Dextromethorphan in Fibromyalgia (F161018005) Study Protocol

Key Personnel

- Dr. Jarred Younger
  - Principal Investigator
  - Dr. Younger has extensive experience in conducting longitudinal treatment studies in chronic multisystem illnesses. He is very familiar with recruiting and retaining participants with chronic pain and fatigue.
- Dr. Timothy Ness
  - Sub-Investigator (Study Physician)
  - Dr. Ness is an active clinician in the UAB Pain Treatment Clinic. Previously, he has served as a protocol medical director and is currently participating in several clinical protocols.
- Dr. Jessica Merlin
  - Sub-Investigator
  - Dr. Merlin is an active clinician in the 1979 clinic. She is currently working on multiple pain protocols as medical director. For this protocol, she will act as external medical review.
- Kate Wesson-Sides
  - Project Coordinator
  - Kate will be the project coordinator, and responsible for all aspects of the study: recruitment, consenting, retention will supervise all the students.

Purpose

The overall objective of this protocol is to test if DXM can suppress symptoms associated with Fibromyalgia. DXM is used in multiple over the counter cough suppressants. We will be observing the effects of DXM. If one of these medications help the symptoms of FM, it will give us information about what is wrong in people with FM.

Background

Fibromyalgia (FM) is a chronic widespread pain syndrome. Those impacted by this syndrome experience pain, fatigue, sleep issues, cognitive impairment, headaches, among other symptoms. Fibromyalgia (FM) affects approximately 5% of all women in the United States. Current treatment options are limited because its pathophysiology is not currently understood. Many patients suffer with decreased quality of life and loss of employment due to this illness.

We do not understand the precise mechanism of Fibromyalgia, and we do not yet have a targeted treatment for the condition. A way to treat the symptoms of FM is paramount as other research concurrently attempts to understand the mechanisms behind the disease. There is current ongoing study of Dr. Younger's that is taking daily blood draws for 25 consecutive days in an attempt to identify the underlying biomarker for Fibromyalgia.

DXM has been used in previous research and have been shown to suppress pain symptoms. An example of this previous research comes from Morel et.al. by which low dose DXM was administered and evaluated pain and cognitive function in rats with spinal cord injuries . This animal model demonstrated DXM has a favorable impact on neuropathic pain.

Previous literature has suggested that dextromethorphan at 0.1mg/kg intraperitoneally reduces central inflammation (Chechneva et al., 2011 – link below). This dosage would translate to approximately 8mg for an average U.S. female weighing 166 pounds. Our dosage of 20mg has been adjusted up to account for rapid first-pass metabolism when administered orally.

In this study, we will be administering no more than a daily dose of DXM (20 mg) to observe the possible suppression of symptoms in Fibromyalgia.

References

1) Mease, P. (2005). Fibromyalgia syndrome: review of clinical presentation, pathogenesis, outcome measures, and treatment. *The Journal of Rheumatology*, *75*, 6-21.

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

3) Wolfe F, Smythe HA, et al. The American college of rheumatology 1990 criteria for the classification of fibromyalgia. Arthritis Rheum 1990, 33: 160-72.

4) Jacob Ablin, Lily Neumann, Dan Buskila, Pathogenesis of fibromyalgia – A review, Joint Bone Spine, Volume 75, Issue 3, May 2008, Pages 273-279

Participants (Screening and Selection)

15 participants with fibromyalgia (FM) will be recruited into this study.

- Sex: Female
- Race/Ethnicity: Any
- Age: 23-65
- Health status: 15 individuals with Fibromyalgia

Inclusion Criteria

1. Age 18-65, inclusive;
2. Meet the 1994 Case Definition criteria for CFS (assessed through semi-structured interview and the DePaul University Fatigue Questionnaire) (attachment #7) & the Fibromyalgia criteria as outlined by American College of Rheumatology (2010).
    a. Severe chronic fatigue ≥6 consecutive months not due to ongoing exertion or other medical condition associated with fatigue;
    b. Fatigue interferes with daily activities and work (;
    c. Reports ≥4 symptoms that started with or after the fatigue, from:
        i. Post-exertion malaise >24 hours;
        ii. Unrefreshing sleep;
        iii. Short-term memory or concentration impairment;
        iv. Muscle pain;
        v. Joint pain without swelling or redness;
        vi. Headaches of a new type/pattern/severity;
        vii. Lymph node tenderness;
        viii. Frequent or recurring sore throat
3. FM symptoms for ≥12 months;
4. Participant completes daily self-report during the baseline period;

