University of Alabama at Birmingham
UAB Digital Commons

All ETDs from UAB | UAB Theses & Dissertations

2015

GABA(A) Receptor Trafficking and Localization in Schizophrenia

Toni Marie Mueller
University of Alabama at Birmingham

Follow this and additional works at: https://digitalcommons.library.uab.edu/etd-collection

 Part of the Medical Sciences Commons

Recommended Citation

Mueller, Toni Marie, "GABA(A) Receptor Trafficking and Localization in Schizophrenia" (2015). *All ETDs from UAB*. 2535.
https://digitalcommons.library.uab.edu/etd-collection/2535

This content has been accepted for inclusion by an authorized administrator of the UAB Digital Commons, and is provided as a free open access item. All inquiries regarding this item or the UAB Digital Commons should be directed to the UAB Libraries Office of Scholarly Communication.

LOW-DOSE DEXTROMETHORPHAN FOR THE TREATMENT OF PAIN IN FIBROMYALGIA: A SINGLE-BLIND PLACEBO-CONTROLLED CROSSOVER TRIAL

by

STEPHANIE CHRISTINA MUELLER

JARRED YOUNGER, COMMITTEE CHAIR
BUREL GOODIN
SYLVIE MRUG
TIMOTHY NESS
ROBERT SORGE

A DISSERTATION

Submitted to the graduate faculty of The University of Alabama at Birmingham,
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy

BIRMINGHAM, ALABAMA

2022

Copyright by
Stephanie Christina Mueller
2022

LOW-DOSE DEXTROMETHORPHAN FOR THE TREATMENT OF PAIN IN FIBROMYALGIA: A SINGLE-BLIND PLACEBO-CONTROLLED CROSSOVER TRIAL

STEPHANIE CHRISTINA MUELLER

UAB MEDICAL/CLINICAL PSYCHOLOGY

ABSTRACT

Fibromyalgia (FM) is a debilitating chronic pain condition. Its pathophysiology is largely unknown, which has hindered the development of effective treatments. Central sensitization and neuroinflammation have been forwarded as models of FM pathophysiology, both of which indicate the antitussive drug dextromethorphan (DXM) as a potentially effective treatment. DXM is an N-Methyl-D-aspartic acid (NMDA)-receptor antagonist and microglial modulator with anti-neuroinflammatory properties at low doses. It is currently available for clinical use, but has not been tested as a treatment for FM at low dosages. The current study evaluated the effectiveness of DXM in treating FM-associated symptoms of pain, fatigue, cognitive problems, and mood abnormalities. In a single-blind, placebo-controlled crossover trial, fourteen women meeting 2010 American College of Rheumatology diagnostic criteria for FM received a placebo for five weeks, followed by 20mg of DXM daily for ten weeks, while providing twice-daily symptom reports. Daily symptom ratings during the placebo period were contrasted with ratings during the active treatment to determine whether DXM reduced FM symptom severity. Generalized pain ratings were 9.9 points lower (on a 0-100 scale) during DXM compared to placebo (b= -9.933, p=0.013), and maximum pain levels were 9.7 points lower during DXM treatment than during placebo (b= -9.657, p=0.016). There were

marginal reductions of 5.3 points in depressive symptoms during DXM (*b*= -5.322, *p*=0.056), and no effects on fatigue or cognitive complaints. DXM may be a safe and effective alternative treatment option for FM.

Keywords: Fibromyalgia, dextromethorphan, clinical trial, neuroinflammation, analgesia

DEDICATION

This work is dedicated to my grandmother.

TABLE OF CONTENTS

ABSTRACT iii

DEDICATION v

LIST OF TABLES x

LIST OF FIGURES xii

LOW-DOSE DEXTROMETHORPHAN FOR THE TREATMENT OF PAIN IN FIBROMYALGIA: A SINGLE-BLIND PLACEBO-CONTROLLED CROSSOVER TRIAL 1

Fibromyalgia 1

Epidemiology and Disease Burden 2

Symptoms and Diagnosis 3

Disease Models 6

Central Sensitization and Neuronal Hyperexcitability 6

Neuroinflammatory Hypothesis of Fibromyalgia 10

The Present Study 13

METHODS 15

Design 15

Participants 17

Procedures 20
Transparency in Reporting 20
Recruitment 20
Screening Visit 21
Study Visits 24
Description of Active Treatment 24
Treatment and Blinding 25
Daily Symptom Reports 26
Compliance Monitoring 26
Adverse Event Reporting 27
Statistical Analyses 27
Data Management 27
Main Analyses 28
Adverse Events 29
RESULTS 30
Participant Demographics 30
Protocol Deviations 37
Treatment Adherence 38
Questionnaire Adherence 39

Normality testing....40
Main Treatment Effects....41
DXM Effects on Generalized Pain....42
Accounting for Treatment Adherence....44
Accounting for Expectancy Effects....44
Other Pain Outcomes....45
Clinical Significance of Pain Improvements....46
Secondary Outcomes....48
Natural FM Disease Course....49
Adverse Events....51
Blinding Efficacy....53
DISCUSSION....55
Main Findings....55
Treatment Mechanism....56
Availability and Safety....58
Limitations....61
CONCLUSION....66
REFERENCES....67
APPENDIX A Regulatory Approvals....90

APPENDIX B Daily Symptom Report Questionnaire 92

APPENDIX C SAS Code 94

APPENDIX D Distribution of the study outcomes during the DXM treatment condition. 104

APPENDIX E Distribution of Generalized Pain Scores during Placebo and DXM, before and after Centering.....106

LIST OF TABLES

Table 1. Individual and group-level illness characteristics, comorbid medical conditions, and medications reported in the sample. 33

Table 2. Individual and group-level characteristics and questionnaire results from the screening visit. 35

Table 3. Medication adherence during the placebo and DXM conditions. 39

Table 4. Individual and group-level completion rates of daily symptom reports in the placebo and active treatment conditions. 40

Table 5. Results from normality testing of study outcomes during the DXM condition.. 41

Table 6. Group means and standard deviations on the primary and secondary treatment outcomes (raw scores)..... 42

Table 7. GEE model estimates predicting generalized pain ratings. 43

Table 8. GEE model estimates predicting generalized pain ratings, accounting for OTC pain medication use..... 44

Table 9. GEE model estimates predicting muscle pain and maximum pain ratings from treatment condition. 45

Table 10. Change scores for participants' average generalized pain ratings during the baseline and DXM conditions. 46

Table 11. Parameter estimates from GEEs predicting secondary outcomes. 50

Table 12. GEE estimates for natural FM symptom course. 51

Table 13. Adverse event occurrences during placebo and DXM treatment. 53

Table 14. Participants' impressions of treatment received. 54

LIST OF FIGURES

Figure 1. Study design. 16

Figure 2. Participant flow chart. 31

Figure 3. Individual changes in generalized pain ratings between the placebo and DXM conditions. 43

Figure 4. Individual and group mean change in generalized pain during the final two weeks of DXM treatment compared to baseline. 48

LOW-DOSE DEXTROMETHORPHAN FOR THE TREATMENT OF PAIN IN FIBROMYALGIA: A SINGLE-BLIND PLACEBO-CONTROLLED CROSSOVER TRIAL

Fibromyalgia

Fibromyalgia (FM) is a chronic pain condition characterized by widespread pain and a combination of associated symptoms, including unrefreshing sleep, excessive fatigue, cognitive abnormalities, and mood disturbances (Wolfe et al., 2016). In part due to an incomplete understanding of its pathophysiology, there is currently no cure for FM. Three medications have been approved by the Food and Drug Administration (FDA) for management of pain in FM: pregabalin (approved since 2007), duloxetine (approved since 2008), and milnacipran (approved since 2009). The mechanisms by which these drugs produce their analgesic effects are incompletely understood, and their efficacy is modest (Arnold et al., 2002; Cording, Derry, Phillips, Moore, & Wiffen, 2015; Walitt, Urrútia, Nishishinya, Cantrell, & Häuser, 2015). Opioid-based pain medications are unsuitable for managing chronic pain due to their severe side effects and high potential for addiction when taken over long periods of time, meaning that many FM patients remain without viable options for pain relief in the long term.

There is a great need to test novel medications for effective FM treatment. The most promising drug candidates will be based on our current understanding of FM pathophysiology derived from the available research, and the search may be further

streamlined by prioritizing compounds that are currently available for clinical use. This report provides results from a clinical trial using low doses of dextromethorphan (DXM) to treat pain and associated symptoms of fibromyalgia.

Epidemiology and Disease Burden

FM affects between 2-8% of the United States general population, or 4-5 million individuals, depending on diagnostic framework applied (Vincent et al., 2013; Walitt, Nahin, Katz, Bergman, & Wolfe, 2015; Wolfe et al., 2016; Wolfe, Ross, Anderson, Russell, & Hebert, 1995; Wolfe et al., 1990). Similar rates are found across the globe, although individuals of East Asian descent are less often affected (Cabo-Meseguer, Cerdá-Olmedo, & Trillo-Mata, 2017). Females are more likely to be diagnosed with FM than males, and the prevalence increases approximately linearly with age, reaching a peak in individuals over the age of 60 (Jones et al., 2015; Vincent et al., 2013; Wolfe, Ross, Anderson, Russell, et al., 1995). FM manifests differently in women than in men, with women having a lower pain threshold and higher number of FM-associated symptoms of fatigue, sleep disturbance, and gastrointestinal complaints (Wolfe, Ross, Anderson, & Russell, 1995).

The burden of the disease is considerable. A recent estimate based on health insurance claims prior to 2017 suggested that FM healthcare costs ranged from $16,857 to $33,638 per individual per year depending on medication regime (Marlow et al., 2018). Individuals with FM are also more likely than people without FM to suffer from comorbid medical and psychiatric diseases, including other chronic pain conditions,

anxiety, and depression (Berger, Dukes, Martin, Edelsberg, & Oster, 2007). The condition comprises a significant societal economic burden due to lost work productivity. Recent studies have estimated that one third of FM patients are disabled and unable to work (Fitzcharles, Ste-Marie, Rampakakis, Sampalis, & Shir, 2016; Wolfe, Walitt, Katz, & Häuser, 2014).

Symptoms and Diagnosis

FM is frequently managed by rheumatologists (Choy et al., 2010) due to its symptom overlap with common rheumatologic and immunological diseases, such as Rheumatoid Arthritis, Sjögren's Syndrome, and Systemic Lupus Erythematosus (Choi, Oh, Lee, & Song, 2016; Gist, Guymer, Eades, Leech, & Littlejohn, 2018; Wolfe et al., 2011; Wolfe et al., 2009). There are no blood tests to positively identify FM, but lab work can aid diagnostic decisions. For example, elevated erythrocyte sedimentation rate (ESR), antinuclear antibodies (ANA), and C-reactive protein (CRP) levels in blood can indicate certain autoimmune conditions that mimic the symptoms of FM but warrant very different treatment approaches (Arnold, Clauw, McCarberg, & FibroCollaborative, 2011). Differential diagnosis is made more difficult by the fact that FM often coexists with these other conditions (Duffield, Miller, Zhao, & Goodson, 2018).

Due to a lack of objective diagnostic markers, FM diagnosis is based on clinical presentation and patient report. In 1990, a multicenter committee designated by the American College of Rheumatology (ACR) published consensus criteria aimed at standardizing the diagnostic process (Wolfe et al., 1990). According to this framework,

FM was diagnosable if a patient suffered from widespread pain for at least 3 months and exhibited 11 out of 18 positive tender points on examination. “Widespread pain” was defined as pain affecting all four quadrants of the body (left, right, above waist, below waist) plus pain in the axial skeletal region (spine, chest, low back). The criteria achieved a sensitivity of 88.4% and specificity of 81.1% (Wolfe et al., 1990).

The 1990 criteria were utilized in research and clinical practice over the following two decades, which revealed that the tender point exam was underutilized, frequently administered incorrectly, and was redundant with patient reports (Buskila, Neumann, Sibirski, & Shvartzman, 1997; Fitzcharles & Boulos, 2003; Wolfe et al., 2010). Updated criteria were published in 2010 that eliminated the tender point exam in favor of an improved symptom report framework (Wolfe et al., 2010). The widespread pain criterion was more precisely defined as pain occurring in 19 distinct body parts. The Widespread Pain Index (WPI), a count measure of affected areas ranging from 0-19, quantifies the extent of FM pain. Fatigue, waking unrefreshed, cognitive abnormalities, and somatic complaints were recognized as central features of FM (Bartkowska, Samborski, & Mojs, 2018; Bohn, Bernardy, Wolfe, & Hauser, 2013; Cedraschi et al., 2012; Croft, Rigby, Boswell, Schollum, & Silman, 1993; Gelonch et al., 2018; Pidal-Miranda, Gonzalez-Villar, Carrillo-de-la-Pena, Andrade, & Rodriguez-Salgado, 2018; Sallinen & Marit Mengshoel, 2018). Their severity is each ranked on a four-point scale (0-3), yielding a total Symptom Severity Scale (SSS) score between 0 and 12. According to the 2010 criteria, FM can be diagnosed if the following are satisfied: a WPI score of at least 7 plus an SSS of at least 5 OR a WPI score of 3-6 plus an SSS of at least 9. As before, the

symptoms must have been present for at least three months, and the pain could not be entirely attributable to another medical condition. The criteria achieved improved sensitivity (86%) and specificity (90%) compared to the previous version (Wolfe et al., 2016).

Based on 14 subsequent validation studies, the criteria were revised once more in 2016 (Wolfe et al., 2016). The 19 body areas determining the WPI score were retained. However, to eliminate misclassification of regional pain syndromes as FM, the new criteria require that painful areas are distributed such that four out of five body regions (left upper, right upper, left lower, right lower, axial) are affected. The WPI criterion was adjusted accordingly to require a minimum score of 4. The SSS retained four-point ratings for fatigue, waking unrefreshed, and cognitive symptoms. Instead of a single somatic symptom rating, clinicians now indicate the presence of 1) headaches, 2) pain or cramps in lower abdomen, and 3) depression, scoring one point each for a range of 0-3 (Wolfe et al., 2011). According to the new criteria, FM is diagnosed if the following are satisfied: 1) a WPI score of at least 7 plus an SSS of at least 5 OR a WPI score of 4-6 plus an SSS of at least 9; 2) presence of generalized pain affecting four out of five body regions; and 3) the symptoms have been present for at least three months. The new criteria also explicitly state that FM can be diagnosed in the presence of other medical conditions. The sum of the WPI and SSS yield a Fibromyalgia Severity (FS) scale that can be used to track clinical course or treatment response over time (Wolfe et al., 2011).

Disease Models

The exact cause of widespread pain in FM is unknown, but the available research suggests that the phenomenon is due to central nervous system abnormalities. In contrast to acute pain, which is felt in response to stimulation of peripheral nociceptors, chronic pain may develop to be independent of nociceptive stimulation. The following paragraphs will provide a brief overview of two prominent theories of FM pathophysiology: "central sensitization" and neuroinflammation. Implications for pain management with DXM arising from both theories will be discussed.

Central Sensitization and Neuronal Hyperexcitability

Human pain perception proceeds from stimulation of peripheral nociceptors connected to fast-conducting Aδ-fibers and slow-conducting C-fibers, which synapse onto neurons within the dorsal horn of the spinal cord. Axon bundles transmit nociceptive signals along afferent pathways through glutamatergic and substance P-mediated neural firing, toward the thalamus, anterior cingulate, and somatosensory cortex, which mediate higher-level pain perception. "Central sensitization", also termed "central pain" in the pain literature, refers to a state of CNS over-reactivity to peripheral noxious stimulation, and has been suggested to underlie chronic pain development in FM (Cagnie et al., 2014). Although it is unclear how the CNS becomes sensitized, temporal summation ("wind-up") may contribute to the phenomenon (Eller-Smith, Nicol, & Christianson, 2018; Herrero, Laird, & Lopez-Garcia, 2000).

The term “wind-up” describes increases in neuronal excitability in response to repeated nociceptive stimulation, alongside a sensation of increasing pain intensity (Herrero et al., 2000). The phenomenon has been well documented in FM patients (de la Coba, Bruehl, Galvez-Sanchez, & Reyes Del Paso, 2018; de la Coba, Bruehl, Moreno-Padilla, & Reyes Del Paso, 2017; O'Brien, Deitos, Trinanes Pego, Fregni, & Carrillo-de-la-Pena, 2018; Price et al., 2002; Staud et al., 2003; Staud, Craggs, Perlstein, Robinson, & Price, 2008; Staud, Robinson, & Price, 2007; Staud, Vierck, Cannon, Mauderli, & Price, 2001; Staud, Weyl, Riley, & Fillingim, 2014). In the generation of wind-up pain, C-fiber stimulation activates N-methyl-D-aspartate (NMDA) receptors on dorsal horn neurons via glutamatergic signaling, with downstream effects of nitrous oxide (NO) synthesis and release of substance P from presynaptic terminals. Substance P induces hyperexcitability of post-synaptic neurons, spinal interneurons and their synapsing second-order neurons, which potentiates nociceptive signaling and leads to the experience of more intense pain (Moraes, Kushmerick, & Naves, 2014). Furthermore, substance P can diffuse through extracellular space over long distances, leading to activation of distal spinal pathways and the “spreading” of pain sensations to a more generalized pain state in the absence of peripheral nociceptive input (Abbadie, Trafton, Liu, Mantyh, & Basbaum, 1997; Allen et al., 1997). It is possible that acute pain in response to an injury can become chronic via this mechanism. In support of this model, FM patients often report onset or worsening of chronic pain following a traumatic injury or medical event (Buskila, Neumann, Vaisberg, Alkalay, & Wolfe, 1997; Neumann, Zeldets, Bolotin, & Buskila, 2003).

Central sensitization would account for the pattern of widespread pain, hyperalgesia, and allodynia observed in FM, as spinal level abnormalities in nociceptive transmission would presumably affect input from all areas of the body, and would exaggerate the sensation of pain to stimuli that are innocuous to healthy persons. The disease model is also supported by the observation that cerebrospinal fluid from FM patients contains increased levels of substance P compared to healthy controls (Russell, Vaeroy, Javors, & Nyberg, 1992). The idea that NMDA receptor-mediated wind-up contributes to the experience of chronic pain in FM suggests that NMDA receptor antagonists may have therapeutic benefits in FM. Supporting this hypothesis, early animal studies demonstrated that the wind-up effect can be reduced through NMDA-receptor antagonism (Davies & Lodge, 1987; Dickenson & Sullivan, 1987; Parada, Luccarini, & Woda, 1997).

Various NMDA receptor antagonists are available for human use, including DXM, ketamine, and memantine. Intravenous administration of ketamine, an NMDA receptor antagonist structurally similar to DXM, reduces sensitivity to mechanical and thermal stimulation as well as ongoing (non-evoked) pain in participants with various chronic pain conditions (Jorum, Warncke, & Stubhaug, 2003; Leung, Wallace, Ridgeway, & Yaksh, 2001). Three studies have investigated low doses of IV ketamine in FM patients (Graven-Nielsen et al., 2000; Noppers et al., 2011; Sorensen, Bengtsson, Backman, Henriksson, & Bengtsson, 1995), with beneficial effects on tender point sensitivity and spontaneous (non-evoked) muscle pain noted in two studies. Ketamine treatment has shown similar effects with other chronic pain conditions, which prompted

an increase in the practice (Maher, Chen, & Mao, 2017; Radvansky, Puri, Sifonios, Eloy, & Le, 2016), and the recent release of specific guidelines regarding the use of ketamine in chronic pain management (Cohen et al., 2018). Because IV drug administration requires medical oversight and is costly and burdensome to patients, the guidelines recommend that oral treatment alternatives should be developed. Unfortunately, ketamine has poor bioavailability when taken orally, and has generally not been successful in clinical trials (Haines & Gaines, 1999; Ishizuka, Garcia, Sakata, Issy, & Mulich, 2007; Jafarinia et al., 2016).

