NEW YORK STATE PSYCHIATRIC INSTITUTE

INSTITUTIONAL REVIEW BOARD

MEMORANDUM

March 14, 2023

TO: Dr. Brian Fallon

FROM: Dr. Agnes Whitaker, Co-Chair, IRB
Dr. Richard Foltin, Interim Co-Chair, IRB

SUBJECT: **APPROVAL NOTICE: CONTINUATION**
Expedited per 45CFR46.110(b)(1)(f)(8)(c)

Your protocol **#7755** entitled **Disulfiram ("Antabuse"): A Test of Symptom Reduction Among Patients with Previously Treated Lyme** (version date 03-14-2023) and Consent Forms have been approved by the New York State Psychiatric Institute - Columbia University Department of Psychiatry Institutional Review Board from **March 25, 2023 to March 24, 2024.**

Consent requirements:

X Not applicable: (DATA BEING ANALYZED)

□ Signature by the person(s) obtaining consent is required to document the consent process.

□ Documentation of an independent assessment of the participant's capacity to consent is also required.

Approved for recruitment of subjects who lack capacity to consent: □ No □ Yes

Field Monitoring Requirements: □ Routine □ Special:

√ **Only copies of consent documents that are currently approved and stamped by the IRB may be used to obtain consent for participation in this study.**

√ **A progress report and application for continuing review is required 2 months prior to the expiration date of IRB approval.**

√ **Changes to this research may be not be initiated without the review and approval of the IRB except when necessary to eliminate immediate hazards to participants.**

√ **All serious and/or unanticipated problems involving risks to subjects or others must be reported immediately to the IRB. Please refer to the PI-IRB website at http://irb.nyspi.org for Adverse Event Reporting Procedures and additional reporting requirements.**

AHW/RWF/Scr

Signed copy on file at IRB

Protocol Title:
Disulfiram ("Antabuse"): A Test of Symptom Reduction Among Patients with Previously Treated Lyme

Version Date:
03/14/2023

Protocol Number:
7755

First Approval:
04/02/2019

Research Area:
Anxiety, Mood, Eating & Related Disorders
Division:
Anxiety/PTSD/OCD

Expiration Date:
03/24/2024

Contact Principal Investigator:
Brian Fallon, MD
Email: baf1@columbia.edu
Telephone: 646-774-8052

Research Chief:
Helen Simpson, MD

Cover Sheet

Choose ONE option from the following that is applicable to your study
If you are creating a new protocol, select "I am submitting a new protocol." As 5 Year Renewals are no longer required, this option remains for historical purposes.
I am submitting an annual continuation without modifications

Department & Unaffiliated Personnel

Department

What Department does the PI belong to?
Mood, Anxiety, Eating, and Related Disorders
Within the department, what Center or group are you affiliated with, if any?
Lyme Disease Research Center

Unaffiliated Personnel

List investigators, if any, who will be participating in this protocol but are not affiliated with New York State Psychiatric Institute or Columbia University. Provide: Full Name, Degrees and Affiliation.
Alessandra Luchini, PhD Professor in the School of Systems Biology Center for Applied Proteomics and Molecular Medicine George Mason University Kim Lewis, PhD University Distinguished Professor

Director, Antimicrobial Discovery Center Northeastern University

Application for Continuation of Research

Status

Current Status of Study:
All research interventions were completed. Only data analysis is ongoing.

Summary of Experiences to Date

Please provide a summary of scientific progress of the study and the experience of research participants, to date. This requirement is designed to allow for the investigator and the IRB to reassess the study's risks and benefits in terms of developments in the field, changing practice patterns, and new IRB policies and procedures.
We are submitting this protocol for annual continuation. The research enrollment is complete, and all subjects have completed all research-related activity. Ongoing activity in this protocol is limited to analysis of previously collected data.