5. Able to attend UAB for all scheduled appointments.

Exclusion Criteria

1. Blood draw contraindicated or otherwise not able to be performed;
2. High-sensitivity c-reactive protein (HS-CRP) ≥ 10 mg/L;
3. Erythrocyte sedimentation rate (ESR) >60 mm/hr;
4. Positive rheumatoid factor;
5. Positive anti-nuclear antibody (ANA);
6. Levels of thyroid stimulating hormone or free thyroxine outside UAB lab reference values;
7. Diagnosed rheumatologic or auto-immune condition;
8. Blood or Clotting disorder;
9. Use of blood thinning medication;
10. Current use of MAOI
11. Daily Consumption of grapefruit juice
12. Oral temperature >100˚F at baseline;
13. Febrile illness or use of antibiotics in the 4 weeks before study commencement;
14. Planned surgery or procedures during the study period, or operated on in the 4 weeks before study commencement;
15. Pregnant or planning on becoming pregnant within 6 months; or currently breastfeeding
16. Regular use of any anti-inflammatory medication (such as aspirin, ibuprofen, naproxen);
17. Significant psychological comorbidity that in the discretion of the investigator compromises study integrity and/or a baseline HADS depression subscale score of ≥16;
18. Current litigation or worker's compensation claim;
19. Current participation in another treatment trial;
20. Planned vaccination during the study period, or vaccinated in the 4 weeks before study commencement.

Recruitment

FM participants will be primarily identified from a database of past research participants in our lab. All such participants have provided permission and expressed interest in being contacted for future studies. Individuals will also be drawn from the local community around Birmingham via referrals from local physicians or from online advertisements.

We will primarily recruit by contacting individuals on our laboratory database; these are individuals with FM who have consented to being contacted about future studies. To recruit individuals with FM, we will also contact local physicians. After the subject's physician presents a brief summary of the study to the potential participant, it will be the responsibility of the potential participant to contact the research team in order to be screened for the study. Our research staff at UAB will not be accepting names or any PHI from the physicians. We will rely on potential study participants to contact us directly if they are interested in learning more about the research study. Participants will also be recruited from the community. Advertisements that are distributed to the public will also require an interested potential participant to contact the research team.

Telephone Screening

To minimize inconvenience to potential participants, the prescreening screening will be conducted over the telephone by a trained member of the research staff: the study aims, protocol, and any possible risks will be described and a series of questions will be asked to determine interest and eligibility for screening for the study. A request to obtain the participant information will be completed via a partial waiver document. Individuals refusing to participate or to provide PHI will be thanked for their time and asked if they want their contact details to be included in the research lab's database to be contacted for future research. If the answer is no,

then all information collected will be destroyed immediately. Following the telephone pre-screening, if the potential participant expresses interest and they are determined to be potentially eligible for the study, an appointment will be made for them to attend an in-person screening visit.

Study Visits

Visit Locations

- UAB Clinical Research Unit (CRU), Jefferson Towers Floor 15, 625 19th St S, Birmingham, AL 35233
- Campbell Hall, 1300 University Blvd, Birmingham, AL 35233

Visit 1 (In-Person Screening)

Individuals who satisfy the telephone pre-screening criteria will be invited to a comprehensive in-person screening session. These sessions will be conducted by the PI or trained research staff. Individuals will first undergo informed consent; the consent form will describe the necessary eligibility confirmation that takes place before proceeding with the full study. Consenting individuals will complete several self-report questionnaires, submit to an examination of their height, weight, and vital signs (blood pressure, heart rate, and temperature), and provide a blood sample to ensure eligibility per the study criteria. Participant will receive a hand held tablet and instructions on how to complete the daily questions via the tablet. Vital signs & blood draws will be taken by the CRU nursing staff, using standardized sterile techniques.

Once the blood test results are available from the UAB Hospital Lab they will be reviewed by the PI and study doctor to confirm eligibility. All eligible participants will be contacted by telephone by a member of the research staff. If a participant's test results do not meet eligibility criteria, the individual will be informed that they are ineligible to participate and asked to return the handheld tablet to the research team. Alternatively, potential participants will be given a self-addressed envelope to return the tablet if they are unwilling to return to the site.

Visit 2

Participants will return to the CRU or Campbell Hall after approximately 14 days following visit 1. At this visit, a member of the study team will conduct an open interview to review the daily at-home symptom reporting and general health since the first visit. Also at this time the study team will instruct the participants on how to take their study medication. The placebo will be purchased from a compounding pharmacy such as Double Oak Pharmacy in Birmingham, Alabama. The participants will receive their initial 5 weeks supply of medication, which is placebo (single-blind). Participants will not be told when they are taking placebo or DXM until the end of study. The participants will also continue to record their symptoms twice a day using the hand-held device throughout the duration of the study for the entire (~20 weeks).