Memantine is an oral NMDA receptor antagonist similar to DXM. To date, three clinical trials have evaluated its efficacy in reducing FM-related pain, all of which reported favorable results (Fayed et al., 2014; Fayed et al., 2019; Olivan-Blazquez et al., 2014). The antitussive medication DXM is an oral NMDA receptor antagonist with good oral bioavailability and a favorable side effect profile, which makes it suitable for evaluation in long-term clinical trials (Bem & Peck, 1992). The only study to evaluate oral DXM in FM to date reported positive results (Cohen et al., 2006). Twelve of the 34 enrolled patients (35%) were classified as treatment responders, which required at least a 50% reduction in pain scores. The study, however, was open label, lacked a placebo control group, and utilized insufficient and insensitive outcome measures (one post-treatment pain severity rating on a visual analog scale). Mean change scores were not presented for the whole sample, which hinders evaluation of the overall treatment effectiveness. The mean daily dose taken by drug responders was 160mg, which is relatively high compared to dosages used in antitussive treatment, although comparable

to those used in previous studies with chronic pain populations (Aiyer, Mehta, Gungor, & Gulati, 2018). High doses of DXM can produce unwanted side effects, including seizures, delirium and coma, euphoria, and psychotic symptoms (Journey & Stern, 2019), which may have discouraged further exploration of its analgesic properties. At low dosages, however, DXM may have a clinical beneficial effect on FM via effects on neuroinflammatory processes, while avoiding most adverse side effects.

Neuroinflammatory Hypothesis of Fibromyalgia

The neuroinflammatory hypothesis of FM suggests that the condition results from abnormal microglia-mediated inflammatory processes in the brain. Microglia are the resident immune cells of the CNS whose primary functions include surveillance and defense against disease-causing pathogens (Nimmerjahn, Kirchhoff, & Helmchen, 2005). As immune cells, microglia are the main mediators of inflammatory responses inside the CNS. Under physiological conditions, these cells exist in a quiescent state characterized by ramified morphology, and are primarily engaged in surveillance of the brain parenchyma. However, in response to CNS insults, microglia rapidly adopt an amoeboid shape and enter an activated state characterized by the production of pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin (IL)-18, IL-6, various chemokines (e.g., CCL2, CCL3, CCL4) and reactive oxygen species (ROS) (D'Ambrosi et al., 2009; Davalos et al., 2005; Lynch, 2009; Ransohoff & Perry, 2009; Sharma, Arbabzada, & Flood, 2019). Cytokines are signaling molecules used in intercellular communication and include the broad classes of chemokines, interferons (IFN), interleukins (IL), and growth factors (e.g., transforming growth factor, TGF). When

released into the extracellular milieu, they affect the proliferation, chemotaxis, and adhesion of their target immune cells, and can trigger phagocytosis. In the short term, these immune responses can be beneficial: Inflammation can eliminate disease-triggering pathogens that have entered the CNS and re-establish homeostatic conditions. However, if microglial activation persists, chronic production of pro-inflammatory cytokines can lead to unwanted symptoms, including widespread pain and pain sensitivity (Bianchi, Sacerdote, Ricciardi-Castagnoli, Mantegazza, & Panerai, 1992), chronic fatigue, and cognitive and mood abnormalities, which are the central features of FM (Aaron, Burke, & Buchwald, 2000; Dantzer, 2001, 2004; Dantzer et al., 1998; Poon, Ho, Chiu, Wong, & Chang, 2015). The presence of neuroinflammation in FM could account for the observed CNS abnormalities, widespread pain, and associated symptoms in the condition.

It is not clear how low-level neuroinflammation could be triggered in FM, as no unifying pathogen or trigger has been identified. However, the hypothesis is supported by research demonstrating that the symptoms of FM are ameliorated by agents with microglia-modulating properties, such as low-dose naltrexone (LDN) (Patten, Schultz, & Berlau, 2018; Younger & Mackey, 2009). LDN exerts its effects via antagonist action on microglial toll-like receptor 4 (TLR-4), which decreases pro-inflammatory cytokine production (Parkitny & Younger, 2017). Although promising, LDN is also an antagonist of μ-opioid receptors, and therefore has limited utility in FM patients taking opioid-based medications for pain relief.

While not designed for the purpose, existing treatments for FM may harness anti-inflammatory mechanisms. It has been suggested that anti-neuroinflammatory effects of

selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) may underlie their analgesic properties (Abdel-Salam, Baiuomy, & Arbid, 2004; Abdel-Salam, Nofal, & El-Shenawy, 2003; Barakat, Hamdy, & Elbadr, 2018; Bardin et al., 2010; Bianchi & Panerai, 1996), as they have been demonstrated to reduce pro-inflammatory cytokines (Sitges, Gomez, & Aldana, 2014). In the brain, this process may be mediated by actions on microglia. SSRIs/SNRIs have been shown to inhibit pro-inflammatory cytokine release from activated microglia *in vitro* (D. Liu et al., 2011; Sacre, Medghalchi, Gregory, Brennan, & Williams, 2010; Tynan et al., 2012) and *in vivo* (Kostadinov et al., 2015; Nazimek et al., 2016; Sitges et al., 2014). One study demonstrated that reductions in pro-inflammatory cytokine expression by spinal cord microglia after SSRI administration coincided with increased pain thresholds in a rat model of neuropathic pain (Saito, Wakai, Sekiguchi, Kikuchi, & Konno, 2014). Although levels of cytokines in the brain are difficult to measure in living humans, one clinical study used proton magnetic resonance spectroscopy (MRS) to demonstrate that treatment with milnacipran, an approved SNRI for FM treatment, reduced both widespread pain as well as levels of inflammatory metabolites in the brains of individuals with FM (Natelson et al., 2015).

In vitro, treatment with DXM reduces microglial production of pro-inflammatory cytokines TNF-α, IL-6, nitric oxide, and superoxide free radicals, with neuroprotective effects (Cheng et al., 2015; Lee et al., 2011; Li et al., 2005; Y. Liu et al., 2003; Song & Yeh, 2012). The authors established that the effect is not NMDA-receptor-mediated, because a pure NMDA receptor antagonist without anti-inflammatory properties

(dizocilpine maleate) failed to replicate the effect. The effect has been replicated in animal models of Multiple Sclerosis, vascular dementia, Parkinson's disease and methamphetamine use (Chechneva et al., 2011; Thomas & Kuhn, 2005; Xu et al., 2016; Zhang et al., 2006). In one study, DXM potentiated the anti-neuroinflammatory effects of oxycodone in a mouse model of neuropathic pain, suggesting that its anti-neuroinflammatory properties are of relevance to its analgesic actions (Yang et al., 2015).

The literature discussed thus far suggests that microglial modulation may have therapeutic benefits in FM, and there is evidence supporting the use of DXM for this purpose. Unlike LDN, DXM may be given in conjunction with opioid medications, and may even potentiate their effects (Chen, Huang, Chow, & Tao, 2005; Wadhwa, Clarke, Goodchild, & Young, 2001; Yang et al., 2015). Because opioids are still widely used to manage FM-related pain (Goldenberg, Clauw, Palmer, & Clair, 2016; Painter & Crofford, 2013), DXM could benefit a large number of people for whom LDN is contraindicated.

The Present Study

The previous sections have reviewed the available evidence that DXM reduces FM-related pain via its NMDA receptor antagonist and anti-inflammatory actions. Although its potential for managing chronic pain conditions has been recognized, DXM has been underutilized in FM due to the scarcity of studies systematically evaluating its effectiveness. The only study which evaluated DXM as a potential treatment for FM had methodological limitations hindering thorough evaluation. The systematic evaluation of

DXM as an anti-inflammatory treatment for FM could have wide-ranging benefits for individuals with FM. Thus, the overall aim of this study was to determine whether DXM, a microglial mediator, can lead to symptom reduction in FM patients. In order to achieve this aim, fourteen women with FM received placebo, and then DXM, over the five-month study period while providing daily symptom reports. Symptoms, drug safety, and potential medication side effects were also assessed during six in-person visits. The placebo-controlled cross-over design allowed for assessment of symptom changes within-person when participants switched from placebo to DXM. By contrasting each participant's responses against their own baseline levels, the design minimizes confounding effects of between-person variables on drug efficacy and increases statistical power to detect treatment-related benefits.

The study was designed to test the following specific hypotheses:

Hypothesis 1: (Statistical significance) Pain will be significantly lower in the DXM condition versus the placebo condition.

Hypothesis 2: (Clinical significance) Pain will be 20 points lower on average in the DXM period versus the baseline period.

Hypothesis 3: (Secondary outcomes) In the DXM period, a) fatigue, b) cognitive dysfunction, and c) mood complaints will be significantly lower than in the placebo period.

METHODS

Design

This clinical trial utilized a longitudinal, single-blind, placebo-controlled crossover design to assess changes in self-reported pain severity as a result of treatment with DXM. Fourteen women with FM completed symptom reports twice daily, in the morning and at bedtime, while taking a placebo or DXM. Participants took one placebo capsule each in the morning and evening for five weeks, followed by one DXM capsule (10mg) in the morning and evening for ten weeks. There was a two-week baseline period preceding placebo, and a two-week end baseline period following the active treatment, during which participants completed daily symptom reports while not taking any capsules. The study design is depicted in Figure 1. The length of the entire protocol was 19 weeks (approximately five months). The DXM treatment is assumed to decrease participants' pain via its anti-inflammatory and/or NMDA receptor antagonist actions. The study also examined effects of DXM on other outcomes associated with microglial activation in the brain, including fatigue, subjective cognitive functioning, and mood abnormalities.

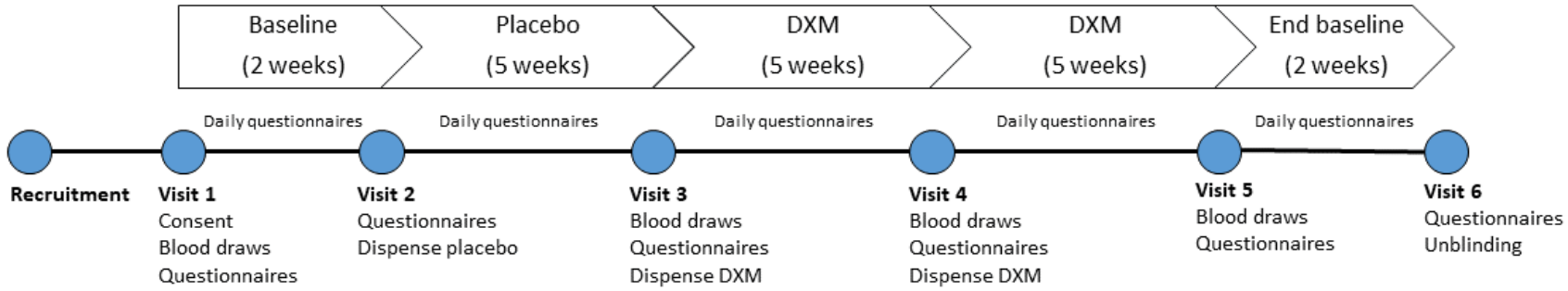


Figure 1. Study design.

Participants

Fourteen women aged 23 to 65 meeting FM criteria as outlined by the American College of Rheumatology (Wolfe et al., 2010) were enrolled in this study. The criteria, including blood tests, were chosen to confirm the FM diagnosis and exclude conditions that can mimic FM, such as Rheumatoid Arthritis, Sjögren's Syndrome, or another autoimmune condition. The lower age limit was set to 23, as DXM has a heightened abuse potential among teenagers and young adults. Current or past substance abuse was exclusionary for the same reason. We also excluded patients currently using monoamine oxidase inhibitors or consuming grapefruit juice daily, as both can cause dangerous interactions when taken with DXM. Finally, daily use of anti-inflammatory medications was exclusionary as it would be difficult to distinguish pain relief experienced from these medications from the benefits of the study medication. Specific inclusion and exclusion criteria are described below.

Inclusion criteria:

1. Aged 23-65;
2. Meets 2010 ACR criteria for FM;
3. FM symptoms have been present for at least 12 months;
4. Average self-reported daily pain of at least 6 on an 11-point scale (0-10);
5. Average self-reported daily fatigue of at least 4 on an 11-point scale (0-10);

6. Participant completes daily self-report during the baseline period (at least 80% response rate);
7. Able to attend UAB for all scheduled appointments.

Exclusion criteria:

1. Blood draw is contraindicated or otherwise not able to be performed;
2. Blood values outside of the following ranges:
    a. High-sensitivity c-reactive protein (HS-CRP) ≥ 10 mg/L;
    b. Erythrocyte sedimentation rate (ESR) >60 mm/hr;
    c. Positive rheumatoid factor;
    d. Levels of thyroid stimulating hormone or free thyroxine outside UAB lab reference values;
8. Diagnosed rheumatologic or auto-immune condition;
9. Blood or clotting disorder;
10. Use of blood thinning medication;
11. Current use of monoamine oxidase inhibitors (DXM contraindication);
12. Daily consumption of grapefruit juice;
13. Oral temperature >100˚F at baseline;
14. Febrile illness or use of antibiotics in the 4 weeks before study commencement;

15. Planned surgery or procedures during the study period, or operated on in the 4 weeks before study commencement;
16. Pregnant or planning on becoming pregnant within 6 months; or currently breastfeeding;
17. Regular use of any anti-inflammatory medication (such as aspirin, ibuprofen, naproxen);
18. Significant psychological comorbidity that in the discretion of the investigator compromises study integrity and/or a baseline HADS depression subscale score of ≥16;
19. Current litigation or worker's compensation claim;
20. Current participation in another treatment trial;
21. Planned vaccination during the study period, or vaccinated in the 4 weeks before study commencement;
22. Participant reports significant problems related to illicit substance use on questionnaire measures.

Procedures

Transparency in Reporting

This trial was registered on ClinicalTrials.gov (NCT03538054) on May 25, 2018, prior to any participant recruitment. The primary outcome measure was daily self-reported pain severity and secondary outcomes were daily self-reported physical activity and patient global impression of change. The purpose of *a priori* defined outcomes was to minimize the likelihood of false positives due to post-hoc exploration of the data. As DXM is a generic medication and its use in FM is in the public domain, there are no financial interests in the treatment.

Recruitment

All study procedures were carried out under UAB IRB approvals. Participants were recruited from the Neuroinflammation, Pain, and Fatigue laboratory's database of over 2,500 individuals who have indicated an interest in participating in research studies. Additional participants were recruited through advertisements posted on the laboratory's online presence and social media, the UAB Clinical Trials Reporter website, flyers distributed to local physicians' offices, and social media advertising.

Participants recruited from the laboratory database were contacted via phone. Those who become aware of the study through advertisements made contact with the research team by phone or e-mail. Interested individuals underwent phone screening, which involved collection of demographic data, medical history, and current symptoms and their severity, specifically with regards to meeting FM diagnostic criteria and the

other inclusion criteria described above. A partial waiver of consent was obtained from the IRB to collect this protected information.

Screening Visit

Those meeting initial inclusion criteria were scheduled for an in-person visit (Visit 1) at the UAB Clinical Research Unit (CRU) where they provided written informed consent, blood samples and vital signs, and underwent pregnancy testing. Eighty (80) cc of blood were withdrawn into vacutainers using an aseptic venipuncture technique. The following tests were obtained in order to rule out DXM contraindications or medical conditions that could mimic the symptoms of FM: Renal function panel (sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, calcium, phosphorus, albumin), hepatic function panel (albumin, alkaline phosphatase, aspartate aminotransferase, total bilirubin, direct bilirubin, indirect bilirubin, alanine aminotransferase, total protein), high-sensitivity C-reactive protein, thyroid stimulating hormone, complete blood count with differential, erythrocyte sedimentation rate, antinuclear antibody screen, rheumatoid factor quantification, vitamin D-25, free T3, and free T4.

To quantify the severity of various FM-associated symptoms in the sample at baseline, participants completed the following questionnaires:

Brief Pain Inventory (BPI): The short form of the BPI (Cleeland & Ryan, 1994) contains nine items rated on an 11-point scale (0-10) that measure aspects of chronic pain. A pain severity subscale (BPI-S) was obtained by averaging responses to items 3

through 6, which measure worst, least, average, and current pain, respectively. Participants also rated the extent to which pain interferes with nine different domains of functioning (e.g., general activity, mood, concentration), to yield the pain interference (BPI-I) score.

Hospital Anxiety and Depression Scale (HADS): The HADS (Stern, 2014) is a 14-item scale measuring symptoms of anxiety and depression. Each item was rated on a four-point scale (0-3), and scores from half of the items were added up to yield depression (HADS-D) and anxiety (HADS-A) subscales, respectively, each ranging from 0-21. Both scales have demonstrated good validity and reliability (Bjelland, Dahl, Haug, & Neckelmann, 2002).

Stanford Expectations of Treatment Scale (SETS): The SETS (Younger, Gandhi, Hubbard, & Mackey, 2012) was administered to measure participant expectancies regarding potential treatment benefits. The SETS contains six items related to positive (e.g., “This treatment will be completely effective”) and negative (e.g. “I am worried about my treatment”) expectations about the study treatment. Responses were indicated on a seven-point scale ranging from “strongly disagree” to “strongly agree”. Half of the items make up the positive and negative treatment expectancy scale, respectively. The scales are calculated by averaging responses from the three items that make up each scale. Both scales have demonstrated good reliability and predictive validity (Younger et al., 2012).

Drug Abuse Screening Test (DAST-10): Because DXM has a mild potential for abuse (Stanciu, Penders, & Rouse, 2016), participants completed the short form of the Drug Abuse Screening Test (Skinner, 1982) to establish the presence of problematic drug use. The DAST-10 contains ten items requiring participants to indicate the presence (yes/no) of a number of cognitions and behaviors related to problematic drug use. Items tap into behaviors exhibited by the respondent and their family members (e.g., "Have you used drugs other than those required for medical reasons?"; Does your spouse or parents ever complain about your involvement with drugs?"). Each item answered affirmatively receives one point, except for item 3 ("Are you always able to stop using drugs when you want to?"), which receives one point for a negative answer. Items are added to yield a total score ranging from 0 to 10. Scores between 1 and 2 indicate a low level of problematic drug use; scores between 3 and 5 indicate a moderate level of problematic drug use; scores of 6 to 8 indicate substantial problematic drug use; and scores of 9 or above indicate severe problematic drug use. Participants must have scored 2 or below, indicating low or no problematic drug use, to be included in this study.

Lastly, at the end of the screening visit, participants received a handheld tablet and instructions for completing symptom questionnaires at home over the following two weeks. The information collected at the screening visit and compliance with baseline questionnaires (at least 80% response rate) determined final eligibility for the study.

Study Visits

Participants who remained eligible returned for five additional study visits (Visits 2 – 6). Each visit involved an assessment of adverse events, measurement of vital signs (blood pressure, pulse, core body temperature), blood draws (Visits 3, 4, and 5), completion of the BPI, and disbursement of medications to cover the following five weeks (Visits 2-4).