Funding

Have there been any changes in funding status since the prior approval?
No
Have the principal investigator and other investigators made all required disclosures of financial interest in the study sponsor/product?
Yes

Summary

Have there been any study findings, recent literature, or untoward events occuring here or at other sites in the past year which might affect the analysis of the safety, risks or benefits of study participation?
No
Have there been any serious adverse events (serious and/or unanticipated problems involving risks to subjects or others at this site which occured in the past year)?
No
Have all study staff with a significant role in the design or implementation of the human subject components of this study received required training in human research subject protections?
Yes
Is the study covered by a certificate of confidentiality?
No

Overall Progress

Approved sample size
24
Total number of participants enrolled to date
11
Number of participants who have completed the study to date
10
Have there been any significant deviations from the anticipated study recruitment, retention or completion estimates?
Yes
Describe actions taken or planned to address these problems.
The study enrollment was stopped in 2021 for the following reasons: a) the treatment drop-out rate in our study due to adverse events has been higher than expected; b) funding for this project is nearly complete; c) our pilot study has provided useful information about the relative safety of lower doses of disulfiram and the possibility of benefit with treatment; and d) based on the literature, disulfiram is a drug with uncommon but serious risk of toxicity.
Comments / additional information

Sample Demographics

Select the # of samples applicable
Specify population
Patients with Post-Treatment Lyme Disease Syndrome
Total number of participants enrolled from this population to date
11
Gender, Racial and Ethnic Breakdown
Sex: Female (6, 54.0%) Male (5, 46.0%) Racial Background: American Indian or Alaska Native (0, 0.0%) Asian (0, 0.0%) Native Hawaiian or Other Pacific Islander (0, 0.0%) Black or African American (1, 9.0%) White (10, 91.0%) More Than One Race (0, 0.0%) Other: (0, 0.0%) Ethnic Background: Hispanic or Latino (2, 18.0%) Not Hispanic or Latino (9, 82.0%)

Summary of Current Year's Enrollment and Drop-out

Number of participants who signed consent in the past year
0
Number of participants currently enrolled
0
Did the investigator withdraw participants from the study?
No
Did participants decide to discontinue study involvement?
No

Procedures

To create the protocol summary form, first indicate if this research will include any of the following procedures

✓ Collection of Biological Specimens
✓ Internet-based Data Collection or Transmission
✓ Medication Trial
✓ Medication-Free Period or Treatment Washout
✓ Neuropsychological Evaluation
✓ Off-label Use of Drug or Device
✓ Psychiatric Assessment
✓ Use of Placebo or Sham Treatment

Population

Indicate which of the following populations will be included in this research

✓ Medically Ill Subjects
✓ Adults
✓ Adults over 50

Protocol Title:
Disulfiram ("Antabuse"): A Test of Symptom Reduction Among Patients with Previously Treated Lyme

Version Date:
03/21/2022

Protocol Number:
7755

First Approval:
04/02/2019

Expiration Date:
03/24/2023

Contact Principal Investigator:
Brian Fallon, MD
Email: baf1@columbia.edu
Telephone: 646-774-8052

Research Chief:
Helen Simpson, MD

Cover Sheet

Choose ONE option from the following that is applicable to your study
If you are creating a new protocol, select "I am submitting a new protocol." As 5 Year Renewals are no longer required, this option remains for historical purposes.
I am submitting an annual continuation with modifications

Department & Unaffiliated Personnel

Department

What Department does the PI belong to?
Mood, Anxiety, Eating, and Related Disorders
Within the department, what Center or group are you affiliated with, if any?
Lyme Disease Research Center

Unaffiliated Personnel

List investigators, if any, who will be participating in this protocol but are not affiliated with New York State Psychiatric Institute or Columbia University. Provide: Full Name, Degrees and Affiliation.

Alessandra Luchini, PhD
Professor in the School of Systems Biology

Center for Applied Proteomics and Molecular Medicine
George Mason University

Kim Lewis, PhD
University Distinguished Professor
Director, Antimicrobial Discovery Center
Northeastern University

Amendment

Describe the change(s) being made
We are making one addition and one modification to the Disulfiram protocol
1. Addition:
We request permission to add to the protocol a new staff member, Dr. Kristen Kendrick.
Dr. Kristen Kendrick, a Family Medicine Physician, is a new clinician for the study. Dr. Kendrick, DO, has completed the CITI training (basic course and a course on Good Clinical Practices).
Dr. Kendrick sees study participants for clinical evaluations under the supervision of Dr. Fallon.

2. Modification:
Under the protocol section entitled "Unaffiliated Personnel", we are removing Dr. Charles Brown and Dr. Edward Dennis; neither has had involvement in this project. I am replacing their names with Dr. Kim Lewis at Northeastern University and Dr. Alessandra Luchini at George Mason University; Dr. Lewis is a microbiome collaborator and Dr. Luchini is a proteomic collaborator.
Provide the rationale for the change(s)

Dr. Kristen Kendrick as a Family Medicine physician working with Dr. Fallon has knowledge of medicine broadly and knowledge of Lyme disease specifically. She joined our team in August 2021.