Visit 3

Approximately 5 weeks after visit 2, the participant will return to the CRU so the nursing staff can record their vital signs and discuss any adverse events. The study staff will review their at home daily symptoms and receive DXM for approximately the next 5 weeks.

Visit 4

Approximately 5 weeks after visit 3, the participant will return to the CRU so the nursing staff can record their vital signs and draw 20cc of blood. The blood will be analyzed by the UAB Hospital lab to monitor the participant's liver & renal function. Also, at this visit the research team will review daily at-home symptoms & any adverse events. If any participant has experienced serious/severe adverse events the participant will be terminated from the study as to ensure there is no increased harm to the participant. If no adverse events have

been experienced the participant will receive the next dose of DXM to take for 5 weeks, and continue the at-home daily symptom review using the hand-held device.

Visit 5

Approximately 5 weeks after visit 4, the participant will return to the CRU so the nursing staff can record their vital signs and draw 20cc of blood. The blood will be analyzed by the UAB Hospital lab to monitor the participant's liver & renal function. Also, at this visit the research team will review daily at-home symptoms & any adverse events. If any participant has experienced serious/severe adverse events the participant will be terminated from the study as to ensure there is no increased harm to the participant. If no adverse events have been experienced the participant will receive the normal dose of DXM to take for 30 days and continue the at-home daily symptom review using the hand-held device.

Visit 6

Approximately Two weeks after visit 5 the participant will return to the CRU or Campbell Hall to turn in their handheld device and have their final interview with the research staff. At this visit, Dr. Younger will review daily symptoms and general health since visit 10 and un-blind the participant to which medications were received during the study.

A +/- 3 day study visit window will be implemented for all study visits to allow for reasonable flexibility in the participant's schedule as well as staff availability.

At any time throughout the study, if a participant reports feeling unwell or having any adverse events from any of the supplements, a review will be conducted by the PI and study doctor. If necessary, appropriate medical management will be provided.

If any participant is terminated from participating in the study, they will be required to return the hand-held device and any unused medicine back to a member of the UAB research study staff.

Study Timeline

The participant will be involved approximately 20 weeks for the entire study; this includes the in person screening, daily symptom reporting which is 10 minutes per day or less, and study medication disbursement. All blood draws will be conducted at the CRU in Jefferson Towers. Study medication disbursement will occur at UAB Campbell Hall or CRU.

Week	Task	Visit		Money
1	Screening	V1	Blood Draw Screening Labs & assays	$50
2	Baseline			
3	Baseline	V2		$100.00
4	Placebo			
5	Placebo			
6	Placebo			
7	Placebo			
8	Placebo	V3		$100.00
9	DXM			
10	DXM			
11	DXM			
12	DXM			

13	DXM	V4	Blood Draw Hepatic / Renal & Assays	$100.00
14	DXM			
15	DXM			
16	DXM			
17	DXM			
18	DXM	V5	Blood Draw Hepatic / Renal & Assays	$100.00
19	Baseline no drug			
20	Baseline no drug	V6	Blood for assays	$100.00
			Total Compensation	$550.00

Compensation

Participants will be compensated with cash at screening, and check or direct deposit at all remaining visit. Cash is necessary at the screening visit as it will allow for most exclusionary criterion to be detected. Participants can receive up to $550 in compensation for completing the study:

- Visit 1 (in-person screening): $50
- Visits 2-6: $100

Biospecimens

Peripheral blood samples will be collected and appropriately processed by the Clinical Research Unit (CRU) staff.

Screening session protocol: A 21/23g needle will be used to collect a maximum of 60cc of blood into labeled blood collection tubes to conduct screening tests. This blood will be tested by the UAB Hospital Lab to ensure that the participant meets the study criteria. The screening tests will include: complete blood count, erythrocyte sedimentation rate, thyroid stimulating hormone, free thyroxine, c-reactive protein, antinuclear antibodies, rheumatoid factor, liver function tests, kidney function tests and human chorionic gonadotropin. The total amount of blood drawn per participant for all study visits is 120cc.