Blood taken at visits 3 and 4 (25cc) was tested for the purposes of drug safety monitoring. Blood values for human chorionic gonadotropin (HCG) must have indicated no pregnancy at each time point. Blood samples taken at Visit 5 (30cc) were used to obtain plasma aliquots for future analyses. Participants were paid $50 at the end of the screening visit, and $100 at each Visit 2 – 6, up to a total amount of $550.

Description of Active Treatment

This trial tested low dosages of DXM for the treatment of neuroinflammation-associated symptoms in FM. DXM reaches peak serum levels at 2.5 hours (Barnhart & Massad, 1979), and has a half-live of approximately four hours. DXM is lipid-soluble, and readily crosses the blood-brain-barrier (Marier et al., 2005). It is used at dosages of 10-120mg daily for antitussive treatment due to its antagonist action at NMDA receptors. Previous literature has suggested that DXM at 0.1mg/kg intraperitoneally reduces central inflammation (Chechneva et al., 2011). This dosage would translate to approximately 8mg for an average U.S. female weighing 166 pounds. The dosage of 20mg per day used in this clinical trial was adjusted to account for rapid first-pass metabolism when DXM is

administered orally. This dosage is well below the threshold which would produce cognitive functioning defects (400mg) (Carter et al., 2013), affect driving performance (120mg) (Perry et al., 2015), or produce hallucinogenic side effects (400mg) (Reissig et al., 2012).

Treatment and Blinding

Dextromethorphan 10mg and placebo capsules were compounded by Double Oak Mountain Pharmacy (Birmingham, AL). The study employed a single-blind design whereby participants did not know the drug administration schedule. Participants were informed that they would receive both the active study medication and placebo during the study, but were not told the order or duration of each component. There was no randomization to treatment, and all participants followed the same administration schedule (five weeks of placebo followed by ten weeks of DXM). All capsules were opaque, green, filled to equal volume using fillers (cellulose) to maintain blinding. Placebo capsules looked identical to DXM capsules but contained only cellulose. Medication bottles were labeled with the participant identifier (e.g., DXM001), followed by a two-digit code that identified the bottle number (e.g., DXM001-02 identified the second bottle for participant DXM001). The research team was not blinded to the drug administration schedule. Participants were unblinded at the final study visit by a member of the research team.

Daily Symptom Reports

The primary outcome measures were designed to capture the symptoms most endorsed by FM patients: pain, fatigue, cognitive impairment, and mood abnormalities. Participants completed a 23-item symptom questionnaire twice per day, after waking and at bedtime, on a handheld tablet, which was provided by the research team. The questionnaire is included in Appendix B. Participants reported symptom severity on a scale ranging from 0-100, with anchor points adjusted to match each item. Participants indicated whether they were taking the survey after waking up or at bedtime, and this information was cross-checked against time stamps logged by the handheld tablet. The questionnaires were implemented in Qualtrics software (Qualtrics, Provo, UT) and uploaded immediately upon completion to secure servers maintained by UAB. When no internet connection existed, participants were contacted at least once per week and instructed to upload any remaining questionnaires by connecting to a wireless network. The reports contained the tablet's IP address, location coordinates, and time stamps for questionnaire initiation and completion. No personally identifying information was transmitted.

Compliance Monitoring

Compliance with the medication regime was established using electronic log files from the medication bottle caps, which recorded the date and time each bottle was opened. The information was read from the caps at each in-person visit. Participants had the option to indicate reasons for medication non-compliance on daily questionnaires

(e.g. medical visit requiring fasting). The target compliance rate was 80%. Compliance with daily questionnaires was assessed on a weekly basis through the Qualtrics (Qualtrics, Provo, UT) online database. The target compliance rate was 80%, and participants were contacted by phone if their completion rate fell below this rate, and prompted to increase participation. Daily reminders were sent via e-mail and text message on an as-needed-basis, and with explicit permission from the participant.

Adverse Event Reporting

Participants were asked to report potential side effects at each in-person study visit, and to contact study staff via phone at any time to request a review by the study physician. Individuals with side effects were given the option to withdraw from the study.

Statistical Analyses

Data Management

Daily symptom report data was downloaded from the Qualtrics server and arranged in long form, with variables indicating study day, time of day (waking, bedtime), and study phase (baseline, placebo, DXM, end baseline). The earlier of any duplicate entries from a single time point for the same participant was excluded unless the participant's comments clearly indicated that the second questionnaire should be disregarded. Questionnaire items were arranged as separate variables for each item. Categorical variables were recoded into dichotomous dummy variables.

Main Analyses

Statistical analyses were performed in SAS software, Version 9.4 of the SAS System for Windows. The main outcome was the difference in daily self-reported pain severity during the placebo period versus the DXM period. Descriptive statistics (group means and standard deviations) of average daily pain scores and secondary outcomes (fatigue, cognitive complaints, positive mood, anxiety, and depression) were obtained during the four study periods - baseline, placebo, DXM, and end baseline. Normality of the distribution of scores during the placebo and DXM conditions was tested using Shapiro-Wilk tests and outcomes not normally distributed were centered on person means. Centering the outcome variable accounts for between-person difference in overall symptom severity, and the resultant analyses reflect relative treatment changes assuming a sample with equal average symptom severity.

To test Hypothesis 1 (statistical significance of DXM analgesic effects), a generalized estimating equations (GEE) model with normal distribution and autoregressive correlation structure was fitted using the "proc genmod" procedure within SAS software to predict daily pain ratings based on study condition (placebo, DXM). Time (days in study) and the time-by-condition interaction were also entered as predictors to assess systematic treatment effects over time in the two study conditions. The grouping variable was subject ID. Separate analyses were conducted in this manner to predict ratings of highest daily pain and muscle pain, and with demographic variables (age, FM duration), study medication adherence, and drug expectancy entered as nuisance variables to examine their effects on the primary outcome. The interactions

between the nuisance variables and DXM condition were also tested in order to determine whether DXM treatment effects varied as a function of these variables. Significance of the parameter estimates was set at $p<0.05$. The SAS code that was used to conduct the analyses is provided in Appendix C.

To test Hypothesis 2 (clinical significance of DXM analgesic effects), the percent change between average pain ratings from the baseline period to the final two weeks of DXM treatment was calculated for each participant, and averaged across the sample. A 20% change on a 100-point scale was assumed to represent a clinically significant change in pain.

Hypothesis 3 (significance of secondary outcomes) was tested as Hypothesis 1. GEEs were used to predict daily ratings of a) fatigue, b) cognitive dysfunction, and c) mood complaints from treatment day, study period (placebo, DXM) and their interactions, using a significance threshold of $p<0.05$.

Adverse Events

Side effects and adverse events were examined at each study visit. Additionally, participants rated the severity of headaches and GI symptoms on the daily symptom questionnaire. The severity of these symptoms in the placebo and DXM condition was compared using the same GEE procedures as above, except that the time-by-condition interaction was not of interest, and was not entered into the model.

RESULTS

Participant Demographics

Of 103 women who were phone screened, 32 met initial screening criteria and were invited to attend the in-person screening. Of the 27 women who attended the visit, eight were excluded due to not meeting criteria (out-of-range values on blood tests: n=5; medication interactions: n=1; scheduled surgery: n=1; illicit substance use: n=1), and 19 women were enrolled in the protocol. One person was excluded during the baseline period for starting a new medication containing DXM (Theraflu), two participants withdrew during the placebo period, and two were excluded for poor medication adherence (n=1) and unreliable symptom reporting (n=1), leaving data from 14 women. Figure 2 shows a flow chart of participants moving through the protocol. All analyses were conducted on data from the 14 completers.

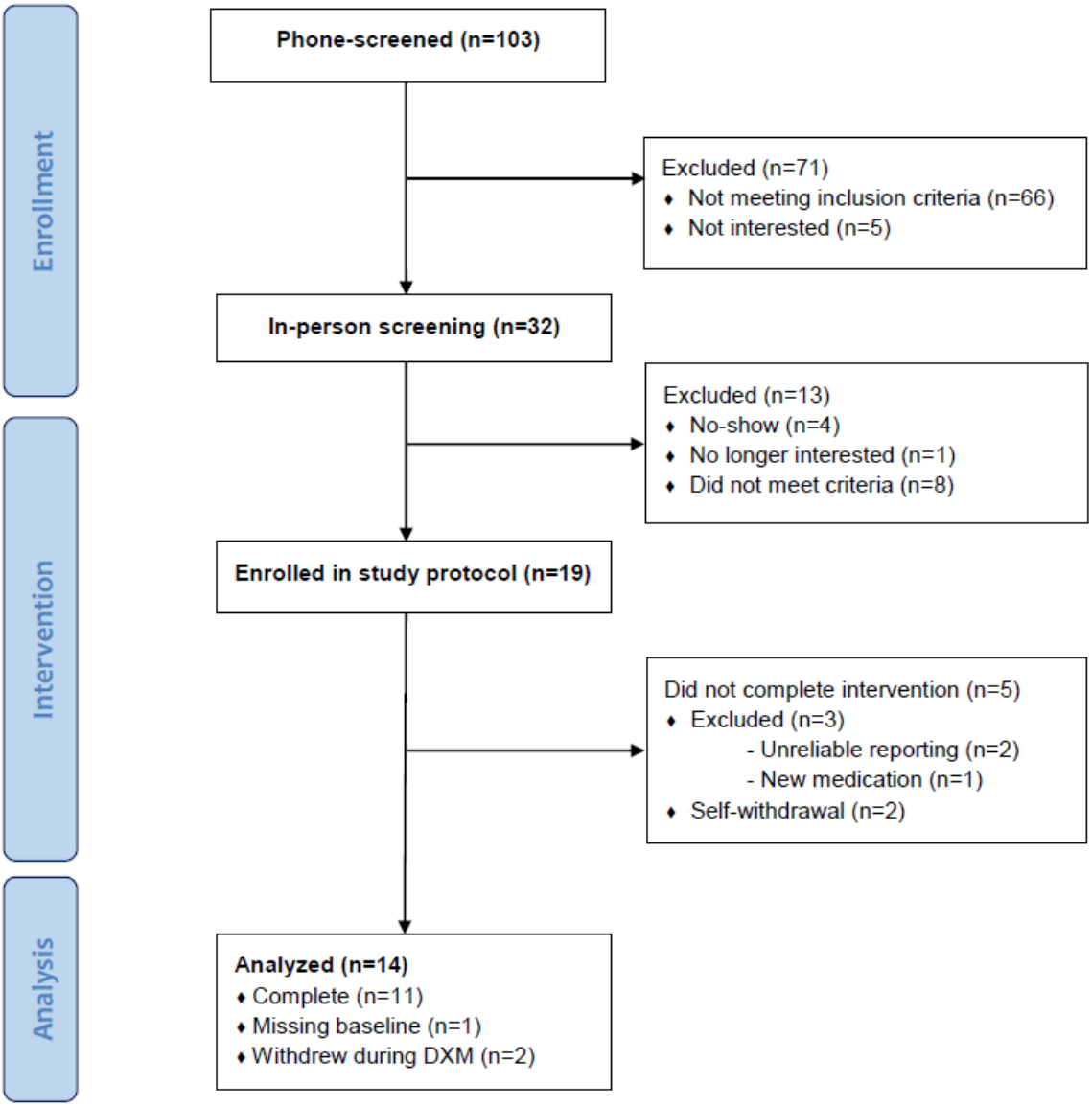


Figure 2. Participant flow chart.

Table 1 presents participant demographics and comorbid medical conditions in the final sample. Participants' average age was 47.07 years (SD=10.74). The mean duration of FM was ten years and two months (M=10.19, SD=6.90), and participants reported an average of 14 painful body regions (M=13.79, SD=2.91) out of a possible 19.

Overall FM severity ranged from 16 to 28 (M=22.14, SD=3.76) out of a possible 31, indicating a sample with moderately severe FM. The most common comorbid medical conditions reported were anxiety (n=6), Chronic Fatigue Syndrome (CFS; n=5), depression (n=5), non-Hashimoto's hypothyroidism (n=4), osteoarthritis (n=4), and hypercholesterolemia (n=4). Ten participants reported as-needed (PRN) use of NSAIDs (ibuprofen, naproxen, aspirin, meloxicam), acetaminophen, or both, during the trial. Other common medications in the sample included anti-depressants (n=9), antihistamines (n=7), sleep-aids (melatonin, zolpidem, trazodone; n=4), proton-pump inhibitors (n=4), muscle relaxants (tizanidine, cyclobenzaprine; n=4), statins (n=3), and benzodiazepines (clonazepam, lorazepam; n=3).

Table 2 presents individual scores and group means on the baseline questionnaires. Participants reported a moderate level of pain severity on the BPI at baseline (M=5.86, SD=1.57), and a moderate level of pain interference in daily activities (M=5.98, SD=1.68). The HADS revealed moderate average anxiety symptoms (M=10.57, SD=4.43) and mild-to-moderate depressive symptoms (M=8.36, SD=4.03). The SETS revealed moderate positive (M=4.14, SD=0.77) and low negative (M=1.79, SD=1.06) expectations for the treatment prior to the start of the intervention.

Table 1. Individual and group-level illness characteristics, comorbid medical conditions, and medications reported in the sample.

PID	Age	FM duration (years)	ACR 2016 WPI (0-19)	ACR 2016 SSS (0-12)	ACR 2016 FM severity (0-31)	Comorbid conditions	Medications
DXM001	56	12.0	11	6	17	Osteoarthritis	Ibuprofen PRN*, acetaminophen PRN*, naproxen PRN*
DXM002	23	5.0	19	9	28	None	Phenazopyridine*
DXM003	41	4.0	16	9	25	CFS, hypothyroidism (non-Hashimoto), sleep apnea, hypercholesterolemia, anxiety, depression	Acetaminophen PRN*, meloxicam PRN, sumatriptan PRN*, melatonin*, trazodone* diphenhydramine PRN*, ranitidine, famotidine, bismuth subsalicylate PRN*, cyclobenzaprine PRN*, Armor Thyroid, atorvastatin, rosuvastatin, amlodipine, sertraline, lorazepam PRN, *iron*
DXM008	48	20.0	14	7	21	CFS, HTN, GERD, hypercholesterolemia, interstitial cystitis, depression, anxiety	Ranitidine, dexlansoprazole, fluoxetine, atorvastatin, amlodipine, carvedilol
DXM012	46	6.2	15	8	23	Depression, anxiety	Tizanidine, topiramate, escitalopram, *biotin, Vitamin D, iron, Vitamin B12 (injections)*
DXM015	48	10.0	14	5	19	Osteoarthritis, tendonitis	Ibuprofen PRN*, acetaminophen PRN*, naproxen PRN*, fenofibrate, aspirin, duloxetine, pseudoephedrine (cold), *Vitamin D, Vitamin B12, turmeric, magnesium*
DXM018	34	19.0	12	12	24	CFS, idiopathic hypersomnia, sleep apnea, chronic migraines, hypothyroidism (non-Hashimoto), fatty liver disease (non-alcoholic), OCD, anxiety	Ibuprofen PRN*, acetaminophen PRN*, clonazepam*, omeprazole, fluoxetine, levothyroxine, Adderall, doxycycline (sinus infection), *multivitamin, Vitamin D3, turmeric*
DXM020	51	4.0	16	12	28	Migraines, HTN, IBS, carpal tunnel syndrome, depression, anxiety	Ibuprofen PRN*, amitriptyline PRN*, tizanidine PRN*, melatonin PRN*,

							diphenhydramine PRN*, losartan, duloxetine, *Vitamin B12, fish oil, calcium, iron*
DXM021	57	15.0	16	9	25	Osteoarthritis, sleep apnea, degenerative disk disease, hypercholesterolemia, pre-diabetes	Acetaminophen PRN*, naproxen PRN*, melatonin PRN*, meloxicam, aspirin, mirabegron, ketorolac injection, ceftriaxone injection, liraglutide, omeprazole, montelukast, cetirizine, vortioxetine, fenofibrate, fluticasone inhaler PRN, sulfamethoxazole / trimethoprim (UTI), *multivitamin, calcium*
DXM025	61	21.2	13	8	21	Osteoporosis	Acetaminophen PRN*, meloxicam PRN*, gabapentin, duloxetine, diphenhydramine (acute allergic reaction), cortisone topical (acute allergic reaction), steroid injection (poison ivy exposure), alendronic acid, *CBD oil*
DXM029	39	5.0	9	10	19	CFS, hypothyroidism (non-Hashimoto)	Acetaminophen PRN*, chlorpheniramine PRN*
DXM036	46	1.5	17	7	24	None	Ibuprofen PRN*, *Vitamin D*
DXM037	46	3.8	11	9	20	CFS, HTN, mitral valve prolapse, acoustic neuroma, migraines, trigeminal neuralgia, cervical disk herniation, hypothyroidism (non-Hashimoto), carpal tunnel syndrome, anxiety, depression	Diclofenac, duloxetine, gabapentin, Adderall XR, carbamazepine, lorazepam, pantoprazole
DXM041	63	16.0	10	6	16	Osteoarthritis, chronic constipation, insomnia, hypercholesterolemia	Aspirin PRN*, tizanidine PRN*, zolpidem PRN*, pravastatin, ranitidine, *calcium, magnesium*
Mean (SD)	**47.07 (10.74)**	**10.19 (6.90)**	**13.79 (2.91)**	**8.36 (2.10)**	**22.14 (3.76)**	--	--

ACR=American College of Rheumatology; CFS=chronic fatigue syndrome; FM=fibromyalgia; GERD=gastroesophageal reflux disease; HTN=hypertension; IBS=Irritable Bowel Syndrome; OCD=obsessive-compulsive disorder; SD=standard deviation; SSS=Symptom Severity Scale; WPI=Widespread Pain Index.
*medication use was reported on daily questionnaires during the trial.
Table 2. Individual and group-level characteristics and questionnaire results from the screening visit.

PID	BPI severity (0-10)	BPI interference (0-10)	HADS-A (0-21)	HADS-D (0-21)	HADS total (0-42)	DAST-10 (0-10)	SETS positive expectations (1-7)	SETS negative expectations (1-7)
DXM001	5.25	4.33	6	6	12	0	4.00	1.00
DXM002	7.00	6.11	16	4	20	1	4.33	2.00
DXM003	3.25	6.22	10	10	20	0	4.00	1.67
DXM008	6.75	4.44	15	14	29	0	3.67	1.00
DXM012	4.25	7.67	10	10	20	1	4.00	4.00
DXM015	3.50	2.78	10	7	17	0	3.67	1.00
DXM018	7.00	7.78	10	9	19	0	4.00	2.67
DXM020	7.00	7.67	15	14	29	0	6.00	2.67
DXM021	4.25	6.00	10	7	17	0	4.00	1.00
DXM025	6.25	5.22	2	3	5	0	4.00	1.33
DXM029	5.50	4.11	8	6	14	0	5.33	1.00
DXM036	7.75	8.78	14	14	28	0	3.00	1.00
DXM037	6.00	5.89	17	11	28	1	3.33	1.00
DXM041	8.25	6.78	5	2	7	0	4.67	3.67

Group mean (SD)	**5.86 (1.57)**	**5.98 (1.68)**	**10.57 (4.43)**	**8.36 (4.03)**	**18.93 (7.78)**	**0.21 (0.43)**	**4.14 (0.77)**	**1.79 (1.06)**

BPI=Brief Pain Inventory; HADS=Hospital Anxiety and Depression Scale; SETS=Stanford Expectations of Treatment Scales

Protocol Deviations

The following describes protocol deviations among the 14 completers. One participant's (DXM008) data during baseline and two weeks of the placebo condition are missing due to tablet malfunction. One participant (DXM020) re-initiated the protocol after a waiting period because a new medication was prescribed during baseline. Another participant (DXM036) re-initiated the protocol due to extended travel and unreliable reporting during the baseline and placebo periods. Data from six weeks during the DXM condition were discarded for the same participant due to a sinus infection and treatment with antibiotics. One participant (DXM015) initiated treatment with duloxetine during the placebo period, so the data were discarded and the placebo condition was repeated after a one-month waiting period. Fifteen questionnaires (one week) from the DXM period were discarded for one participant (DXM018) due to treatment with antibiotics for a sinus infection. Similarly, data for the placebo period were discarded from one participants' dataset (DXM021) who received treatment with cephalexin for a sinus infection, causing the participant to repeat the placebo period. Questionnaires were also discarded for receipt of a steroid injection (DXM020; one questionnaire) and use of DXM-containing cough syrup (DXM015; one questionnaire). Sixty-nine questionnaires throughout the protocol were discarded from DXM025's dataset due to unreliable reporting outside of the acceptable time frame (e.g. completing evening questionnaires on subsequent mornings).