Dr. Charles Brown and Dr. Edward Dennis are not participating in this study. However, both Dr. Kim Lewis and Dr. Alessandra Luchini are collaborating with Dr. Fallon in aspects of this study. Dr. Kim Lewis will analyze the fecal matter change during the course of treatment with disulfiram in our study participants and Dr. Luchini will analyze the urine for proteomic markers of tick-borne infection. The collection of fecal matter and urine for these studies has been in the protocol and consent forms from the start of this study.

Comment on the extent to which the proposed change(s) alter or affect risks/benefits to subjects
These changes do not alter or affect the risks/benefits to subjects.
Comment on if the proposed change(s) require a modification to the Consent Form (CF)
The consent form does not need to be modified.

Application for Continuation of Research

Status

Current Status of Study:
All research interventions were completed. Only data analysis is ongoing.

Summary of Experiences to Date

Please provide a summary of scientific progress of the study and the experience of research participants, to date. This requirement is designed to allow for the investigator and the IRB to reassess the study's risks and benefits in terms of developments in the field, changing practice patterns, and new IRB policies and procedures.

Over the last year:
4 new participants entered treatment in the study in 2021. The last person to sign study consent for this study signed on 7.18.2021
Of these 4 new completers, 0 signed the fully on-site consent, 1 signed the fully remote consent, and 3 signed the hybrid consent.
No individuals are currently enrolled.

Summary of study from onset to present:
Since study onset, we have had a total of 11 patients sign consent who were randomized to study drug. Of these 11, 10 started medication; 1 was randomized to study drug but did not start medication due to onset of COVID-19. He would not be considered a completer as he didn't start study drug.
Of these 10 who started study medication, all 10 have completed the study.
3 of the 10 completed the full 8 weeks of study medication without complications.
1 of the 10 withdrew on his own after 4 weeks as he didn't want to risk placebo randomization in the latter 4 weeks of the study.
1 of the 10 were withdrawn by us due to the onset of COVID-19 – she had completed 2 weeks of study medication.
3 of the 10 were withdrawn from the study by the PI due to mildly-moderately elevated liver function tests which resolved after termination of study medication; only one in this latter group had symptoms associated with the elevated LFTs (abdominal pain) which led to a short-term hospitalization for evaluation (previously reported to the IRB as a SAE - possibly related to a disulfiram reaction due to inadvertent alcohol consumption in food).
1 of the 10 withdrew on her own due to headaches and 10 days after ending disulfiram treatment, she had an episode of throat tightness that led her to an ER evaluation for a possible emerging allergic reaction (reported to the IRB in 2019, but not likely to be due to disulfiram).

1 of the 10 was withdrawn by the PI due a slightly elevated serum creatinine (1.5) at wk 2. Although there was no history of kidney disease, the patient did have slightly elevated creatinine prior to study entry (1.3/1.4) considered normal by his PCP. For the patient's safety, the PI withdrew him from the study because he also had a marginally low glomerular filtration rate (58) at week 2; the patient was recommended to have a full kidney function work-up and this information was conveyed to his PCP. (In a subsequent call to us 1 month later, he indicated his PCP reviewed his labs and viewed him as healthy from a renal perspective.)

Among all 11 who signed consent and were randomized to study drug, 7 signed the fully on-site consent, 1

signed the fully remote consent, and 3 signed the hybrid consent.

Decisions on the study:
We have decided to end enrollment this study at this point for four reasons: a) the treatment drop-out rate in our study thus far due to adverse events has been higher than expected; b) funding for this project is nearly complete; c) our pilot study has provided useful information about the relative safety of lower doses of disulfiram and the possibility of benefit with treatment; and d) based on the literature, disulfiram is a drug with uncommon but serious risk of toxicity. We are pleased to see that 60% of participants were "responders" on the primary outcome fatigue measure at the primary endpoint and that 50% of participants reported sustained improvement 4 weeks later.

