discussing the case in the weekly caseload review meetings, communicating and coordinating care with MS specialty and primary care providers, and documenting in the electronic medical record. Most of the patients were taking multiple medications and were seen by multiple health care providers, requiring considerable communication and coordination given this complexity of care. In patients who responded to treatment, the care-management

sessions and care coordination typically decreased over time. Because MS Care occurred in the context of a clinical trial with a defined end point, the care-management sessions were capped at 12 sessions with 1 follow-up call. This differs from collaborative care in many real-world settings, where an episode of collaborative care may last 6 to 12 months and entail an unlimited number of sessions that typically decrease in frequency and duration depending on treatment response. Estimating caseloads should take into account that the necessary care manager effort varies depending on the frequency and duration of the sessions as well as the complexity of the patient population.

Implementing the system-level changes inherent in collaborative care required adapting communication systems and electronic medical record documentation to MS Care and the setting. Collaborative care aims to improve care for the patient and support the health care system and providers to deliver high-quality care for depression and pain. Thus, we developed documentation templates and systems for communicating and tracking treatment plans and outcomes. The care managers communicated with MS clinic providers via their preferred method (eg, electronic medical record, in person) about treatment recommendations and updates from the MS Care team.

The MS Care model also differs from most other collaborative care models in its inclusion of psychologists with expertise in rehabilitation psychology and neuropsychology as domain experts. A psychologist attended the weekly caseload review meetings and provided ongoing consultation to the care manager and other team members about neuropsychological and rehabilitation factors influencing patients' treatment needs and progress. Rehabilitation psychologists and neuropsychologists also adapted the MS Care behavioral and educational materials to the needs of patients with MS and trained the care manager in the psychosocial and neuropsychological aspects of living with MS. These types of expertise and modifications are important for adapting collaborative care to the MS population and would be useful in adapting it to other neurologic or MS populations or settings.

A particularly important implementation feature of MS Care was the flexible use of telehealth to deliver the care-management sessions. Weekly face-to-face sessions are typically

not feasible for patients who come to the clinic from a distance or have driving or mobility restrictions. Therefore, we offered patients the option of participating by telephone or in person at each session. This promoted more flexible, patient-centered care, and was a highly valued aspect of the program per the focus-group participants. Although telehealth is not uniformly reimbursed by all payers, it is increasingly an accepted and covered treatment-delivery mode, given its building evidence base.

A challenge to the widespread implementation of MS Care and other models of collaborative care in MS specialty care settings is that it is not currently standard treatment. Barriers include a lack of knowledge about collaborative care, upfront costs for implementing systems changes (eg, tracking systems, care managers), and concerns about payment for the model. Two trends suggest potential solutions for addressing these barriers. Collaborative care is increasingly becoming standard care in primary care and other settings. As of 2017, the Centers for Medicare & Medicaid Services also developed common procedural technology (CPT) codes to bill for the care manager sessions and the expert consultants' time spent overseeing collaborative care. These evolving changes may reduce the barriers to implementing collaborative care interventions such as MS Care in MS specialty settings.

Subpopulation Considerations

We did not conduct heterogeneity of treatment effects analyses to identify if and how subgroups responded to the MS Care intervention, because we had insufficient power to conduct such analyses. A multicenter study with a larger sample size is needed to examine the effects of MS Care in subpopulations.

It is possible, if not likely, that patients with depressive disorders, including more severe depressive disorders, were under-enrolled in this study. Fewer than 6% of the sample had only a depressive disorder at enrollment, and only 23% of the sample had both depression and pain at the time of screening. Throughout the study, we discussed the perceived under-enrollment of patients with MS with our stakeholders. They posited that the apathy, anhedonia, isolation, and hopelessness often associated with depression might have presented barriers to depressed patients joining the study. Our patient partners also described their perception that people with

MS who are depressed may not always self-identify as depressed, given that many of the symptoms of a depressive disorder are also symptoms of MS (eg, fatigue, concentration difficulties, insomnia). Future research should devise strategies for improving enrollment of individuals with depression. Studies on collaborative care in the MS population should also examine other important subgroups of individuals at risk for poorer depression and pain outcomes, such as those with progressive MS or severe cognitive impairment.

Study Limitations

As noted previously, patients with depression were underrepresented in this study, and thus the extent to which these findings generalize to all MS patients with a depressive disorder is not known. We were unable to collect information about the 389 patients who declined to participate in the study screening process, as we did not have IRB approval to do so. Thus, we do not know why these patients were not interested in learning about the study or participating in screening. Likely some did not have pain or depression; others potentially did not identify as being depressed. It is possible that some were dissuaded from participating in screening because of the stigma associated with having or being labeled with depression; our focus-group participants and stakeholders indicated that this was a potential barrier to study participation and depression care in general. Our patient partners and focus-group participants also highlighted that characteristics of depression—including apathy, anhedonia, poor energy, and hopelessness—may also hinder help-seeking by people who are depressed.