Treatment Adherence

Treatment adherence in summarized in Table 3. Participants spent an average of 33 days in the placebo period (range: 26 – 48 days) and 67 days in the DXM period (range: 38 – 96). Two participants withdrew from the study during the active treatment, resulting in shorter treatment periods for those individuals. Medication adherence during the placebo and DXM period was calculated as the number of pills taken divided by number of pills indicated for that period (number of treatment days × 2). The number of pills taken was determined through the electronic bottle caps. Only partial data were available for two participants (DXM025 and DXM036) due to incorrect use of the bottle caps. The treatment goal of 80% adherence during each study period was met in all cases except in one participant during the placebo period, and one participant during DXM, who fell just under the threshold (above 78%).

Table 3. Medication adherence during the placebo and DXM conditions.

PID	Placebo period (days)	Adherence (%)	DXM period (days)	Adherence (%)
DXM001	28	96.43%	70	81.43
DXM002	27	90.74	71	79.58
DXM003	28	98.25	49†	99.00
DXM008	28	84.21	68	89.78
DXM012	28	100.00	71	92.96
DXM015	35	100.00	72	97.92
DXM018	35	92.86	70	82.14
DXM020	32	92.19	84	84.52
DXM021	42	78.57	70	80.71
DXM025	35	100.00	38†	93.55*
DXM029	34	98.53	96	88.48
DXM036	26	88.89*	43††	93.33*
DXM037	48	90.43	70	83.57
DXM041	32	100.00	70	96.43
Mean (SD)	33 (6)	**93.65 (6.65)**	67 (15)	**88.81 (6.80)**

DXM=dextromethorphan, SD=standard deviation
†shortened treatment period due to participant withdrawal.
††shortened treatment period due to participant illness.
*adherence is based on partial data, due to user error.

Questionnaire Adherence

Questionnaire counts and completion rates were similarly determined as the ratio of available questionnaires to the number of treatment days × 2. Table 4 presents available questionnaires after data cleaning, therefore, the numbers do not necessarily reflect the number of questionnaires submitted by the participants, but rather the number of questionnaires used in the final analyses. The target completion rate for symptom reports was 80%, which was missed by two participants during the placebo period, and seven participants during the DXM period.

Table 4. Individual and group-level completion rates of daily symptom reports in the placebo and active treatment conditions.

PID	Placebo period (days)	Available (%)	DXM period (days)	Available (%)
DXM001	28	96.43	70	82.86
DXM002	27	87.04	71	75.35
DXM003	28	96.43	49†	79.80
DXM008	28	43.86*	68	81.75
DXM012	28	96.43	71	77.46
DXM015	35	100.00	72	100.00
DXM018	35	70.00	70	60.00
DXM020	32	96.88	84	86.90
DXM021	42	83.33	70	65.71
DXM025	35	87.32	38†	48.68
DXM029	34	97.06	96	86.98
DXM036	26	71.70	43††	79.07
DXM037	48	87.63	70	80.00
DXM041	32	100.00	70	98.57
Mean (SD)	33 (6)	**86.72 (15.69)**	67 (15)	**78.80 (13.72)**

DXM=dextromethorphan, SD=standard deviation
†shortened treatment period due to participant withdrawal.
††shortened treatment period due to participant illness.
*questionnaires from the first 16 days of placebo were lost due to technical problems. The participant had a 100% completion rate for the remaining questionnaires.

Normality testing

The results from normality testing are displayed in Table 5 for the DXM condition, and results from the placebo condition were equivalent. Distribution plots for the DXM condition are included in Appendix D. All outcome variables were determined to be non-normally distributed. The outcomes were centered on the participant's own mean of scores over the entire treatment period (placebo and DXM). The result of the transformation for generalized pain ratings is displayed in Appendix E. Transformations of the other outcomes produced similar results. Final statistical tests were conducted on centered outcomes assuming normal distributions.

Table 5. Results from normality testing of study outcomes during the DXM condition.

Outcome	**Skewness**	**Kurtosis**	**Shapiro-Wilk W**	***p***	**Distribution**
Generalized pain	0.222	-1.471	0.899	<0.0001	Bimodal
Highest pain	0.244	-1.304	0.922	<0.0001	Bimodal
Muscle pain	0.283	-1.398	0.905	<0.0001	Bimodal
Fatigue	0.001	-1.146	0.954	<0.0001	Bimodal
Cognition	-0.631	0.129	0.967	<0.0001	Non-normal
Positive mood	-0.597	0.787	0.946	<0.0001	Bimodal
Depression	1.450	1.800	0.801	<0.0001	Zero-inflated
Anxiety	1.518	1.588	0.778	<0.0001	Zero-inflated
Stress	1.677	1.939	0.747	<0.0001	Zero-inflated

Main Treatment Effects

The main analyses were conducted on daily questionnaire data completed at bedtime, due to the limited exposure to the main outcomes (pain, fatigue, cognitive complaints, positive mood, anxiety, depression, and stress) immediately after waking. Table 6 displays their group means (raw scores) during the four study periods (baseline, placebo, DXM, end baseline).

Table 6. Group means and standard deviations on the primary and secondary treatment outcomes (raw scores).

	Baseline	**Placebo**	**DXM**	**End baseline**
Generalized pain	55.30 (17.46)	45.99 (24.38)	40.76 (24.38)	44.90 (26.23)
Highest pain	62.26 (19.06)	51.40 (26.64)	45.55 (26.41)	49.05 (27.87)
Muscle pain	55.30 (20.55)	44.72 (25.99)	40.39 (25.30)	42.31 (28.61)
Fatigue	67.52 (10.95)	52.74 (15.50)	46.41 (21.75)	50.56 (23.88)
Cognitive complaints	62.75 (13.18)	65.54 (15.88)	66.25 (18.41)	63.41 (21.68)
Positive mood	64.29 (10.46)	66.36 (12.39)	68.09 (13.89)	67.11 (17.06)
Depression	26.67 (16.66)	21.72 (18.33)	20.70 (18.73)	24.05 (21.74)
Anxiety	23.92 (15.05)	18.02 (15.25)	20.37 (18.68)	24.99 (22.33)
Stress	30.55 (13.24)	20.26 (15.43)	19.76 (20.50)	22.41 (22.86)

DXM=dextromethorphan. Scores are on a 0-100 scale.

DXM Effects on Generalized Pain

Figure 3 displays individual changes in generalized pain ratings between the placebo and DXM conditions, as well as the mean change for the entire sample. As can be seen in Figure 3 and Table 6, the mean generalized pain rating was 45.99 during the placebo condition and 40.76 during the DXM condition. Table 7 displays parameter estimates from the GEE model predicting generalized pain ratings based on treatment condition. The main effect of treatment condition was significant (b=-9.933, p=0.013), with generalized pain ratings being 9.9 points lower on average during the DXM condition than during the placebo condition. The time-by-condition interaction was significant (b=0.241, p=0.002), whereby the trend of pain ratings over time was -0.251 in the placebo condition and -0.010, i.e. flatter, in the DXM condition.

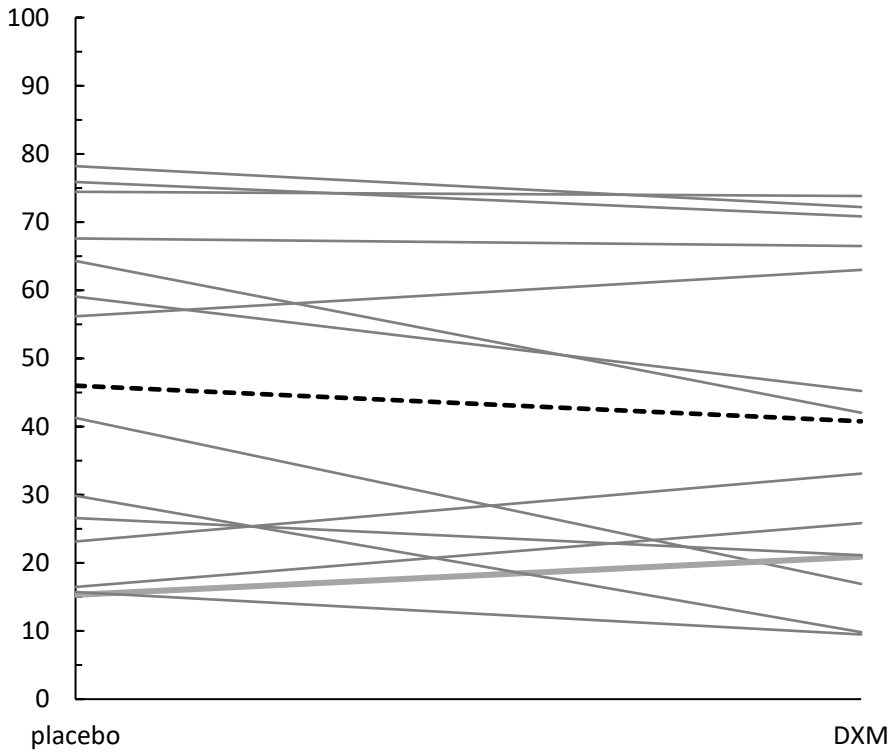


Figure 3. Individual changes in generalized pain ratings between the placebo and DXM conditions.
DXM=dextromethorphan. The bold dashed line represents the change from mean placebo and mean DXM scores across participants.

Table 7. GEE model estimates predicting generalized pain ratings.

Parameter	**Estimate (*b*)**	**SE**	**Z**	***p***
Intercept	9.009	3.323	2.71	0.007
Day	-0.251	0.087	-2.89	0.004
Condition (DXM)	-9.933	3.987	-2.49	0.013
Day*Condition	0.241	0.079	3.04	0.002

DXM=dextromethorphan, SE=standard error

Entering demographic variables (age, FM duration) into the model revealed no significant effect of either variable (age: b= -0.197, p=0.281; FM duration: b= -0.143,

p=0.588), or interactions with the treatment effect (age*condition: *b*=0.324, *p*=0.236; FM duration*condition: *b*=0.211, *p*=0.607), so these variables were left out of the final model and subsequent analyses.

Accounting for Treatment Adherence

There was no unique effect of compliance with daily study medication on generalized pain scores (*b*=0.925, *p*=0.254), and no interaction between medication compliance and the treatment condition (*b*= -0.832, *p*=0.758), meaning that day-to-day variability in treatment compliance did not predict the outcome above the general DXM treatment effect.

Table 8. GEE model estimates predicting generalized pain ratings, accounting for OTC pain medication use.

Parameter	**Estimate (*b*)**	**SE**	**Z**	***p***
Intercept	6.598	2.572	2.57	0.010
Day	-0.219	0.067	-3.26	0.001
Condition (DXM)	-8.790	3.682	-2.39	0.017
Day*Condition	0.215	0.064	3.37	<0.001
Painmed	16.229	5.458	2.97	0.003
Painmed*Condition	-7.960	3.222	-2.47	0.014

DXM=dextromethorphan, SE=standard error

Accounting for Expectancy Effects

Entering positive and negative treatment expectation scores from the SETS questionnaire revealed that these variables were not a significant predictor of generalized pain, as there were no significant main effects (positive expectations: *b*=0.339, *p*=0.868; negative expectations: *b*= -2.830, *p*=0.101) or interactions of these variables with

treatment condition (pos*condition: *b*= -0.871, *p*=0.756; neg*condition: *b*=3.287, *p*=0.194).

Other Pain Outcomes

GEE models estimating treatment effects for muscle pain and maximum pain severity per day revealed similar outcomes to those observed for generalized pain (see Table 9). The main effect of treatment condition on muscle pain was not significant (*b*= -6.738, *p*=0.159), although the trend was similar to generalized pain, with lower scores during DXM than placebo. Treatment condition predicted the highest level of pain reported each day (*b*= -9.657, *p*=0.016), whereby maximum pain levels were 9.657 points lower during DXM treatment than during placebo treatment. The time-by-condition interaction was also significant, indicating that the negative trend over time during the placebo condition (*b*= -0.264, *p*<0.001) was partially reversed during DXM treatment (day*condition: *b*=0.236, *p*=0.002; slope= -0.028).

Table 9. GEE model estimates predicting muscle pain and maximum pain ratings from treatment condition.

Parameter	**Estimate (*b*)**	**SE**	**Z**	***p***
		Muscle Pain		
Intercept	8.294	3.390	2.45	0.014
Day	-0.244	0.094	-2.59	0.010
Condition (DXM)	-6.738	4.789	-1.41	0.159
Day*Condition	0.208	0.094	2.21	0.027
		Highest Pain		
Intercept	9.768	2.996	3.26	0.001
Day	-0.264	0.077	-3.41	<0.001
Condition (DXM)	-9.657	4.012	-2.41	0.016
Day*Condition	0.236	0.075	3.17	0.002

DXM=dextromethorphan, SE=standard error

Clinical Significance of Pain Improvements

Table 10 presents the percent change between average pain ratings from the baseline period to the final two weeks of DXM treatment for each participant, as well as the average change across the sample. One participant (DXM008) did not provide baseline data, so the participant was excluded from this analysis. Pain ratings were 17.12 points lower during the final two weeks of DXM treatment compared to the baseline period, corresponding to a 30.96% average reduction from participants' baseline pain. Eight out of the thirteen participants experienced a reduction of 30% or greater from the DXM treatment, and can be considered treatment responders. Two additional participants experienced pain reduction of less than 20%, and three participants experienced worsened pain while taking DXM compared to their respective baseline pain. The treatment response is also visualized in Figure 4.

Table 10. Change scores for participants' average generalized pain ratings during the baseline and DXM conditions.

PID	baseline	DXM	change	% change
DXM001	45.10	11.30	-33.80	-74.94 %
DXM002	58.67	83.10	+24.43	+41.64 %
DXM003	23.00	24.00	+1.00	+4.35 %
DXM012	41.50	18.89	-22.61	-54.48 %
DXM015	31.93	15.57	-16.36	-51.24 %
DXM018	70.00	25.75	-44.25	-63.21 %
DXM020	83.64	68.00	-15.64	-18.70 %
DXM021	53.00	33.00	-20.00	-37.74 %
DXM025	68.67	77.50	+8.83	+12.86 %
DXM029	62.93	7.71	-55.22	-87.75 %
DXM036	64.45	42.69	-21.76	-33.76 %
DXM037	72.19	63.64	-8.55	-11.84 %
DXM041	43.78	25.14	-18.64	-42.58 %

mean	**55.30**	**38.18**	**-17.12**	**-30.96 %**

DXM=dextromethorphan

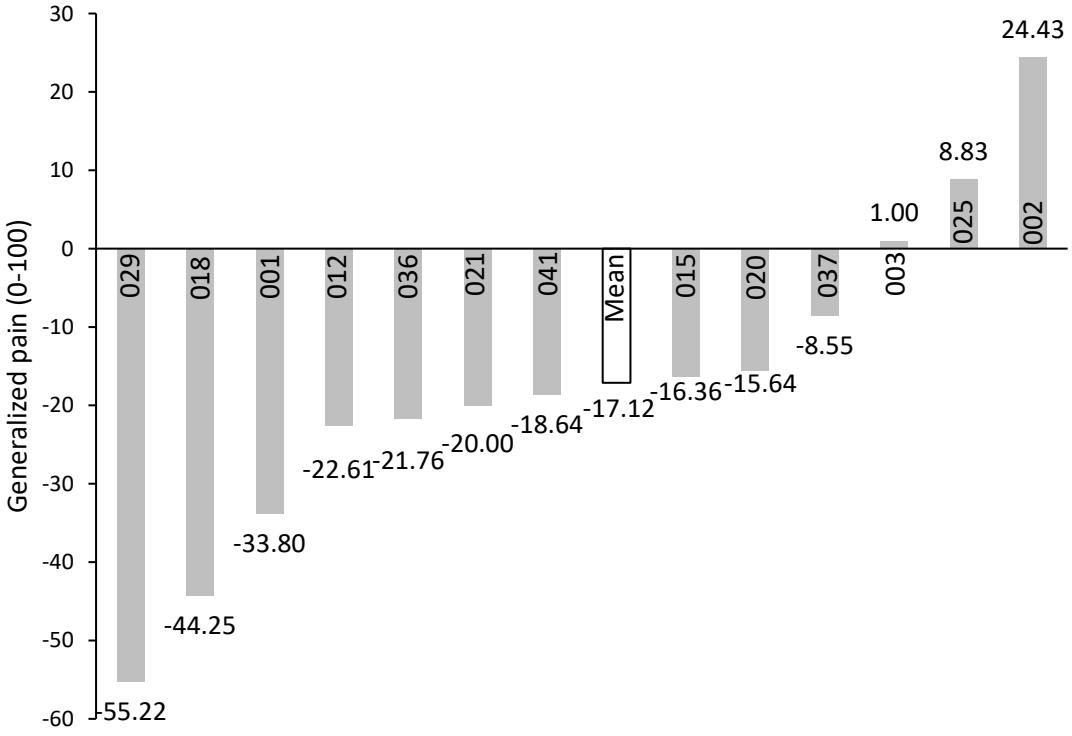


Figure 4. Individual and group mean change in generalized pain during the final two weeks of DXM treatment compared to baseline.

Secondary Outcomes

There was a marginal effect of treatment condition on depressed mood (*b*= -5.322, *p*=0.056), whereby depression ratings were 5.32 points lower during DXM treatment than during placebo. The time-by-condition interaction was also marginally significant (*b*=0.132, *p*=0.060), meaning that the negative trajectory of depression scores during placebo (*b*= -0.101) was reversed during treatment with DXM (*b*=0.031). There were no significant effects of treatment condition on daily fatigue, cognitive complaints, positive mood, anxiety, or stress (see Table 11).

Natural FM Disease Course

Additional analyses were conducted to compare the DXM treatment effects described above to the natural disease course of FM over a similar period of time. Data from 47 participants with FM who had provided daily symptom reports in a separate study were used for these analyses. The study did not involve any interventions (participants provided daily blood samples). The data were cleaned and coded in the same manner as the current study. GEEs were conducted to predict daily symptom ratings (raw scores) based on study day. No other variables were entered into the models. Study day had no impact on symptom scores for any of the outcomes (all $p>0.05$; see Table 12), meaning that the natural symptom course followed a flat linear trajectory over the course of the study.

Table 11. Parameter estimates from GEEs predicting secondary outcomes.