Note: In the 2021 ACAR, we indicated that there were 6 individuals in total who enrolled and started on study medication and in this 2022 ACAR we indicate that there were 10 individuals in total who enrolled and started on study medication (4 of whom were added since the prior ACAR.) Using the definition of enrollment (eligible and randomized to study medication), we have had 11 enrolled in the study to date. The prior ACAR indicated 9 had been "enrolled"; the definition of "enrolled" was overly broad – we report here in this ACAR only those who were eligible and randomized to study medication (as per pharmacy confirmation). Using a definition of "completer" as individuals who were randomized, started study medication and either completed the full study or were withdrawn by us or dropped out for other reasons, we had 10 who completed the study. Dr. Fallon has personally reviewed all data for the preparation of this 2022 ACAR (both our research data and pharmacy data) and certifies these numbers are correct.

Funding

Have there been any changes in funding status since the prior approval?
Yes
Have the principal investigator and other investigators made all required disclosures of financial interest in the study sponsor/product?
Yes
Is the previous funding completed?
Yes
Has new funding been obtained?
No

Summary

Have there been any study findings, recent literature, or untoward events occuring here or at other sites in the past year which might affect the analysis of the safety, risks or benefits of study participation?
Yes
Please indicate how the new information affects the study's risk/benefit analysis and comment on whether consent form changes are necessary.
1. Our study findings this past year:
a. Safety: The pattern of elevated liver function tests associated with disulfiram treatment observed in 2 of the first 6 patients continued this past year in that 1 of the 4 also developed asymptomatic elevated LFTs

which resolved after study medication discontinuation; he had been on 250mg qd of disulfiram for 6 weeks.
b. Benefit: Of the 4 newly treated participants this year, 3 met criteria for meaningful improvement on the primary outcome Fatigue Severity Scale, including the individual whose study med treatment was stopped after 6 weeks.
2. Our study findings to date:
a. Safety overall: Disulfiram in our small study has been associated with more adverse events than we had anticipated. All participants recovered. One participant had a serious adverse event requiring hospitalization related to abdominal pain and elevated LFTs (and recovered); one had discontinued disulfiram due to headaches (which she had prior to study medication) but then had an ER evaluation for a possible emerging allergic reaction 10 days later; two others had asymptomatic elevations of LFTs that led to study medication discontinuation. In summary of the 10 study completers, 4 had adverse events that required study medication discontinuation.
b. Safety of dosing: Of the 2 of the 10 participants who had reached 500 mg qd of study medication, both had elevated LFTs that required study discontinuation. Lower doses appeared better tolerated.
c. Benefit: Of the 10 study completers (using last observation for dropouts), 6 met criteria for meaningful improvement on the Fatigue severity scale at the primary outcome of week 10 and 5 continued to show meaningful improvement in fatigue at the week 14 follow-up rating. A 60% responder rate at week 10 and 50% at week 14 is of interest (NB: improvement on other clinical measures as well), but it is also hard to interpret given the lack of a placebo-control group.

3. **A recent article.** A retrospective review from a private practice clinician's office evaluated 3 years of clinical experience with disulfiram among patients with persistent Lyme disease symptoms (Gao et al., Antibiotics, Dec 2020). 71 patients were included, treated over a 3 year interval. No standardized clinical ratings were used during the evaluation and treatment; the report was based on clinical impressions in the chart notes. 62 of 67 (92%) endorsed a "net benefit of the treatment". Individuals who had received one to two courses of higher dose therapy (4-5+ mg/kg/day) were more likely to have an "enduring remission" than the group at lower doses (36.4% vs 0%); the high dose group corresponds to a dose of 272-340+/day for a 150 lb person or 360-450+/day for a 200 lb person. Side effects were dose related. Common side effects in the higher dose group included: fatigue (67%); psychiatric symptoms (49%); paresthesias (27%), and mild to moderate elevation of liver enzymes (15%). The article indicates that paresthesias resolved in all but 1 case, in which mild residuum remained. Psychiatric symptoms included "emotional instability ranging from hypomania to anxiety and/or depression". The authors stated that adverse events thought to be due to disulfiram resolved in nearly all individuals; no serious adverse events were reported.
Comment: As no rating scales were used in this clinical series to monitor adverse effects, it is hard to know which symptoms were Lyme disease related and present prior to disulfiram treatment vs adverse effects due to disulfiram. Fatigue, paresthesias, and psychiatric symptoms are common among patients with post-treatment Lyme disease. The absence of serious adverse events is encouraging. Our disulfiram study excludes individuals with a history of psychosis or bipolar disorder; it is unclear if the same was true in this clinician's practice. Nevertheless, disulfiram can induce mania, psychosis, or other psychiatric disorders due its inhibition of dopamine beta-hydroxylase, resulting in an excess of dopamine. Disulfiram is known to have side effects that are dose-related, consistent with the above results. The rate of paresthesias are high, but these are also common post-treatment Lyme symptoms; given the absence of peripheral neuropathy assessments before and after treatment, it is hard to interpret this finding. Our study consent form lists these risks; our study results (though sample size is small) will add clarification on the side effect profile.