As is common in effectiveness trials of collaborative care, usual care was the comparator in this trial. We chose this comparator to test the hypothesis that a collaborative care approach to treating depression and pain in MS would significantly improve outcomes relative to usual care. Usual care comparisons are particularly useful when the goal is to establish the value added by including an intervention in an existing health care system.[77,78] Nonetheless, it is possible that the study results were influenced by the lack of an attention control comparator. Spillover of the intervention was also possible, since the study took place within the same system of care, although the usual care participants did not receive care management or key

components of MS Care. MS Care was time-limited to 16 weeks, whereas in real-world settings, an episode of collaborative care may last longer or be spread out over a longer time.

Other limitations include the lack of sufficient subgroup sizes to explore outcomes for these subgroups and the lack of outcomes beyond 6 months. The study design and utilization of a multicomponent intervention preclude identification of the possible treatment mechanisms underlying the MS Care intervention. Because of budget constraints and sample size, only 2 care managers provided care to the participants assigned to MS Care over the course of the study. This may limit the external validity of the findings.

Future Research

An important future direction for this line of research is to develop strategies to bolster the effects of MS Care in this population requiring chronic care. Ideas for increasing collaborative care's effectiveness include increasing the duration of care, which would allow for more time to integrate self-management strategies and adjust treatments, including depression medications. Increasing the duration of MS Care would align with other collaborative care interventions. Other strategies include optimizing nonopioid, analgesic medications or augmentation strategies. Physical activity was encouraged in MS Care but was not the focus. Given that exercise is a potent treatment for depression and pain, including physical activity goals and supporting exercise behavior are potential strategies for improving the benefits of MS Care in this population. Integrating physical therapy more formally into MS Care would also potentially enhance its benefits for pain and mood. This could include not only in-person physical therapy but also physical therapy delivered via telehealth, an approach with increasing evidence for its benefits. Given the difficulty people have engaging in physical activity when sedentary, it will be important to consider behavioral and other strategies for helping patients manage the temporary increases in pain that come from exercise. Future research should also consider the option of offering collaborative care for MS on a regional basis (off-site) rather than clinic by clinic, as this has been shown to be effective in improving depression outcomes at federally qualified health centers serving medically underserved populations. Future research should consider expanding collaborative care research to other neurorehabilitation

populations, including people with traumatic brain injury, where pain and depression are common and access to evidence-based pharmacologic and nonpharmacologic treatments limited.

CONCLUSIONS

The MS Care study sought to build on the strong evidence base for collaborative care in improving depression and pain outcomes and to increase the potential to benefit people with MS via several innovations, including (1) tailoring the intervention to the unique needs of the MS population (eg, complex symptoms, cognitive dysfunction, varying levels of disability); (2) adapting collaborative care to address pain, depression, or both, thus ensuring relevance to a larger proportion of the MS population; (3) offering the option of telehealth delivery to reach MS patients who live in rural areas or are unable to access regular in-person care; and (4) improving the intervention and its relevance using stakeholder engagement.

This randomized controlled effectiveness trial compared MS Care, a patient-centered collaborative care approach to treating depression and pain in individuals with MS, with usual care, in reducing pain and depression posttreatment (primary end point) and at the 6-month follow-up. We also examined the impact of MS Care on secondary patient-reported outcomes important to patients with MS, including pain interference, fatigue, disability, and patient satisfaction. Although MS Care was not superior to usual care in controlling pain and depression posttreatment, MS Care improved other outcomes of importance to people with MS and resulted in high rates of satisfaction.

Given the prevalence of chronic pain and depression in the MS population, combined with the difficulties in accessing evidence-based treatments, this trial's findings have important implications for clinicians, policy makers, health care systems, and patients.

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RELATED PUBLICATION

Ehde DM, Alschuler KN, Sullivan MD, et al. Improving the quality of depression and pain care in multiple sclerosis using collaborative care: the MS-Care trial protocol. *Contemp Clin Trials*. 2018;64:219-229.

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The MS Care trial was also the product of ongoing engagement with a dedicated team of stakeholders who were central to the study's design, conduct, and dissemination. Collaborating with a diverse team of patients, community organizations (particularly the National Multiple Sclerosis Society), providers, and administrators increased the relevance of the MS Care intervention and study findings to people affected by MS as well as their providers, communities, and the health care system. Their engagement also built a strong foundation for future dissemination and implementation of the intervention and findings to other settings. Although this trial has ended, our patient partners continue to engage with our scientists on several new projects addressing patient-centered questions with the ultimate goal of improving the lives of people affected by MS.

APPENDICES

Appendix A: Key Principles of Effective Collaborative Care

An **integrated patient-centered team care approach** is achieved by re-designing how depression and pain care are organized in the clinic setting. An MS care manager is added to the healthcare team and responsible for providing front-line care. Domain specialists, often not readily available in outpatient settings, are also added to the team to provide pain and depression expertise for a panel of patients. In partnership with the patient, the care manager ensures that patients, their healthcare providers, domain experts, and community resources collaborate together toward a shared care plan built upon the patient's needs and goals.