Parameter	**Estimate**	**SE**	**Z**	***p***
Fatigue				
Intercept	8.019	4.216	1.90	0.057
Day	-0.177	0.104	-1.70	0.088
Condition (DXM)	-5.383	5.244	-1.03	0.305
Day*Condition	0.114	0.092	1.25	0.213
Cognitive Complaints				
Intercept	-1.033	2.078	-0.50	0.619
Day	0.026	0.048	0.53	0.595
Condition (DXM)	0.203	3.206	0.06	0.950
Day*Condition	-0.012	0.057	-0.20	0.840
Positive Mood				
Intercept	-1.421	2.349	-0.60	0.545
Day	0.036	0.051	0.71	0.477
Condition (DXM)	1.642	2.359	0.70	0.486
Day*Condition	-0.036	0.047	-0.77	0.441
Depression				
Intercept	2.937	1.651	1.78	0.075
Day	-0.101	0.052	-1.94	0.053
Condition (DXM)	-5.322	2.789	-1.91	0.056
Day*Condition	0.132	0.070	1.88	0.060
Anxiety				
Intercept	-2.022	2.717	-0.74	0.457
Day	0.018	0.039	0.45	0.654
Condition (DXM)	-1.013	2.933	-0.35	0.730
Day*Condition	0.038	0.069	0.56	0.576
Stress				
Intercept	1.055	3.088	0.34	0.733
Day	-0.030	0.064	-0.47	0.636
Condition (DXM)	-2.103	3.323	-0.63	0.527
Day*Condition	0.043	0.060	0.72	0.471

DXM=dextromethorphan, SE=standard error.

Table 12. GEE estimates for natural FM symptom course.

Outcome	Intercept (SE)	Slope (SE)	Z (slope)	*p* (slope)
Generalized Pain	52.776 (3.047)	0.010 (0.043)	0.24	0.811
Highest Pain	59.317 (3.249)	0.014 (0.049)	0.28	0.776
Fatigue	64.993 (2.259)	-0.025 (0.041)	-0.61	0.543
Cognitive Complaints	63.316 (2.243)	-0.014 (0.040)	-0.36	0.721
Positive Mood	65.307 (2.028)	-0.051 (0.041)	-1.26	0.206
Depression*	3.258 (0.085)	<-0.001 (0.002)	-0.04	0.968
Anxiety*	3.181 (0.117)	0.003 (0.002)	1.53	0.125
Stress*	3.334 (0.092)	-0.001 (0.002)	0.41	0.685

SE=standard error. *estimated using negative binomial distributions due to data non-normality.

Adverse Events

Table 13 summarizes adverse events for the 14 study completers. The first eight participants (DXM001-DXM020) did not have any blood draws during the placebo period, so their adverse event data are not available in the respective categories. Overall, few adverse events were reported. ALT was elevated in three participants during the DXM period (DXM001, DXM008, DXM018). Two participants (DXM008, DXM0037) reported nausea and vomiting during DXM, and two participants (DXM002, DXM008) reported constipation and diarrhea during DXM. None of these symptoms were reported during placebo. Gastrointestinal symptoms are known side effects of DXM. When tested directly, the severity of gastrointestinal problems was not significantly different between placebo and DXM (b=2.409, p=0.412). Two participants (DXM008, DXM025) reported increased wakefulness and trouble sleeping during DXM treatment, and one participant (DXM003) reported this symptom during placebo. Insomnia is a known side effect of DXM. Two participants (DXM002, DXM025) reported anxiety during DXM treatment

but not placebo treatment. One participant (DXM025) reported hot flashes and worsening pain during week six of DXM treatment, after switching to a new medication bottle. The participant withdrew from the study at that time. One participant (DXM022) reported vomiting, diarrhea, and stomach pain during the placebo period, and withdrew from the study at that time. Her data were not used in the analyses. The severity of headaches was not different between the placebo and DXM conditions (b=-2.93, p=0.388). No serious adverse events were reported during any trial phase.

Table 13. Adverse event occurrences during placebo and DXM treatment.

Event	Placebo	DXM
Achilles Tendonitis	--	DXM008
Anxiety	--	DXM002, DXM025
Bloating	DXM008	DXM008
Chest tightness	--	DXM002
Cold/Respiratory Infection	DXM036	--
Constipation	--	DXM002, DXM008
Depressed Mood	DXM003	DXM002
Diarrhea	--	DXM002, DXM008
Ear Infection	DXM029	--
Elevated Alk Phosphatase	--	DXM008, DXM012
Elevated ALT	--	DXM001, DXM008, DXM018
Elevated Chloride	--	DXM012
Elevated HCG Serum	DXM025*, DXM037*	DXM025*, DXM037*
Eye Redness	--	DXM041
Fever	DXM021	--
Gallbladder dysfunction	--	DXM012
Gastrointestinal Upset	DXM002	DXM002, DXM021
Hot Flashes	--	DXM015, DXM025
Increased Wakefulness	DXM003	DXM008, DXM025
Low Alk Phosphatase	DXM036	--
Low ALT	--	DXM041
Low AST	DXM036	DXM036
Muscle Weakness	DXM008	--
Nausea	--	DXM008, DXM037
Rash	DXM025	--
Sinus Infection	DXM015	DXM018
Sore Throat	--	DXM021
Urinary Tract Infection	--	DXM021
Vomiting	--	DXM008, DXM037
Worsening Pain	--	DXM025

ALT=alanine aminotransferase, DXM=dextromethorphan, ESR=erythrocyte sedimentation rate, HCG=Human chorionic gonadotropin, HS CRP=high-sensitivity C-reactive protein, TSH=thyroid stimulating hormone. *false positive pregnancy test in women with documented hysterectomy.

Blinding Efficacy

Participants were asked to indicate at each in-person visit whether they believed to have been taking placebo or DXM during the previous five weeks. The results are

summarized in Table 14. Participants guessed the correct treatment 57% of the time. Participants did not guess above chance level during either the placebo period [$X^2(1)= 2.236$, $p= 0.135$], the first five weeks of DXM treatment [$X^2(1)= 0.286$, $p= 0.593$], or the last five weeks of DXM [$X^2(1)= 0.627$, $p= 0.429$].

Table 14. Participants' impressions of treatment received.

Treatment received:	**Placebo**	**DXM**	**DXM**	**% correct**
PID				
DXM001	DXM	DXM	DXM	66%
DXM002	placebo	DXM	placebo	66%
DXM003	DXM	placebo	N/A	0%
DXM008	placebo	placebo	DXM	66%
DXM012	DXM	placebo	placebo	0%
DXM015	DXM	DXM	placebo	33%
DXM018	placebo	placebo	DXM	66%
DXM020	placebo	placebo	placebo	33%
DXM021	DXM	DXM	DXM	66%
DXM025	placebo	placebo	DXM	66%
DXM029	placebo	DXM	DXM	100%
DXM036	N/A	DXM	DXM	100%
DXM037	placebo	placebo	DXM	66%
DXM041	placebo	DXM	placebo	66%
mean	62%	50%	62%	**57%**

DXM=dextromethorphan

DISCUSSION

Main Findings

This study tested the effectiveness of low-dose DXM for improving pain and other symptoms in FM. We tested three specific hypotheses regarding 1) DXM effects on generalized pain, 2) clinical significance of pain reductions, and 3) reduction in secondary FM symptoms. Fourteen women with FM received placebo and DXM over 15 weeks in a single-blind trial. DXM significantly reduced generalized pain compared to placebo, as well as maximum pain levels experienced by the participants. The changes were clinically meaningful, as evidenced by an overall improvement of over 30% compared to baseline pain. The effects persisted when treatment compliance and treatment expectations were taken into account, reflecting real-life scenarios. We also found marginal benefits of DXM on depressed mood, and no effects on fatigue or cognitive complaints. These results are especially meaningful given that the natural disease course of FM does not improve over time. The current outcomes are consistent with the open-label high-dose DXM study by Cohen et al. (2006), but demonstrate that DXM is superior to placebo and can be used at low dosages (20mg versus 160mg).

A direct comparison with FDA-approved medications is difficult given the large differences in trial methodologies, including the absence of any trials that have used daily

outcomes measurement, however, our estimated effect size for the pain reductions (Z= -2.49) is large compared to low and moderate effect sizes reported in previous studies (Calandre, Rico-Villademoros, & Slim, 2015). If the effect is replicated in future studies, DXM could be used to treat pain in FM, although given only marginal effects on depression in the current study, anti-depressives may be more suited to patients for whom depression is a primary concern.

Treatment Mechanism

The mechanism by which DXM produces these effects remains to be uncovered, but one potential pathway is the mediation of chronic inflammatory processes in the brain. Although we did not analyze DXM's effects on inflammatory markers directly, the low dosages used in the current trial point towards the anti-inflammatory theory, given that NMDA antagonism has typically required dosages of around 5-30 mg/kg (Morel et al., 2014; Seddighfar, Ghasemzadeh, & Rezayof, 2019; Shi, Hao, Wiesenfeld-Hallin, & Xu, 2018), while low doses (0.1mg/kg), but not high doses (10mg/kg), have been shown to reduce inflammatory markers in animal models (Chechneva et al., 2011). Thus, the 0.26 mg/kg dosage (for a women of average weight) used in the current trial may have worked by reducing peripheral and/or central inflammatory mediators in FM patients. A systemic anti-inflammatory effect of DXM would also account for the marginal reduction in depressive symptoms observed, as anti-inflammatory therapies are known to ameliorate depression in part by reducing pro-inflammatory cytokines (Kohler, Krogh, Mors, & Benros, 2016; Raison, Capuron, & Miller, 2006).

Studies have shown that circulating cytokines and imaging markers of brain inflammation can be reliable indicators of symptom severity in FM, so these tools could be used in future studies to track physiological changes related to DXM treatment (Andrés-Rodríguez et al., 2019; Fayed et al., 2019; Mueller, Lin, Sheriff, Maudsley, & Younger, 2019). For example, Natelson et al. (2015) used MRS to visualize reductions in inflammatory brain metabolites following milnacipran treatment, and Fayed et al. (2019) used MRS to monitor metabolites following memantine treatment. Due to the similarities between DXM and memantine, Fayed et al.'s results may provide clues regarding likely metabolic changes in the brain following DXM treatment. Fayed et al. (2019) found that three months of memantine treatment increased the levels of choline and glutamate in several brain regions, suggesting beneficial effects on brain metabolism. Nevertheless, memantine and DXM often behave quite differently in vivo (Morel et al., 2014), thus, DXM's effects on brain metabolites will need to be assessed in a separate study. If anti-inflammatory mechanisms are determined to underlie the treatment benefits of DXM, other central inflammatory conditions, such as Chronic Fatigue Syndrome, may benefit from the medication.

Some have argued that existing FM medications may improve pain outcomes indirectly via their anti-depressive properties (Wessely & Hindmarch, 2004). Because the analgesic benefits of DXM in our study far outweighed its anti-depressive effects, it appears that anti-depressive action is not a primary mechanism of action for the analgesic benefits of DXM in FM. However, depressive symptoms in our sample were low, and potential anti-depressive benefits of DXM may not have been apparent in this sample.

Availability and Safety

Generic DXM in capsule form must be obtained from a compounding pharmacy, which may limit its availability to the general public. It is available over-the-counter in the form of cough syrup and liquid capsules (e.g. Delsym, Reckitt Benckiser; NyQuil, Procter & Gamble), which may tempt patients to obtain these formulations for pain relief. Unfortunately, the products are often combine DXM with acetaminophen, antihistamines, or expectorants, and may lead to liver damage or overdose when used chronically. Dosing of liquid formulations is more error-prone than tablet dispensing, which may lead to inconsistent dosages between administrations. DXM is also available as a prescription medication combined with quinidine (Nuedexta, Avanir Pharmaceuticals, Inc.), although the cost may be prohibitive and its biological effects may be quite different to DXM. Thus, the safest way to obtain DXM for long-term use in FM may be through a compounding pharmacy, although patients are advised to consult with their physician to rule out contraindications and interactions with existing medications.

Few side effects were reported in the current study, suggesting that the drug could be a safe and tolerable adjunct to conventional FM medications. However, some concerns remain regarding its widespread use in FM, which should be addressed. We observed ALT elevations during DXM treatment that were absent during the placebo phase and indicate that DXM increased demands on liver metabolism. ALT is a liver enzyme, with high levels indicating liver disease. Although the elevations observed during the study

period did not necessitate treatment or study termination, our trial was relatively short, and future studies should closely monitor the effects of long-term DXM use on liver functioning.

We administered DXM alone, but as mentioned above, formulations combining DXM and quinidine are also available. When given alone, DXM is rapidly metabolized to dextrorphan by the CYP2D6 enzyme. Quinidine interrupts this process, which improves the bioavailability of DXM. Although this may potentiate its clinical benefits, side-effects, including liver demands, may also increase beyond those noted in the current study. Thus, further trials are needed to test the safety of Nuedexta in FM before off-label use can be recommended in this population. Notably, DXM, but not dextrorphan, can penetrate the blood-brain-brain barrier, so a specific advantage of Nuedexta may be increased central availability of DXM. If DXM exerts its analgesic effects centrally, this may be crucial to achieving more global symptom relief in FM, including fatigue, unrefreshing sleep, and post-exertional malaise, which are thought to be driven by central inflammation. Future studies could compare the effects of DXM with and without quinidine, as well as assessing the metabolizer status (CYP2D6 expression) of participants to determine whether central availability of DXM improves its benefits in FM. Until such a time, DXM may be used alone at dosages tested in this study under the direction of a physician. While combination drugs may act as abuse deterrents, pure DXM can be consumed at high doses to produce euphoria and hallucinogenic effects. The abuse potential is especially high in teenagers and young adults (Boyer, 2004). Physicians

may consider drug abuse screening, follow-up monitoring, or medication dispensers to mitigate the abuse potential in at-risk individuals.

There are alternatives to DXM. Physicians may consider off-label use of LDN for patients not taking opiate medications. LDN has a similar safety profile to DXM and has preliminary support as a treatment reducing FM-related pain. Its use is widespread in the FM community, but requires a prescription and must be compounded by a pharmacy (Cote, Ross, Fortner, & Rao, 2018). Another alternative may be the NMDA receptor antagonist memantine, given its similar structure and mechanism of action. Memantine is currently used to treat cognitive deficits in dementia due to Alzheimer's Disease, and requires a prescription. Three studies have reported beneficial effects in FM (Fayed et al., 2014; Fayed et al., 2019; Olivan-Blazquez et al., 2014), although, as stated previously, central anti-inflammatory effects of memantine have yet to be demonstrated. Like DXM, memantine can be administered to patients for whom naltrexone is contraindicated. It is available in the 20mg strength that was tested in the research studies, so a compounding pharmacy is not necessary to obtain the required dosages.

It should be noted that current practice guidelines suggest that physicians offer cognitive-behavioral therapy as a first-line treatment for FM, followed by an FDA-approved medication. Experimental medications, including DXM, should not be used as a first-line treatment due to the limited amount of evidence that currently supports their use in this population.

Limitations

The current study has certain limitations that should be considered. First, in this pilot study, the medication was tested in only a small number of FM patients. The longitudinal design allowed us to assess the main outcomes frequently, leading to improved sensitivity to detect treatment effects compared to conventional designs which have utilized a small number of assessment points. However, the small sample size limits generalizability to the broader FM population. Additional trials with larger sample sizes will need to corroborate the current findings before the widespread use of DXM in FM can be recommended.

Testing with small samples also precludes an assessment of which FM subgroups are most suitable for this treatment. In the open-label trial, IV ketamine predicted the subsequent response to oral DXM in FM patients, suggesting the presence of important subgroups of patients who may benefit (Cohen et al., 2006). In the current study, eight patients experienced clinically significant improvements in pain, and five did not. We showed that patient age or FM symptom duration was not predictive of treatment success, but other clinical variables may account for the discrepancy. For example, patients with low symptom severity at baseline may respond differently to patients with more severe symptomatology, and DXM may alternatively work better as a standalone treatment or as an adjunct to FDA-approved medications. Future studies should incorporate an assessment of these and other personal and clinical factors that may predict treatment

success so that treatment can be targeted toward individuals who are most likely to benefit.

We administered 10mg of DXM in the morning and evening. The daily dose was estimated based on previous animal studies and assuming a woman of average weight, however, this dose and dosing schedule may not be ideal. Future trials could compare different daily doses between subgroups to determine if a smaller or larger dosage should be used. The trials could also vary the dosing schedule, as additional dosing (e.g. three times per day) may better stabilize blood levels of DXM throughout the day compared to twice-daily dosing, especially given the short half-life of four hours. The goal of such analyses should be to determine the daily dose which maximizes treatment benefits while limiting side effects. Although the optimal dosage is likely to depend on patient gender and weight, such adjustments are rarely made in practice. Nevertheless, because pure DXM is currently only available from compounding pharmacies, patients and physicians may benefit from further guidance regarding these variables.

We used linear models to predict the outcome trajectories in the current study, however, it is possible that the treatment response is better characterized by a different model shape. A linear model was chosen for ease of interpretation and in the absence of prior knowledge about DXM treatment effects. Thus, our model was able to show an immediate initial decrease in symptoms with the initiation of DXM treatment, followed by a relatively flat trajectory with little change in symptom ratings thereafter. Linear models have the obvious disadvantage of being unable to visualize curvilinear change and inflection points, so we could not test whether the benefits of DXM were immediate

or gradual, and whether the long-term response was as stable as the linear model suggests. For example, because many naturalistic processes follow exponential growth and decay, it is conceivable that a logarithmic function could have fit the data better. In contrast, if DXM benefits are short-lived, a curvilinear shape may best fit the data. Future studies should assess the fit of various statistical models in order to answer these questions. Although these are statistical concerns, inaccurate models can over- or underestimate treatment effects and lead to false conclusions about drug efficacy.

A related concern is that we did not model outcomes beyond the treatment period (i.e. end baseline and beyond), as this was outside of the scope of the current report. Thus, we do not know if patients retained the treatment benefits beyond the 10-week period. A look at the condition means in Table 6 suggests that most of the study outcomes worsened after DXM treatment was stopped, albeit not to baseline levels. Future studies should extend treatment and follow-up duration to determine the durability of the DXM treatment. This has important implications for clinical management, as short-lived treatments may be better suited for acute management, while those with long-term benefits may be better suited as chronic pain treatments.

Next, there is a possibility that experimenter bias could have influenced the treatment's success in the current study. Although our single-blind design minimized the likelihood that participant expectations inflated the effect sizes, the research team was not blinded to the medication schedule, and could have inadvertently communicated expectations to the participants. Our experimental controls found that blinding was effective, as participants performed near chance level when guessing the administration

schedule. However, future studies can further minimize such problems by utilizing double-blind designs and randomization to treatment conditions.

There is also a potential for biased symptom reporting if FM symptoms prevent participants from completing questionnaires during “flares”, or days with particularly severe symptoms. The potential impact of this was mitigated by our crossover design, as every participant received placebo and DXM during the trial, and natural symptom fluctuations could have occurred during both conditions. The potential for biased reporting was not particular to the current study, but is known a source of error in many clinical trials. Future studies could mitigate such risks by incorporating objective outcome measures that do not solely rely on patient reports, such as pain threshold and pain tolerance testing.