4. **A recent case report.** A troubling case report by Frankl et. al. (Mayo Clin Proceedings July 2021) described a middle-aged man being treated with minocycline (100 bid), disulfiram (375 mg), and tinidazole (500 bid) for "chronic Lyme disease" who developed mental status changes and lethargy and was hospitalized; according to his wife, he took his medications at higher doses than prescribed and had been on disulfiram for 8 months. Brain MRI showed T2 hyperintensities in bilateral thalami and diffusion restriction in the posterior putamen. Axonal neuropathy was documented 8 months earlier shortly after he started disulfiram. The patient went into respiratory failure, suffered hospital acquired infections, and died 2.5 months later.
Comment: This case report documents the recognized potential neurotoxicity of disulfiram, especially in combination with other medication and at higher doses. When disulfiram is taken with nitroimidazoles (such as tinidazole or metronidazole), psychosis and confusion have been reported. It is likely that taking both disulfiram and tinidazole together had an additive toxic effect, as both have been associated with CNS hyperintensities. (Concurrent antibiotic therapy is an exclusion for entry in our study). One prior case of extremely high dose disulfiram (1 gm of implanted disulfiram) (Peddawad, Neurology 2018) led to a fulminant encephalopathy. In the Frankl case report, this man's wife reported he took higher doses of his medication than prescribed; it is unknown how much he had been taking prior to his hospital evaluation, but a very high dose of disulfiram (>500 mg) may have led to this bad outcome.

5. **Disulfiram and immune function**. Other recent literature has explored the potential benefits of disulfiram on immune function, including reduction of the damaging effects of inflammation. A recent article by Schwartz et al in the Journal of Clinical Insight (March 2022) reported that disulfiram protected rodents from immune-mediated lung injury, presumably by its ability to block the formation of neutrophil extracellular traps (NETS). In SARS-CoV-2-infected golden hamsters, disulfiram reduced NETs and perivascular fibrosis in the lungs, and it downregulated innate immune and complement/coagulation pathways, suggesting that it could be beneficial for patients with COVID-19. There are currently 2 human clinical trials listed on clinicaltrials.gov examining disulfiram as a treatment for COVID-19 based on its anti-inflammatory and anti-viral properties.
Have there been any serious adverse events (serious and/or unanticipated problems involving risks to subjects or others at this site which occured in the past year)?
No
Have all study staff with a significant role in the design or implementation of the human subject components of this study received required training in human research subject protections?
Yes
Is the study covered by a certificate of confidentiality?
No

Overall Progress

Approved sample size
24
Total number of participants enrolled to date
11
Number of participants who have completed the study to date
10

Have there been any significant deviations from the anticipated study recruitment, retention or completion estimates?
Yes
Describe actions taken or planned to address these problems.

Our anticipated study completion date was March 2022. The study enrollment was drastically impacted by the pause of the study at onset due to the COVID-19 pandemic, by the need to schedule the baseline visit far enough away from COVID-19 vaccine shots to be able to distinguish adverse events from COVID-19 vaccine reactions vs study medication, by participant reluctance to enroll prior to major holidays (i.e., unwilling to avoid alcohol use), by delay in obtaining disulfiram due to supply-chain shortages, and by the difficulty potential participants had in finding local physicians willing to assist in the fully remote version of the study.