A **population-based approach** is used to track patients systematically using outcomes monitoring for all patients, an electronic case registry, and planned follow up contacts. The semi-automated case registry facilitates information flow, tracks critical clinical information including treatment response, and identifies patients in need of treatment adjustment, intensification, and/or outreach.

Measurement-based treatment to target (remission) is achieved via the routine use of validated pain and depression outcome measures to guide treatment adjustments and intensification. This facilitates prompt, responsive treatment adjustments and reduces the use of treatments that are not producing improvements.

Evidence-based care is provided to the patient based upon their goals and needs, including: strategies to engage, educate, and motivate the patient and enhance treatment adherence; brief evidence-based behavioral or physical activity interventions for depression and pain provided by the care manager, guideline-concordant recommendations for optimizing pharmacotherapy for depression and pain; and intensification or adjustment of treatments in patients not responding to initial treatment strategies.

Accountable care is facilitated by weekly team caseload review and supervision of care managers by pain and depression experts toward achieving patient and population treatment targets.

Appendix B: Detailed Description of the MS Care Intervention

Session 1: Patient-centered assessment and treatment planning session (45-60 minutes): Although participants can choose to engage in sessions by telephone or in person, an in person first visit is encouraged if possible to establish rapport. The aims of this session are to foster a therapeutic alliance and develop a preliminary treatment plan based upon a structured clinical assessment. The assessment includes the patient's current pain/depression symptoms, treatment history, current medications, and goals and preferences for depression and pain treatment. The care manager explains the rationale for and parameters of the intervention and collaborates with the patient to develop the overall initial treatment plan, which is reviewed, placed in the electronic medical record, and shared with the other team members.

Care Management Sessions: Each 30-60-minute session starts with a brief assessment in which the care manager administers standardized measures of pain intensity, pain interference, depressive symptoms, and depression interference. The care manager reviews the patient's adherence to pharmacological and non-pharmacological treatments over the past week and collaboratively addresses barriers to adherence, using problem-solving and motivational enhancement strategies. The care manager discusses any new treatment recommendations from the team and educates the patient on the rationale for the changes. Each session includes instruction in and rehearsal of a behavioral self-management skill (e.g., goal-setting, mindfulness meditation, relaxation), which they are encouraged to practice between sessions. Time is also spent reviewing the patient's homework from the past session, including their practice and application of self-management skills for pain and mood. A summary of each session is documented in the electronic medical record, and the patient's scores on the pain and depression measures is recorded in the electronic caseload registry for review in the weekly team caseload review meetings.

The care managers utilize a Care Manager Manual which was developed specifically for MS Care to guide them in delivering collaborative care for pain and depression in the context of MS. The manual provides an outline of the essential elements of a typical care management session. It also includes information about and modules for other components of MS Care. A patient workbook (paper and/or electronic copy) is provided to MS Care participants; the workbook is tailored to each patient based upon their specific symptoms, needs, and treatment plan. The workbook is used to facilitate review of information in session, particularly for those participating by phone, and to

are not improving or worsening at the top, with remitted cases at the bottom. Cases who are not improving are reviewed first, followed by new cases and, as time permits, remaining cases. The care manager is responsible for briefly summarizing each participant's treatment goals and progress, and the team discusses the case and may suggest treatment adjustments as indicated. The care manager also communicates any recommendations or changes in care to the patient and MS providers.

Treatment Monitoring/Intensification: In consultation with the supervisors, the care manager offers the participant choices for modified or intensified treatment if the outcome measures indicate that the participant's pain and depression are not in remission or clinically improved. Partial- and non-responders are offered an intensified treatment, which may include combined medical and behavioral interventions, and/or in-person or telephone consultation with the appropriate expert. Care may also include referral to the specialist with expertise in that condition for consultation and/or referral to outside specialists for treatment, depending on the judgment of the MS provider and MS Care team.

Relapse Prevention Plan: Participants who are in remission work with the care manager to come up with a relapse prevention plan based on the successful elements of their treatment, potential relapse triggers, foreseeable barriers to continuation, and a plan for how they will cope with relapse. A copy of the relapse prevention plan is provided to the participant; a summary of this plan and any final recommendations is provided in the electronic medical record. Participants not in remission are referred for further support or treatment if they could benefit from further treatment.

Follow-up Call (week 24). All participants receive a follow-up call from their care manager at 24 weeks to maximize continuation and maintenance of treatment gains. This call includes a review of pain, depressive symptoms, treatment adherence, side effects, and current stressors. They review the patient's implementation of the relapse prevention plan and discuss recommendations for ongoing treatment or self-management strategies. The care manager helps coordinate additional follow up in the clinic or the community if indicated.