In summary, the following improvements could me made when conducting future trials: 1) recruiting larger sample sizes to improve generalizability to the broader FM patient population; 2) assessing FM subgroups based on severity, length of diagnosis, current treatment regimen, and other clinical characteristics to determine which patients are most likely to benefit; 3) varying the dosage and dosing schedule to determine which yields the most effective symptom relief while minimizing side effects; 4) expanding the treatment and follow-up periods to determine the durability of DXM benefits; 5) utilizing a double-blind trial design and random assignment to treatment conditions to minimize experimenter and participant bias; 6) incorporating cytokine analyses and/or brain imaging to determine the treatment mechanism; and 7) utilizing objective pain

assessments, such as pain threshold testing, to mitigate differences in participants' self-report response style.

CONCLUSION

This project tested an FDA-approved medication (DXM) that is indicated as a cough suppressant, but which has not been used to treat symptoms of FM. The medication would require approval from the FDA as a novel indication before being marketed to treat FM. Future studies with larger sample sizes are warranted before off-label use in FM can be recommended, however, implementation could proceed rapidly due to the medication's existing availability for clinical use and established safety profile.

REFERENCES

Aaron, L. A., Burke, M. M., & Buchwald, D. (2000). Overlapping conditions among patients with chronic fatigue syndrome, fibromyalgia, and temporomandibular disorder. *Arch Intern Med, 160*(2), 221-227.

Abbadie, C., Trafton, J., Liu, H., Mantyh, P. W., & Basbaum, A. I. (1997). Inflammation increases the distribution of dorsal horn neurons that internalize the neurokinin-1 receptor in response to noxious and non-noxious stimulation. *J Neurosci, 17*(20), 8049-8060.

Abdel-Salam, O. M., Baiuomy, A. R., & Arbid, M. S. (2004). Studies on the anti-inflammatory effect of fluoxetine in the rat. *Pharmacol Res, 49*(2), 119-131.

Abdel-Salam, O. M., Nofal, S. M., & El-Shenawy, S. M. (2003). Evaluation of the anti-inflammatory and anti-nociceptive effects of different antidepressants in the rat. *Pharmacological Research, 48*(2), 157-165. doi:https://doi.org/10.1016/S1043-6618(03)00106-3

Aiyer, R., Mehta, N., Gungor, S., & Gulati, A. (2018). A Systematic Review of NMDA Receptor Antagonists for Treatment of Neuropathic Pain in Clinical Practice. *Clin J Pain, 34*(5), 450-467. doi:10.1097/ajp.0000000000000547

Allen, B. J., Rogers, S. D., Ghilardi, J. R., Menning, P. M., Kuskowski, M. A., Basbaum, A. I., . . . Mantyh, P. W. (1997). Noxious cutaneous thermal stimuli induce a

graded release of endogenous substance P in the spinal cord: imaging peptide action in vivo. *J Neurosci, 17*(15), 5921-5927.

Andrés-Rodríguez, L., Borràs, X., Feliu-Soler, A., Pérez-Aranda, A., Rozadilla-Sacanell, A., Arranz, B., . . . Luciano, J. V. (2019). Machine Learning to Understand the Immune-Inflammatory Pathways in Fibromyalgia. *International journal of molecular sciences, 20*(17), 4231. doi:10.3390/ijms20174231

Arnold, L. M., Clauw, D. J., McCarberg, B. H., & FibroCollaborative. (2011). Improving the recognition and diagnosis of fibromyalgia. *Mayo Clinic proceedings, 86*(5), 457-464. doi:10.4065/mcp.2010.0738

Arnold, L. M., Hess, E. V., Hudson, J. I., Welge, J. A., Berno, S. E., & Keck, P. E. (2002). A randomized, placebo-controlled, double-blind, flexible-dose study of fluoxetine in the treatment of women with fibromyalgia. *The American Journal of Medicine, 112*(3), 191-197. doi:https://doi.org/10.1016/S0002-9343(01)01089-0

Barakat, A., Hamdy, M. M., & Elbadr, M. M. (2018). Uses of fluoxetine in nociceptive pain management: A literature overview. *Eur J Pharmacol, 829*, 12-25. doi:10.1016/j.ejphar.2018.03.042

Bardin, L., Gregoire, S., Aliaga, M., Malfetes, N., Vitton, O., Ladure, P., . . . Depoortere, R. (2010). Comparison of milnacipran, duloxetine and pregabalin in the formalin pain test and in a model of stress-induced ultrasonic vocalizations in rats. *Neurosci Res, 66*(2), 135-140. doi:10.1016/j.neures.2009.10.009

Barnhart, J. W., & Massad, E. N. (1979). Determination of dextromethorphan in serum by gas chromatography. *J Chromatogr, 163*(4), 390-395.

Bartkowska, W., Samborski, W., & Mojs, E. (2018). Cognitive functions, emotions and personality in woman with fibromyalgia. *Anthropol Anz, 75*(4), 271-277. doi:10.1127/anthranz/2018/0900

Bem, J. L., & Peck, R. (1992). Dextromethorphan. An overview of safety issues. *Drug Saf, 7*(3), 190-199. doi:10.2165/00002018-199207030-00004

Berger, A., Dukes, E., Martin, S., Edelsberg, J., & Oster, G. (2007). Characteristics and healthcare costs of patients with fibromyalgia syndrome. *International journal of clinical practice, 61*(9), 1498-1508. doi:10.1111/j.1742-1241.2007.01480.x

Bianchi, M., & Panerai, A. E. (1996). Antidepressant drugs and experimental inflammation. *Pharmacological Research, 33*(4), 235-238. doi:https://doi.org/10.1006/phrs.1996.0032

Bianchi, M., Sacerdote, P., Ricciardi-Castagnoli, P., Mantegazza, P., & Panerai, A. E. (1992). Central effects of tumor necrosis factor α and interleukin-1α on nociceptive thresholds and spontaneous locomotor activity. *Neurosci Lett, 148*(1), 76-80. doi:https://doi.org/10.1016/0304-3940(92)90808-K

Bjelland, I., Dahl, A. A., Haug, T. T., & Neckelmann, D. (2002). The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res, 52*(2), 69-77.

Bohn, D., Bernardy, K., Wolfe, F., & Hauser, W. (2013). The association among childhood maltreatment, somatic symptom intensity, depression, and somatoform dissociative symptoms in patients with fibromyalgia syndrome: a single-center

cohort study. *J Trauma Dissociation, 14*(3), 342-358. doi:10.1080/15299732.2012.736930

Boyer, E. W. (2004). Dextromethorphan abuse. *Pediatr Emerg Care, 20*(12), 858-863. doi:10.1097/01.pec.0000148039.14588.d0

Buskila, D., Neumann, L., Sibirski, D., & Shvartzman, P. (1997). Awareness of diagnostic and clinical features of fibromyalgia among family physicians. *Fam Pract, 14*(3), 238-241.

Buskila, D., Neumann, L., Vaisberg, G., Alkalay, D., & Wolfe, F. (1997). Increased rates of fibromyalgia following cervical spine injury. A controlled study of 161 cases of traumatic injury. *Arthritis Rheum, 40*(3), 446-452.

Cabo-Meseguer, A., Cerdá-Olmedo, G., & Trillo-Mata, J. L. (2017). Fibromyalgia: Prevalence, epidemiologic profiles and economic costs. *Medicina Clínica (English Edition), 149*(10), 441-448. doi:https://doi.org/10.1016/j.medcle.2017.10.011

Cagnie, B., Coppieters, I., Denecker, S., Six, J., Danneels, L., & Meeus, M. (2014). Central sensitization in fibromyalgia? A systematic review on structural and functional brain MRI. *Semin Arthritis Rheum, 44*(1), 68-75. doi:10.1016/j.semarthrit.2014.01.001

Calandre, E. P., Rico-Villademoros, F., & Slim, M. (2015). An update on pharmacotherapy for the treatment of fibromyalgia. *Expert Opinion on Pharmacotherapy, 16*(9), 1347-1368. doi:10.1517/14656566.2015.1047343

Carter, L. P., Reissig, C. J., Johnson, M. W., Klinedinst, M. A., Griffiths, R. R., & Mintzer, M. Z. (2013). Acute cognitive effects of high doses of dextromethorphan relative to triazolam in humans. *Drug Alcohol Depend, 128*(3), 206-213. doi:10.1016/j.drugalcdep.2012.08.025

Cedraschi, C., Luthy, C., Girard, E., Piguet, V., Desmeules, J., & Allaz, A. F. (2012). Representations of symptom history in women with fibromyalgia vs chronic low back pain: a qualitative study. *Pain Med, 13*(12), 1562-1570. doi:10.1111/j.1526-4637.2012.01501.x

Chechneva, O. V., Mayrhofer, F., Daugherty, D. J., Pleasure, D. E., Hong, J. S., & Deng, W. (2011). Low dose dextromethorphan attenuates moderate experimental autoimmune encephalomyelitis by inhibiting NOX2 and reducing peripheral immune cells infiltration in the spinal cord. *Neurobiol Dis, 44*(1), 63-72. doi:10.1016/j.nbd.2011.06.004

Chen, S.-L., Huang, E. Y.-K., Chow, L.-H., & Tao, P.-L. (2005). Dextromethorphan differentially affects opioid antinociception in rats. *British journal of pharmacology, 144*(3), 400-404. doi:10.1038/sj.bjp.0706086

Cheng, W., Li, Y., Hou, X., Bai, B., Li, F., Ding, F., . . . Wang, Y. (2015). Determining the neuroprotective effects of dextromethorphan in lipopolysaccharidestimulated BV2 microglia. *Mol Med Rep, 11*(2), 1132-1138. doi:10.3892/mmr.2014.2794

Choi, B. Y., Oh, H. J., Lee, Y. J., & Song, Y. W. (2016). Prevalence and clinical impact of fibromyalgia in patients with primary Sjogren's syndrome. *Clin Exp Rheumatol, 34*(2 Suppl 96), S9-13.

Choy, E., Perrot, S., Leon, T., Kaplan, J., Petersel, D., Ginovker, A., & Kramer, E. (2010). A patient survey of the impact of fibromyalgia and the journey to diagnosis. *BMC health services research, 10*, 102-102. doi:10.1186/1472-6963-10-102

Cleeland, C. S., & Ryan, K. M. (1994). Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singapore, 23*(2), 129-138.

Cohen, S. P., Bhatia, A., Buvanendran, A., Schwenk, E. S., Wasan, A. D., Hurley, R. W., . . . Hooten, W. M. (2018). Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Chronic Pain From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. *Regional anesthesia and pain medicine, 43*(5), 521-546. doi:10.1097/AAP.0000000000000808

Cohen, S. P., Verdolin, M. H., Chang, A. S., Kurihara, C., Morlando, B. J., & Mao, J. (2006). The intravenous ketamine test predicts subsequent response to an oral dextromethorphan treatment regimen in fibromyalgia patients. *J Pain, 7*(6), 391-398. doi:10.1016/j.jpain.2005.12.010

Cording, M., Derry, S., Phillips, T., Moore, R. A., & Wiffen, P. J. (2015). Milnacipran for pain in fibromyalgia in adults. *Cochrane Database of Systematic Reviews*(10). doi:10.1002/14651858.CD008244.pub3

Cote, B., Ross, B., Fortner, J., & Rao, D. (2018). The Use and Utility of Low-dose Naltrexone Capsules for Patients with Fibromyalgia. *Int J Pharm Compd, 22*(3), 252-256.

Croft, P., Rigby, A. S., Boswell, R., Schollum, J., & Silman, A. (1993). The prevalence of chronic widespread pain in the general population. *J Rheumatol, 20*(4), 710-713.

D'Ambrosi, N., Finocchi, P., Apolloni, S., Cozzolino, M., Ferri, A., Padovano, V., . . . Volonte, C. (2009). The proinflammatory action of microglial P2 receptors is enhanced in SOD1 models for amyotrophic lateral sclerosis. *J Immunol, 183*(7), 4648-4656. doi:10.4049/jimmunol.0901212

Dantzer, R. (2001). Cytokine-induced sickness behavior: mechanisms and implications. *Ann N Y Acad Sci, 933*, 222-234.

Dantzer, R. (2004). Cytokine-induced sickness behaviour: a neuroimmune response to activation of innate immunity. *Eur J Pharmacol, 500*(1-3), 399-411. doi:10.1016/j.ejphar.2004.07.040

Dantzer, R., Bluthe, R. M., Gheusi, G., Cremona, S., Laye, S., Parnet, P., & Kelley, K. W. (1998). Molecular basis of sickness behavior. *Ann N Y Acad Sci, 856*, 132-138.

Davalos, D., Grutzendler, J., Yang, G., Kim, J. V., Zuo, Y., Jung, S., . . . Gan, W. B. (2005). ATP mediates rapid microglial response to local brain injury in vivo. *Nat Neurosci, 8*(6), 752-758. doi:10.1038/nn1472

Davies, S. N., & Lodge, D. (1987). Evidence for involvement of N-methylaspartate receptors in 'wind-up' of class 2 neurones in the dorsal horn of the rat. *Brain Res, 424*(2), 402-406.

de la Coba, P., Bruehl, S., Galvez-Sanchez, C. M., & Reyes Del Paso, G. A. (2018). Slowly Repeated Evoked Pain as a Marker of Central Sensitization in Fibromyalgia: Diagnostic Accuracy and Reliability in Comparison With Temporal Summation of Pain. *Psychosom Med, 80*(6), 573-580. doi:10.1097/psy.0000000000000599

de la Coba, P., Bruehl, S., Moreno-Padilla, M., & Reyes Del Paso, G. A. (2017). Responses to Slowly Repeated Evoked Pain Stimuli in Fibromyalgia Patients: Evidence of Enhanced Pain Sensitization. *Pain Med, 18*(9), 1778-1786. doi:10.1093/pm/pnw361

Dickenson, A. H., & Sullivan, A. F. (1987). Evidence for a role of the NMDA receptor in the frequency dependent potentiation of deep rat dorsal horn nociceptive neurones following C fibre stimulation. *Neuropharmacology, 26*(8), 1235-1238.

Duffield, S. J., Miller, N., Zhao, S., & Goodson, N. J. (2018). Concomitant fibromyalgia complicating chronic inflammatory arthritis: a systematic review and meta-analysis. *Rheumatology (Oxford), 57*(8), 1453-1460. doi:10.1093/rheumatology/key112

Eller-Smith, O. C., Nicol, A. L., & Christianson, J. A. (2018). Potential Mechanisms Underlying Centralized Pain and Emerging Therapeutic Interventions. *Front Cell Neurosci, 12*, 35. doi:10.3389/fncel.2018.00035

Fayed, N., Olivan-Blazquez, B., Herrera-Mercadal, P., Puebla-Guedea, M., Perez-Yus, M. C., Andres, E., . . . Garcia-Campayo, J. (2014). Changes in metabolites after treatment with memantine in fibromyalgia. A double-blind randomized controlled

trial with magnetic resonance spectroscopy with a 6-month follow-up. *CNS Neurosci Ther, 20*(11), 999-1007. doi:10.1111/cns.12314

Fayed, N., Oliván, B., Lopez Del Hoyo, Y., Andrés, E., Perez-Yus, M. C., Fayed, A., . . . Garcia Campayo, J. (2019). Changes in metabolites in the brain of patients with fibromyalgia after treatment with an NMDA receptor antagonist. *Neuroradiol J, 32*(6), 408-419. doi:10.1177/1971400919857544

Fitzcharles, M. A., & Boulos, P. (2003). Inaccuracy in the diagnosis of fibromyalgia syndrome: analysis of referrals. *Rheumatology (Oxford), 42*(2), 263-267.

Fitzcharles, M. A., Ste-Marie, P. A., Rampakakis, E., Sampalis, J. S., & Shir, Y. (2016). Disability in Fibromyalgia Associates with Symptom Severity and Occupation Characteristics. *J Rheumatol, 43*(5), 931-936. doi:10.3899/jrheum.151041

Gelonch, O., Garolera, M., Valls, J., Castella, G., Varela, O., Rossello, L., & Pifarre, J. (2018). The effect of depressive symptoms on cognition in patients with fibromyalgia. *PLoS One, 13*(7), e0200057. doi:10.1371/journal.pone.0200057

Gist, A. C., Guymer, E. K., Eades, L. E., Leech, M., & Littlejohn, G. O. (2018). Fibromyalgia remains a significant burden in rheumatoid arthritis patients in Australia. *Int J Rheum Dis, 21*(3), 639-646. doi:10.1111/1756-185x.13055

Goldenberg, D. L., Clauw, D. J., Palmer, R. E., & Clair, A. G. (2016). Opioid Use in Fibromyalgia: A Cautionary Tale. *Mayo Clin Proc, 91*(5), 640-648. doi:10.1016/j.mayocp.2016.02.002

Graven-Nielsen, T., Aspegren Kendall, S., Henriksson, K. G., Bengtsson, M., Sorensen, J., Johnson, A., . . . Arendt-Nielsen, L. (2000). Ketamine reduces muscle pain,

temporal summation, and referred pain in fibromyalgia patients. *Pain, 85*(3), 483-491.

Haines, D. R., & Gaines, S. P. (1999). N of 1 randomised controlled trials of oral ketamine in patients with chronic pain. *Pain, 83*(2), 283-287.

Herrero, J. F., Laird, J. M., & Lopez-Garcia, J. A. (2000). Wind-up of spinal cord neurones and pain sensation: much ado about something? *Prog Neurobiol, 61*(2), 169-203.

Ishizuka, P., Garcia, J. B., Sakata, R. K., Issy, A. M., & Mulich, S. L. (2007). Assessment of oral S+ ketamine associated with morphine for the treatment of oncologic pain. *Rev Bras Anestesiol, 57*(1), 19-31.

Jafarinia, M., Afarideh, M., Tafakhori, A., Arbabi, M., Ghajar, A., Noorbala, A. A., . . . Akhondzadeh, S. (2016). Efficacy and safety of oral ketamine versus diclofenac to alleviate mild to moderate depression in chronic pain patients: A double-blind, randomized, controlled trial. *J Affect Disord, 204*, 1-8. doi:10.1016/j.jad.2016.05.076

Jones, G. T., Atzeni, F., Beasley, M., Fluss, E., Sarzi-Puttini, P., & Macfarlane, G. J. (2015). The prevalence of fibromyalgia in the general population: a comparison of the American College of Rheumatology 1990, 2010, and modified 2010 classification criteria. *Arthritis Rheumatol, 67*(2), 568-575. doi:10.1002/art.38905

Jorum, E., Warncke, T., & Stubhaug, A. (2003). Cold allodynia and hyperalgesia in neuropathic pain: the effect of N-methyl-D-aspartate (NMDA) receptor antagonist

ketamine--a double-blind, cross-over comparison with alfentanil and placebo. *Pain, 101*(3), 229-235.

Journey, J. D., & Stern, E. (2019). In *Dextromethorphan Toxicity*. Treasure Island (FL): StatPearls Publishing.

Kohler, O., Krogh, J., Mors, O., & Benros, M. E. (2016). Inflammation in Depression and the Potential for Anti-Inflammatory Treatment. *Curr Neuropharmacol, 14*(7), 732-742. doi:10.2174/1570159x14666151208113700

Kostadinov, I., Delev, D., Petrova, A., Stanimirova, I., Draganova, K., Kruzliak, P., . . . Murdjeva, M. (2015). Study on anti-inflammatory and immunomodulatory effects of fluoxetine in rat models of inflammation. *European Journal of Inflammation, 13*(3), 173-182. doi:10.1177/1721727x15618671

Lee, J.-H., Choi, S.-H., Shin, T.-J., Lee, B.-H., Hwang, S.-H., Kim, H.-C., & Nah, S.-Y. (2011). Effect of dextromethorphan on human Kv1.3 channel activity: Involvement of C-type inactivation. *Eur J Pharmacol, 651*(1), 122-127. doi:https://doi.org/10.1016/j.ejphar.2010.10.091

Leung, A., Wallace, M. S., Ridgeway, B., & Yaksh, T. (2001). Concentration-effect relationship of intravenous alfentanil and ketamine on peripheral neurosensory thresholds, allodynia and hyperalgesia of neuropathic pain. *Pain, 91*(1-2), 177-187.