Baseline and drug monitoring phases: At the screening visit and 3 blood draws during the drug monitoring phase, we will test the levels of expressed cytokines in blood as a marker of immune activity. Blood will be drawn via venipuncture into one 8-10cc (approximately 2 teaspoons) vacutainer. The blood will be centrifuged and will be extracted and placed into cryovials. The cryovials will then be stored at -80°C until ready for analysis. All specimens will be collected and processed by the nursing staff and CCTS lab.

Specimens will be labelled with: 1) participant identification number (PID), (2) date of blood draw, 3) study identifier 4) study principal investigator. We will assign a 3-digit participant ID that is based on the order of the in-person screening. The number is assigned at the time of screening. The first person to be screened will be given number 001, preceded by the study identifier (DXM); the first participant will be DXM-001. The computer file linking the PIDs to personal information will be kept on a single computer in the office of the PI. The computer hard drive will be encrypted and password protected. The file itself will require a password for access. No specimens will contain personally identifying information.

Samples will be stored at -80C, for a period not exceeding 5 years after participant completion, for later use by study personnel. Use of the stored samples will be restricted to the condition under study that is identified in this protocol.

Risks and Benefits

Benefits

It is possible that some participants may experience an improvement in their symptoms. It is also possible that a better understanding of the mechanisms underlying FM will allow treatments to more effectively target the disease for current and future patients.

Risks

The physical risks of venipuncture include discomfort and bruising around the blood draw site. There is also the risk of infection. The risks associated with this study concern the discomfort associated with having blood drawn and receiving the Dextromethorphan.

Participants should not take Dextromethorphan (DXM) if they have been diagnosed with phenylketonuria (PKU) because it could contain phenylalanine, if they are currently using or have used an MAO inhibitor, or if they have one of the following conditions: chronic bronchitis, emphysema, asthma, diabetes, liver disease, and mucus with cough or slowed breathing. These will be reviewed at the during the phone screen, in person screening and throughout the study. Dextromethorphan is known to produce side effects in individuals which include: slight drowsiness / dizziness, nausea or vomiting. Rarely, severe drowsiness can occur, participants will be instructed to notify study staff if they experience any of these side effects.

Grapefruit juice interacts with Dextromethorphan, participants will be asked to not drink grapefruit juice for the duration of the study.

Dextromethorphan is known to produce side effects in individuals which include: diarrhea, dizziness, cough, vomiting, swelling in the hands, ankles and or feet. Rarely slight drowsiness can occur; participants will be instructed to notify study staff if they experience any of these side effects. The most severe possible complication is serotonin toxicity.

The participant may experience some discomfort, bruising and the possibility of infection at the site of the blood draw on visits 1,3,6,9. Bruising should be minimal and should go away with a 2-3 days of the blood draw. We will minimize these risks by having only certified nurses or trained phlebotomist conduct the blood draws using standard sterile techniques.

The risks associated with taking the study medications can be primarily be avoided through proper screening of the participant and having a clear understanding of the medication the participant takes, educating the participant to contact the study staff of any and all changes to their medication. If an adverse event or side effect arises, a determination of severity and proper medical care will be advised and depending on the severity of the symptom the participant would be removed from the study and an evaluation of how to continue would be made by the study staff.

Minimization of Risks

Our screening procedures will minimize the probability of enrolling a patient who has a greater than normal risk of suffering adverse events from the medication (DXM). Any remaining risks for adverse events will be reduced by several checks:

1. The risks associated with the blood draw will be minimized by using trained and licensed CRU nursing staff to perform the blood draw. Standard sterilization procedures will be followed to minimize the risk of infection. The blood draw site will be examined carefully to ensure no adverse events have occurred, and it is safe to proceed.

2. A more thorough investigation of adverse events will be collected at each laboratory visit. This includes a qualitative open interview assessment of symptoms and general health during the preceding month.
3. Also, blood tests will be collected at the mid-point of each treatment condition (visits 1, 3, 6, 9) to monitor liver and kidney function.
4. The relatively short duration of each study medication treatment (10 weeks)
5. Participants will be explained the symptoms of serotonin syndrome/ toxicity and will be instructed to report to the study staff if any symptoms occur. Also, individuals that have experienced an allergic reaction to any of the medication used in this study will be excluded from participating during the pre-screening or at Visit 1.

Procedures to Maintain Confidentiality

Name, contact information, and medical history (participant reported –no medical records) are required to assess safety and eligibility for the study. Personally identifying information will also be collected as an identification requirement for study procedures. Identifying information will be stored on a single computer that is encrypted, and password protected at both operating system levels, and at the file level. All data maintained on paper-based records will be locked in a file cabinet in a locked room in the lab of the PI accessible only to the research study team.