Li, G., Cui, G., Tzeng, N.-S., Wei, S.-J., Wang, T., Block, M. L., & Hong, J.-S. (2005). Femtomolar concentrations of dextromethorphan protect mesencephalic

dopaminergic neurons from inflammatory damage. *The FASEB Journal, 19*(6), 489-496. doi:10.1096/fj.04-2555com

Liu, D., Wang, Z., Liu, S., Wang, F., Zhao, S., & Hao, A. (2011). Anti-inflammatory effects of fluoxetine in lipopolysaccharide(LPS)-stimulated microglial cells. *Neuropharmacology, 61*(4), 592-599. doi:https://doi.org/10.1016/j.neuropharm.2011.04.033

Liu, Y., Qin, L., Li, G., Zhang, W., An, L., Liu, B., & Hong, J.-S. (2003). Dextromethorphan Protects Dopaminergic Neurons against Inflammation-Mediated Degeneration through Inhibition of Microglial Activation. *Journal of Pharmacology and Experimental Therapeutics, 305*(1), 212-218. doi:10.1124/jpet.102.043166

Lynch, M. A. (2009). The multifaceted profile of activated microglia. *Mol Neurobiol, 40*(2), 139-156. doi:10.1007/s12035-009-8077-9

Maher, D. P., Chen, L., & Mao, J. (2017). Intravenous Ketamine Infusions for Neuropathic Pain Management: A Promising Therapy in Need of Optimization. *Anesth Analg, 124*(2), 661-674. doi:10.1213/ane.0000000000001787

Marier, J. F., Deschenes, J. L., Hage, A., Seliniotakis, E., Gritsas, A., Flarakos, T., . . . Vachon, P. (2005). Enhancing the uptake of dextromethorphan in the CNS of rats by concomitant administration of the P-gp inhibitor verapamil. *Life Sci, 77*(23), 2911-2926. doi:10.1016/j.lfs.2005.04.025

Marlow, N. M., Simpson, K. N., Vaughn, I. A., Jo, A., Zoller, J. S., & Short, E. B. (2018). Healthcare Costs and Medication Adherence Among Patients with

Fibromyalgia: Combination Medication vs. Duloxetine, Milnacipran, Venlafaxine, and Pregabalin Initiators. *Pain practice : the official journal of World Institute of Pain, 18*(2), 154-169. doi:10.1111/papr.12585

Moraes, E. R., Kushmerick, C., & Naves, L. A. (2014). Characteristics of dorsal root ganglia neurons sensitive to Substance P. *Mol Pain, 10*, 73. doi:10.1186/1744-8069-10-73

Morel, V., Pickering, G., Etienne, M., Dupuis, A., Privat, A.-M., Chalus, M., . . . Daulhac, L. (2014). Low doses of dextromethorphan have a beneficial effect in the treatment of neuropathic pain. *Fundamental & Clinical Pharmacology, 28*(6), 671-680. doi:10.1111/fcp.12076

Mueller, C., Lin, J. C., Sheriff, S., Maudsley, A. A., & Younger, J. W. (2019). Evidence of widespread metabolite abnormalities in Myalgic encephalomyelitis/chronic fatigue syndrome: assessment with whole-brain magnetic resonance spectroscopy. *Brain Imaging Behav*. doi:10.1007/s11682-018-0029-4

Natelson, B. H., Vu, D., Mao, X., Weiduschat, N., Togo, F., Lange, G., . . . Shungu, D. C. (2015). Effect of Milnacipran Treatment on Ventricular Lactate in Fibromyalgia: A Randomized, Double-Blind, Placebo-Controlled Trial. *J Pain, 16*(11), 1211-1219. doi:10.1016/j.jpain.2015.08.004

Nazimek, K., Kozlowski, M., Bryniarski, P., Strobel, S., Bryk, A., Myszka, M., . . . Filipczak-Bryniarska, I. (2016). Repeatedly administered antidepressant drugs modulate humoral and cellular immune response in mice through action on

macrophages. *Exp Biol Med (Maywood), 241*(14), 1540-1550. doi:10.1177/1535370216643769

Neumann, L., Zeldets, V., Bolotin, A., & Buskila, D. (2003). Outcome of posttraumatic fibromyalgia: a 3-year follow-up of 78 cases of cervical spine injuries. *Semin Arthritis Rheum, 32*(5), 320-325. doi:10.1053/sarh.2003.50009

Nimmerjahn, A., Kirchhoff, F., & Helmchen, F. (2005). Resting microglial cells are highly dynamic surveillants of brain parenchyma in vivo. *Science, 308*(5726), 1314-1318. doi:10.1126/science.1110647

Noppers, I., Niesters, M., Swartjes, M., Bauer, M., Aarts, L., Geleijnse, N., . . . Sarton, E. (2011). Absence of long-term analgesic effect from a short-term S-ketamine infusion on fibromyalgia pain: a randomized, prospective, double blind, active placebo-controlled trial. *Eur J Pain, 15*(9), 942-949. doi:10.1016/j.ejpain.2011.03.008

O'Brien, A. T., Deitos, A., Trinanes Pego, Y., Fregni, F., & Carrillo-de-la-Pena, M. T. (2018). Defective Endogenous Pain Modulation in Fibromyalgia: A Meta-Analysis of Temporal Summation and Conditioned Pain Modulation Paradigms. *J Pain, 19*(8), 819-836. doi:10.1016/j.jpain.2018.01.010

Olivan-Blazquez, B., Herrera-Mercadal, P., Puebla-Guedea, M., Perez-Yus, M. C., Andres, E., Fayed, N., . . . Garcia-Campayo, J. (2014). Efficacy of memantine in the treatment of fibromyalgia: A double-blind, randomised, controlled trial with 6-month follow-up. *Pain, 155*(12), 2517-2525. doi:10.1016/j.pain.2014.09.004

Painter, J. T., & Crofford, L. J. (2013). Chronic opioid use in fibromyalgia syndrome: a clinical review. *J Clin Rheumatol, 19*(2), 72-77. doi:10.1097/RHU.0b013e3182863447

Parada, C. A., Luccarini, P., & Woda, A. (1997). Effect of an NMDA receptor antagonist on the wind-up of neurons in the trigeminal oralis subnucleus. *Brain Res, 761*(2), 313-320.

Parkitny, L., & Younger, J. (2017). Reduced Pro-Inflammatory Cytokines after Eight Weeks of Low-Dose Naltrexone for Fibromyalgia. *Biomedicines, 5*(2). doi:10.3390/biomedicines5020016

Patten, D. K., Schultz, B. G., & Berlau, D. J. (2018). The Safety and Efficacy of Low-Dose Naltrexone in the Management of Chronic Pain and Inflammation in Multiple Sclerosis, Fibromyalgia, Crohn's Disease, and Other Chronic Pain Disorders. *Pharmacotherapy, 38*(3), 382-389. doi:10.1002/phar.2086

Perry, P. J., Fredriksen, K., Chew, S., Ip, E. J., Lopes, I., Doroudgar, S., & Thomas, K. (2015). The Effects of Dextromethorphan on Driving Performance and the Standardized Field Sobriety Test. *J Forensic Sci, 60*(5), 1258-1262. doi:10.1111/1556-4029.12833

Pidal-Miranda, M., Gonzalez-Villar, A. J., Carrillo-de-la-Pena, M. T., Andrade, E., & Rodriguez-Salgado, D. (2018). Broad cognitive complaints but subtle objective working memory impairment in fibromyalgia patients. *PeerJ, 6*, e5907. doi:10.7717/peerj.5907

Poon, D. C., Ho, Y. S., Chiu, K., Wong, H. L., & Chang, R. C. (2015). Sickness: From the focus on cytokines, prostaglandins, and complement factors to the perspectives of neurons. *Neurosci Biobehav Rev, 57*, 30-45. doi:10.1016/j.neubiorev.2015.07.015

Price, D. D., Staud, R., Robinson, M. E., Mauderli, A. P., Cannon, R., & Vierck, C. J. (2002). Enhanced temporal summation of second pain and its central modulation in fibromyalgia patients. *Pain, 99*(1-2), 49-59.

Radvansky, B. M., Puri, S., Sifonios, A. N., Eloy, J. D., & Le, V. (2016). Ketamine-A Narrative Review of Its Uses in Medicine. *Am J Ther, 23*(6), e1414-e1426. doi:10.1097/mjt.0000000000000257

Raison, C. L., Capuron, L., & Miller, A. H. (2006). Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends Immunol, 27*(1), 24-31. doi:10.1016/j.it.2005.11.006

Ransohoff, R. M., & Perry, V. H. (2009). Microglial physiology: unique stimuli, specialized responses. *Annu Rev Immunol, 27*, 119-145. doi:10.1146/annurev.immunol.021908.132528

Reissig, C. J., Carter, L. P., Johnson, M. W., Mintzer, M. Z., Klinedinst, M. A., & Griffiths, R. R. (2012). High doses of dextromethorphan, an NMDA antagonist, produce effects similar to classic hallucinogens. *Psychopharmacology (Berl), 223*(1), 1-15. doi:10.1007/s00213-012-2680-6

Russell, I. J., Vaeroy, H., Javors, M., & Nyberg, F. (1992). Cerebrospinal fluid biogenic amine metabolites in fibromyalgia/fibrositis syndrome and rheumatoid arthritis. *Arthritis & Rheumatism, 35*(5), 550-556. doi:10.1002/art.1780350509

Sacre, S., Medghalchi, M., Gregory, B., Brennan, F., & Williams, R. (2010). Fluoxetine and citalopram exhibit potent antiinflammatory activity in human and murine models of rheumatoid arthritis and inhibit toll-like receptors. *Arthritis & Rheumatism, 62*(3), 683-693. doi:10.1002/art.27304

Saito, H., Wakai, J., Sekiguchi, M., Kikuchi, S., & Konno, S. (2014). The effect of selective serotonin reuptake inhibitor (SSRI) on pain-related behavior in a rat model of neuropathic pain. *Eur Spine J, 23*(11), 2401-2409. doi:10.1007/s00586-014-3392-x

Sallinen, M., & Marit Mengshoel, A. (2018). Memory gaps, lost words and crucial mistakes - Men's experiences of cognitive difficulties in fibromyalgia. *Chronic Illn*, 1742395318815947. doi:10.1177/1742395318815947

Seddighfar, M., Ghasemzadeh, Z., & Rezayof, A. (2019). The blockade of 5-HT(1A) receptors in the ventral tegmental area inhibited morphine/dextromethorphan-induced analgesia in pain rat models. *Brain Res, 1715*, 27-34. doi:10.1016/j.brainres.2019.03.018

Sharma, M., Arbabzada, N., & Flood, P. M. (2019). Mechanism underlying beta2-AR agonist-mediated phenotypic conversion of LPS-activated microglial cells. *J Neuroimmunol, 332*, 37-48. doi:10.1016/j.jneuroim.2019.03.017

Shi, T., Hao, J.-X., Wiesenfeld-Hallin, Z., & Xu, X.-J. (2018). Gabapentin and NMDA receptor antagonists interacts synergistically to alleviate allodynia in two rat models of neuropathic pain. *18*(4), 687. doi:https://doi.org/10.1515/sjpain-2018-0083

Sitges, M., Gomez, C. D., & Aldana, B. I. (2014). Sertraline reduces IL-1beta and TNF-alpha mRNA expression and overcomes their rise induced by seizures in the rat hippocampus. *PLoS One, 9*(11), e111665. doi:10.1371/journal.pone.0111665

Skinner, H. A. (1982). *Drug use questionnaire (DAST-20)*: Addiction Research Foundation.

Song, J.-H., & Yeh, J. Z. (2012). Dextromethorphan inhibition of voltage-gated proton currents in BV2 microglial cells. *Neurosci Lett, 516*(1), 94-98. doi:https://doi.org/10.1016/j.neulet.2012.03.065

Sorensen, J., Bengtsson, A., Backman, E., Henriksson, K. G., & Bengtsson, M. (1995). Pain analysis in patients with fibromyalgia. Effects of intravenous morphine, lidocaine, and ketamine. *Scand J Rheumatol, 24*(6), 360-365.

Stanciu, C. N., Penders, T. M., & Rouse, E. M. (2016). Recreational use of dextromethorphan, "Robotripping"-A brief review. *Am J Addict, 25*(5), 374-377. doi:10.1111/ajad.12389

Staud, R., Cannon, R. C., Mauderli, A. P., Robinson, M. E., Price, D. D., & Vierck, C. J., Jr. (2003). Temporal summation of pain from mechanical stimulation of muscle tissue in normal controls and subjects with fibromyalgia syndrome. *Pain, 102*(1-2), 87-95.

Staud, R., Craggs, J. G., Perlstein, W. M., Robinson, M. E., & Price, D. D. (2008). Brain activity associated with slow temporal summation of C-fiber evoked pain in fibromyalgia patients and healthy controls. *European journal of pain (London, England), 12*(8), 1078-1089. doi:10.1016/j.ejpain.2008.02.002

Staud, R., Robinson, M. E., & Price, D. D. (2007). Temporal summation of second pain and its maintenance are useful for characterizing widespread central sensitization of fibromyalgia patients. *J Pain, 8*(11), 893-901. doi:10.1016/j.jpain.2007.06.006

Staud, R., Vierck, C. J., Cannon, R. L., Mauderli, A. P., & Price, D. D. (2001). Abnormal sensitization and temporal summation of second pain (wind-up) in patients with fibromyalgia syndrome. *Pain, 91*(1-2), 165-175.

Staud, R., Weyl, E. E., Riley, J. L., 3rd, & Fillingim, R. B. (2014). Slow temporal summation of pain for assessment of central pain sensitivity and clinical pain of fibromyalgia patients. *PLoS One, 9*(2), e89086. doi:10.1371/journal.pone.0089086

Stern, A. F. (2014). The hospital anxiety and depression scale. *Occup Med (Lond), 64*(5), 393-394. doi:10.1093/occmed/kqu024

Thomas, D. M., & Kuhn, D. M. (2005). MK-801 and dextromethorphan block microglial activation and protect against methamphetamine-induced neurotoxicity. *Brain Res, 1050*(1-2), 190-198. doi:10.1016/j.brainres.2005.05.049

Tynan, R. J., Weidenhofer, J., Hinwood, M., Cairns, M. J., Day, T. A., & Walker, F. R. (2012). A comparative examination of the anti-inflammatory effects of SSRI and

SNRI antidepressants on LPS stimulated microglia. *Brain, Behavior, and Immunity, 26*(3), 469-479. doi:https://doi.org/10.1016/j.bbi.2011.12.011

Vincent, A., Lahr, B. D., Wolfe, F., Clauw, D. J., Whipple, M. O., Oh, T. H., . . . St Sauver, J. (2013). Prevalence of fibromyalgia: a population-based study in Olmsted County, Minnesota, utilizing the Rochester Epidemiology Project. *Arthritis Care Res (Hoboken), 65*(5), 786-792. doi:10.1002/acr.21896

Wadhwa, A., Clarke, D., Goodchild, C. S., & Young, D. (2001). Large-dose oral dextromethorphan as an adjunct to patient-controlled analgesia with morphine after knee surgery. *Anesth Analg, 92*(2), 448-454.

Walitt, B., Nahin, R. L., Katz, R. S., Bergman, M. J., & Wolfe, F. (2015). The Prevalence and Characteristics of Fibromyalgia in the 2012 National Health Interview Survey. *PLoS One, 10*(9), e0138024. doi:10.1371/journal.pone.0138024

Walitt, B., Urrútia, G., Nishishinya, M. B., Cantrell, S. E., & Häuser, W. (2015). Selective serotonin reuptake inhibitors for fibromyalgia syndrome. *Cochrane Database of Systematic Reviews*(6). doi:10.1002/14651858.CD011735

Wessely, S., & Hindmarch, I. (2004). Taking the pain out of depression: dual action antidepressants in the relief of pain in depression, fibromyalgia and other chronic pain syndromes. *Human Psychopharmacology: Clinical and Experimental, 19*(S1), S1-S2. doi:10.1002/hup.617

Wolfe, F., Clauw, D. J., Fitzcharles, M. A., Goldenberg, D. L., Hauser, W., Katz, R. L., . . . Walitt, B. (2016). 2016 Revisions to the 2010/2011 fibromyalgia diagnostic

criteria. *Semin Arthritis Rheum, 46*(3), 319-329. doi:10.1016/j.semarthrit.2016.08.012

Wolfe, F., Clauw, D. J., Fitzcharles, M. A., Goldenberg, D. L., Hauser, W., Katz, R. S., . . . Winfield, J. B. (2011). Fibromyalgia criteria and severity scales for clinical and epidemiological studies: a modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia. *J Rheumatol, 38*(6), 1113-1122. doi:10.3899/jrheum.100594

Wolfe, F., Clauw, D. J., Fitzcharles, M. A., Goldenberg, D. L., Katz, R. S., Mease, P., . . . Yunus, M. B. (2010). The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res (Hoboken), 62*(5), 600-610. doi:10.1002/acr.20140

Wolfe, F., Petri, M., Alarcon, G. S., Goldman, J., Chakravarty, E. F., Katz, R. S., & Karlson, E. W. (2009). Fibromyalgia, systemic lupus erythematosus (SLE), and evaluation of SLE activity. *J Rheumatol, 36*(1), 82-88. doi:10.3899/jrheum.080212

Wolfe, F., Ross, K., Anderson, J., & Russell, I. J. (1995). Aspects of fibromyalgia in the general population: sex, pain threshold, and fibromyalgia symptoms. *J Rheumatol, 22*(1), 151-156.

Wolfe, F., Ross, K., Anderson, J., Russell, I. J., & Hebert, L. (1995). The prevalence and characteristics of fibromyalgia in the general population. *Arthritis Rheum, 38*(1), 19-28.

Wolfe, F., Smythe, H. A., Yunus, M. B., Bennett, R. M., Bombardier, C., Goldenberg, D. L., . . . et al. (1990). The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum, 33*(2), 160-172.

Wolfe, F., Walitt, B. T., Katz, R. S., & Häuser, W. (2014). Social Security Work Disability and Its Predictors in Patients With Fibromyalgia. *Arthritis Care Res (Hoboken), 66*(9), 1354-1363. doi:10.1002/acr.22305

Xu, X., Zhang, B., Lu, K., Deng, J., Zhao, F., Zhao, B.-q., & Zhao, Y. (2016). Prevention of Hippocampal Neuronal Damage and Cognitive Function Deficits in Vascular Dementia by Dextromethorphan. *Mol Neurobiol, 53*(5), 3494-3502. doi:10.1007/s12035-016-9786-5

Yang, P. P., Yeh, G. C., Huang, E. Y., Law, P. Y., Loh, H. H., & Tao, P. L. (2015). Effects of dextromethorphan and oxycodone on treatment of neuropathic pain in mice. *J Biomed Sci, 22*, 81. doi:10.1186/s12929-015-0186-3

Younger, J., Gandhi, V., Hubbard, E., & Mackey, S. (2012). Development of the Stanford Expectations of Treatment Scale (SETS): a tool for measuring patient outcome expectancy in clinical trials. *Clin Trials, 9*(6), 767-776. doi:10.1177/1740774512465064

Younger, J., & Mackey, S. (2009). Fibromyalgia symptoms are reduced by low-dose naltrexone: a pilot study. *Pain Med, 10*(4), 663-672. doi:10.1111/j.1526-4637.2009.00613.x

Zhang, W., Shin, E. J., Wang, T., Lee, P. H., Pang, H., Wie, M. B., . . . Kim, H. C. (2006). 3-Hydroxymorphinan, a metabolite of dextromethorphan, protects nigrostriatal pathway against MPTP-elicited damage both in vivo and in vitro. *Faseb j, 20*(14), 2496-2511. doi:10.1096/fj.06-6006com

APPENDIX A

REGULATORY APPROVALS

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
Office of the Institutional Review Board for Human Use

470 Administration Building
701 20th Street South
Birmingham, AL 35294-0104
205.934.3789 | Fax 205.934.1301 |
irb@uab.edu

APPROVAL LETTER

TO: Younger, Jarred W

FROM: University of Alabama at Birmingham Institutional Review Board
Federalwide Assurance # FWA00005960
IORG Registration # IRB00000196 (IRB 01)
IORG Registration # IRB00000726 (IRB 02)

DATE: 09-Apr-2020

RE: IRB-161018005
Dextromethorphan in Fibromyalgia

The IRB reviewed and approved the Continuing Review submitted on 06-Apr-2020 for the above referenced project. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services.

Type of Review: Full (Institutional Review Board 02 (UAB))
Determination: Approved
Approval Date: 09-Apr-2020
Approval Period: One Year
Expiration Date: 31-Mar-2021

The following apply to this project related to informed consent and/or assent:

- Waiver (Partial) of HIPAA

Documents Included in Review:

- IPR.200323.pdf

APPENDIX B

DAILY SYMPTOM REPORT QUESTIONNAIRE

Item #	Item	Scale (Anchors)
1	How would you rate your general satisfaction with life today?	0 (not satisfied at all) – 100 (completely satisfied)
2	Overall, how severe have your symptoms been today?	0 (no symptoms at all) – 100 (severe symptoms)
3	How would you rate your general level of pain today?	0 (no pain at all) – 100 (severe pain)
4	What was your highest level of pain today?	0 (no pain at all) – 100 (severe pain)
5	Do you have any muscle pain?	0 (no muscle pain at all) – 100 (severe pain)
6	Do you have any joint pain?	0 (no joint pain at all) – 100 (severe pain)
7a	Have you taken any over-the-counter medicine for pain relief today?	Yes / No
7b	If yes, what kind?	Free response
8	How fatigued have you felt today?	0 (not fatigued at all) – 100 (severely fatigued)
9	How sad, down, or blue have you felt today?	0 (not sad at all) – 100 (severe sadness)
10	How anxious have you felt today?	0 (not anxious at all) – 100 (severely anxious)
11	How stressed have you felt today?	0 (not stressed at all) – 100 (severely stressed)
12	Overall, how good has your mood been today?	0 (not good at all) – 100 (extremely good)
13	How much trouble did you have getting to sleep last night?	0 (no trouble at all) – 100 (severe trouble)
14	Overall, how well did you sleep last night?	0 (did not sleep well at all) – 100 (slept extremely well)
15a	Did you take any sleep medication last night?	Yes / No
15b	If yes, what medication did you take?	Free response
16	How well were you able to think and remember things today?	0 (could not think clearly at all) – 100 (could think extremely well)
17	Did you suffer from any headaches today?	0 (no headaches at all) – 100 (severe headaches)
18	What was your overall level of activity today?	0 (not active at all) – 100 (extremely active)
19	What percentage of normal activities were you able to perform today?	0 (none) – 100 (100%)
20	How much did you physically exert yourself today, such as gardening, exercising, or walking?	0 (no physical activity at all) – 100 (extremely physically active)
21	Did you experience any bowel or gastrointestinal problems today?	0 (no GI problems at all) – 100 (severe GI problems)
22a	Did you experience any unusual stressful events today?	Yes / No
22b	If yes, please briefly describe…	Free response
23a	Did you take any new medication today? (Please do not include your regular or daily medications.)	Yes / No
23b	If yes, what kind…	Free response

APPENDIX C

SAS CODE

```
options nofmterr;

*import data;
proc import
datafile='Z:\PROJECTS\DXM\Data_Files\main_analyses\csv_files_for_
SAS\pm_clean.csv' out=dxmpm
dbms=csv replace;
run;

proc import
datafile='Z:\PROJECTS\DXM\Data_Files\main_analyses\csv_files_for_
SAS\pm_clean_pldxm.csv' out=pldxm
dbms=csv replace;
run;

*create dummy variable for dxm phase;
data dxmpm;
set dxmpm;
if phase=3 then dxm=1;
else if phase=1 or 2 or 4 then dxm=0;
run;

*create SAS library called dissert;
libname dissert 'C:\Users\cm1.UAB\Desktop';

*create a permanent data set in the dissert library that is
identical to the work.dxmpm data set;
data dissert.dxmpm;
set dxmpm;
run;

data dissert.pldxm;
set pldxm;
run;

proc sort data=dxmpm;
by phase;
run;

title 'checking distributions';
*check univariate distribution of outcomes;
proc univariate data=dxmpm normal; *compares to normal
distribution;
by phase;
var genpain highpain muspain fatigue cognition mood sad anx
stress;
histogram genpain fatigue muspain fatigue cognition mood sad anx
stress / midpoints =0 to 100 by 5;;
run;

*make sure data are sorted by id and day before centering;
proc sort data=pldxm;
by PID day;
```

```
run;

*center outcome variables on person-mean;
*generalized pain;
data pldxm; set pldxm;
cgenpain=genpain;
run;
proc standard data=pldxm mean=0 out=pldxm;
by pid;
var cgenpain;
run;

*muscle pain;
data pldxm; set pldxm;
cmuspain=muspain;
run;
proc standard data=pldxm mean=0 out=pldxm;
by pid;
var cmuspain;
run;

*highest pain;
data pldxm; set pldxm;
chighpain=highpain;
run;
proc standard data=pldxm mean=0 out=pldxm;
by pid;
var chighpain;
run;

*fatigue;
data pldxm; set pldxm;
cfatigue=fatigue;
run;
proc standard data=pldxm mean=0 out=pldxm;
by pid;
var cfatigue;
run;

*cognition;
data pldxm; set pldxm;
ccognition=cognition;
run;
proc standard data=pldxm mean=0 out=pldxm;
by pid;
var ccognition;
run;

*mood;
data pldxm; set pldxm;
cmood=mood;
run;
proc standard data=pldxm mean=0 out=pldxm;
```

```
by pid;
var cmood;
run;

*sad;
data pldxm; set pldxm;
csad=sad;
run;
proc standard data=pldxm mean=0 out=pldxm;
by pid;
var csad;
run;

*anx;
data pldxm; set pldxm;
canx=anx;
run;
proc standard data=pldxm mean=0 out=pldxm;
by pid;
var canx;
run;

*stress;
data pldxm; set pldxm;
cstress=stress;
run;
proc standard data=pldxm mean=0 out=pldxm;
by pid;
var cstress;
run;

*grand-mean-center age and dxdur;
proc sort data=pldxm;
by PID day;
run;
data pldxm; set pldxm;
cage=age-47.07;
cdxdur=dxdur-10.19;
run;

*grand-mean-center SETS scores;
data pldxm; set pldxm;
cSETS_pos=SETS_pos-4.14;
cSETS_neg=SETS_neg-1.79;
run;



*check univariate distribution of CENTERED outcomes per phase;
proc sort data=pldxm;
by phase;
run;
```

```
proc univariate data=pldxm normal; *compares to normal
distribution;
by phase;
var cgenpain cmuspain chighpain cfatigue ccognition cmood csad
canx cstress;
histogram cgenpain cmuspain chighpain cfatigue ccognition cmood
csad canx cstress / midpoints =-100 to 100 by 5;
run;

*create phase averages per person;
data pldxm; set pldxm;
genpain_phase=genpain-cgenpain;
muspain_phase=muspain-cmuspain;
highpain_phase=highpain-chighpain;
fatigue_phase=fatigue-cfatigue;
cognition_phase=cognition-ccognition;
mood_phase=mood-cmood;
sad_phase=sad-csad;
anx_phase=anx-canx;
stress_phase=stress-cstress;
run;

*save dataset as permanent dataset for later;
data dissert.dxmpm;
set dxmpm;
run;

data dissert.pldxm;
set pldxm;
run;

*GEE to predict outcomes based on treatment phase;
*using normal distribution;
proc genmod data=pldxm;
title 'predicting DXM effects on generalized pain';
class pid;
model cgenpain= dxm /dist=normal;
repeated subject=pid / type=ar corrw;
run;
proc genmod data=pldxm;
title 'predicting DXM effects on generalized pain';
class pid;
model cgenpain= day dxm /dist=normal;
repeated subject=pid / type=ar corrw;
run;
proc genmod data=pldxm;
title 'predicting DXM effects on generalized pain';
class pid;
model cgenpain= day dxm day*dxm /dist=normal;
repeated subject=pid / type=ar corrw;
run;

proc genmod data=pldxm;
```

```
title 'predicting DXM effects on generalized pain - accounting
for age';
class pid;
model cgenpain= day dxm day*dxm cage cage*dxm /dist=normal;
repeated subject=pid / type=ar corrw;
run;

proc genmod data=pldxm;
title 'predicting DXM effects on generalized pain - accounting
for FM duration';
class pid;
model cgenpain= day dxm day*dxm cdxdur cdxdur*dxm /dist=normal;
repeated subject=pid / type=ar corrw;
run;

proc genmod data=pldxm;
title 'predicting DXM effects on generalized pain - accounting
for treatment adherence';
class pid;
model cgenpain= day dxm day*dxm medcomply medcomply*dxm
/dist=normal;
repeated subject=pid / type=ar corrw;
run;


proc genmod data=pldxm;
title 'predicting DXM effects on generalized pain - accounting
for OTC pain medication use';
class pid;
model cgenpain= day dxm day*dxm painmed painmed*dxm /dist=normal;
repeated subject=pid / type=ar corrw;
run;


proc genmod data=pldxm;
title 'predicting DXM effects on generalized pain - accounting
for positive treatment expectations';
class pid;
model cgenpain= day dxm day*dxm cSETS_pos dxm*cSETs_pos
/dist=normal;
repeated subject=pid / type=ar corrw;
run;

proc genmod data=pldxm;
title 'predicting DXM effects on generalized pain - accounting
for negative treatment expectations';
class pid;
model cgenpain= day dxm day*dxm cSETS_neg dxm*cSETs_neg
/dist=normal;
repeated subject=pid / type=ar corrw;
run;
```

```
proc genmod data=pldxm;
title 'predicting DXM effects on generalized pain, accounting for
tx adherence';
class pid;
model cgenpain= day dxm day*dxm medcomply dxm*medcomply
dxm*day*medcomply /dist=normal;
repeated subject=pid / type=ar corrw;
run;

proc genmod data=pldxm;
title 'predicting DXM effects on generalized pain, accounting for
FM duration';
class pid;
model cgenpain= day dxm day*dxm cage cdxdur dxm*cdxdur
dxm*day*cdxdur /dist=normal;
repeated subject=pid / type=ar corrw;
run;

*muscle pain;
proc genmod data=pldxm;
title 'predicting DXM effects on muscle pain';
class pid;
model cmuspain= day dxm day*dxm /dist=normal;
repeated subject=pid / type=ar corrw;
run;

*highest pain;
proc genmod data=pldxm;
title 'predicting DXM effects on highest pain';
class pid;
model chighpain= day dxm day*dxm /dist=normal;
repeated subject=pid / type=ar corrw;
run;

*fatigue;
proc genmod data=pldxm;
title 'predicting DXM effects on fatigue';
class pid;
model cfatigue= day dxm day*dxm /dist=normal;
repeated subject=pid / type=ar corrw;
run;

*depression;
proc genmod data=pldxm;
title 'predicting DXM effects on depressed mood';
class pid;
model csad= day dxm day*dxm /dist=normal;
repeated subject=pid / type=ar corrw;
run;

*anxiety;
proc genmod data=pldxm;
title 'predicting DXM effects on anxiety';
```

```
class pid;
model canx= day dxm day*dxm /dist=normal;
repeated subject=pid / type=ar corrw;
run;

*mood;
proc genmod data=pldxm;
title 'predicting DXM effects on positive mood';
class pid;
model cmood= day dxm day*dxm /dist=normal;
repeated subject=pid / type=ar corrw;
run;

*cognition;
proc genmod data=pldxm;
title 'predicting DXM effects on cognitive complaints';
class pid;
model ccognition= day dxm day*dxm /dist=normal;
repeated subject=pid / type=ar corrw;
run;

*stress;
proc genmod data=pldxm;
title 'predicting DXM effects on stress';
class pid;
model cstress= day dxm day*dxm /dist=normal;
repeated subject=pid / type=ar corrw;
run;

*get condition means;
title 'condition means';
proc sort data=pldxm;
by phase;
run;

proc means data=dxmpm mean std median;
by phase;
run;

proc means data=dxmpm mean std median;
by phase;
run;

*rerun using binomial distribution;
proc genmod data=pldxm;
title 'predicting DXM effects on generalized pain - binomial
distribution';
class pid;
model cgenpain= day dxm /dist=negbin link=log;
repeated subject=pid / type=ar corrw;
estimate '1 dxm' dxm 1;
run;
```

```
proc genmod data=pldxm;
title 'predicting DXM effects on generalized pain - binomial
distribution';
class pid;
model cgenpain= day dxm day*dxm /dist=negbin link=log;
repeated subject=pid / type=ar corrw;
estimate '1 dxm' dxm 1;
run;


*FM natural disease course;
proc import
datafile='Z:\PROJECTS\DXM\Data_Files\main_analyses\csv_files_for_
SAS\DIMS_FM.csv' out=dims
dbms=csv replace;
run;

*grand-mean-center age;
proc sort data=dims;
by PID day;
run;
data dims; set dims;
cage=age-42.71;
run;

*save;
data dissert.dims;
set dims;
run;

title 'checking distributions';
*check univariate distribution of outcomes;
proc univariate data=dims normal; *compares to normal
distribution;
var genpain highpain fatigue cognition mood sad anx stress;
histogram genpain highpain fatigue cognition mood sad anx stress
/ midpoints =0 to 100 by 5;;
run;

proc genmod data=dims;
title 'predicting generalized pain trajectories';
class pid;
model genpain= day /dist=normal;
repeated subject=pid / type=ar corrw;
run;

proc genmod data=dims;
title 'predicting highest pain trajectories';
class pid;
model highpain= day /dist=normal;
repeated subject=pid / type=ar corrw;
run;
```

```
proc genmod data=dims;
title 'predicting fatigue trajectories';
class pid;
model fatigue= day /dist=normal;
repeated subject=pid / type=ar corrw;
run;

proc genmod data=dims;
title 'predicting cognition trajectories';
class pid;
model cognition= day /dist=normal;
repeated subject=pid / type=ar corrw;
run;

proc genmod data=dims;
title 'predicting positive mood trajectories';
class pid;
model mood= day /dist=normal;
repeated subject=pid / type=ar corrw;
run;

proc means data=dims;
var sad anx stress;
run;

proc genmod data=dims;
title 'predicting depression trajectories';
class pid;
model sad= day /dist=nb link=log;
repeated subject=pid / type=ar;
estimate '1 day' day 1;
run;

proc genmod data=dims;
title 'predicting anxiety trajectories';
class pid;
model anx= day /dist=nb link=log;
repeated subject=pid / type=ar;
estimate '1 day' day 1;
run;

proc genmod data=dims;
title 'predicting stress trajectories';
class pid;
model stress= day /dist=nb link=log;
repeated subject=pid / type=ar;
estimate '1 day' day 1;
run;
```

APPENDIX D

DISTRIBUTION OF THE STUDY OUTCOMES DURING THE DXM TREATMENT CONDITION.

Generalized pain

Highest pain

Muscle pain

Fatigue

Cognitive complaints

Positive mood

Depression

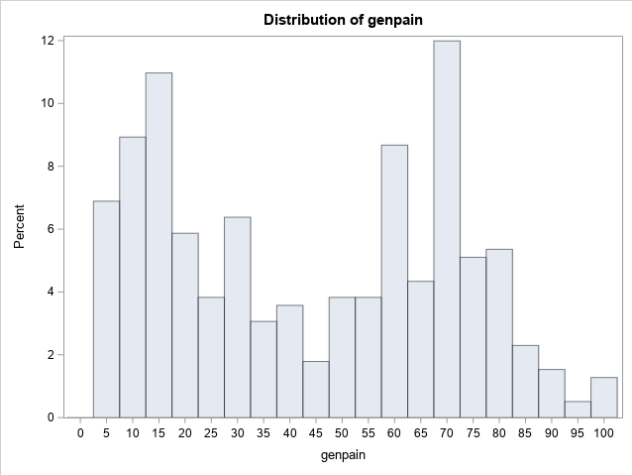
Anxiety

Stress

APPENDIX E

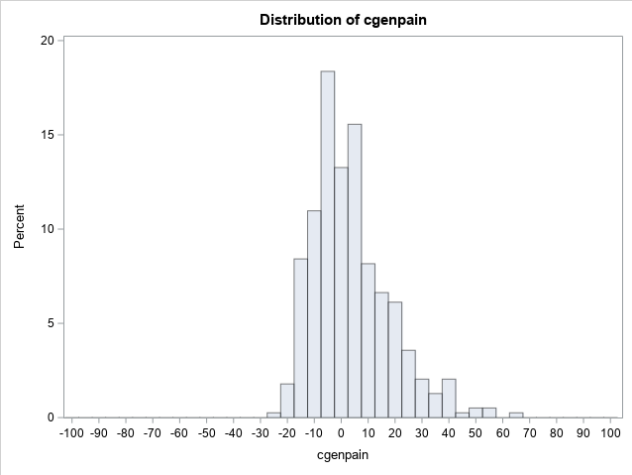
DISTRIBUTION OF GENERALIZED PAIN SCORES DURING PLACEBO AND DXM, BEFORE AND AFTER CENTERING

Placebo

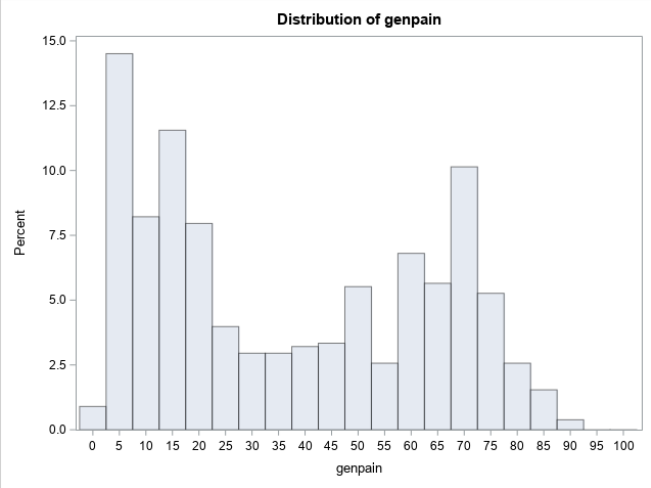


→

Placebo – centered



DXM



→

DXM – centered