Hybrid option approval by the IRB since the last ACAR: The IRB approved a "hybrid" option for study participation. This hybrid option allows for telehealth except for two visits (one at the start of the study and the other two weeks after stopping study medication) that require the participant to come in person for a physical exam. New consent forms and procedures were created to accommodate this hybrid participation.
Comments / additional information

Sample Demographics

Specify population
Patients with Post-Treatment Lyme Disease Syndrome
Total number of participants enrolled from this population to date
11
Gender, Racial and Ethnic Breakdown
Sex:
Female (6, 54.0%)
Male (5, 46.0%)

Racial Background:

American Indian or Alaska Native (0, 0.0%)
Asian (0, 0.0%)
Native Hawaiian or Other Pacific Islander (0, 0.0%)
Black or African American (1, 9.0%)
White (10, 91.0%)
More Than One Race (0, 0.0%)
Other: (0, 0.0%)

Ethnic Background:
Hispanic or Latino (2, 18.0%)
Not Hispanic or Latino (9, 82.0%)

Summary of Current Year's Enrollment and Drop-out

Number of participants who signed consent in the past year
6
Did the investigator withdraw participants from the study?
Yes
Circumstances of withdrawal:

Two of six participants who signed consent during 2021 were deemed not eligible for the study.

A participant who enrolled in the study was withdrawn by the PI due a slightly elevated serum creatinine (1.5) and slightly decreased GFR (glomerular filtration rate) at week 2. Although there was no history of kidney disease, the patient did have slightly elevated creatinine prior to study entry (1.3/1.4) that he reported was considered normal by his PCP. For the patient's safety, the PI withdrew him from the study because he also had a marginally low glomerular filtration rate (58) at week 2; the patient was recommended to have a full kidney function work-up and this information was conveyed to his PCP. (In a subsequent call to us 1 month later, this participant indicated his PCP had reviewed his labs and viewed him as healthy from a renal perspective.)

Did participants decide to discontinue study involvement?
No

Procedures

To create the protocol summary form, first indicate if this research will include any of the following procedures

✓ Collection of Biological Specimens
✓ Internet-based Data Collection or Transmission
✓ Medication Trial
✓ Neuropsychological Evaluation
✓ Off-label Use of Drug or Device
✓ Psychiatric Assessment
✓ Use of Placebo or Sham Treatment

Population

Indicate which of the following populations will be included in this research

✓ Medically Ill Subjects
✓ Adults
✓ Adults over 50

Research Support/Funding

Will an existing internal account be used to support the project?
No
Is the project externally funded or is external funding planned?
Yes
Select the number of external sources of funding that will be applicable to this study
2

Funding Source #1

Is the PI of the grant/contract the same as the PI of the IRB protocol?
Yes
Select one of the following
The grant/contract is currently funded
Source of Funding
Foundation
Sponsor
FDC
Select one of the following
Single Site
Business Office
CU
Does the grant/contract involve a subcontract?
No

Funding Source #2

Is the PI of the grant/contract the same as the PI of the IRB protocol?
Yes
Select one of the following
The grant/contract is currently funded
Source of Funding
Foundation
Sponsor
Anonymous Donor
Select one of the following
Single Site
Business Office
RFMH
Does the grant/contract involve a subcontract?
No

Study Location

Indicate if the research is/will be conducted at any of the following
✓ NYSPI
This protocol describes research conducted by the PI at other facilities/locations
Yes
✓ Hospital, clinics and other healthcare facilities

Hospitals,clinics and other healthcare facilities

Select from the list
or type in location(s)..
Some aspects of data collection for participants who choose to participate in the study remotely will be conducted in the offices of collaborating consulting physicians. Participants who participate remotely or via the hybrid protocol will also have some data collection conducted at Quest Diagnostics testing centers**.**

Lay Summary of Proposed Research

Lay Summary of Proposed Research

Lyme disease, caused by the spirochete Borrelia burgdorferi, is the most common tick-borne illness in the United States. Typically, after being bitten by an infected tick, patients will notice an expanding rash and flu-like symptoms. Most patients recover fully after initial treatment with antibiotics such as doxycycline or amoxicillin. Some patients, however, do not recover fully or their symptoms return within a few months after having completed antibiotic treatment. Common persistent symptoms include fatigue, joint pain, muscle pain, numbness, tingling, burning pains, and changes in mood, memory or mental clarity. These symptoms can last months to years after treatment and, when accompanied by functional impairment, are collectively referred to by the academic community as “Post Treatment Lyme Disease Syndrome (PTLDS)”. Patients however typically refer to this constellation of persistent symptoms as “Chronic Lyme Disease”. One of the potential explanations for persistent symptoms is that some patients may have persistent infection. Some scientists and medical doctors suggest that persistent infection with the agent of Lyme disease could be treated more effectively with other medications or combinations of medications.

Scientists recently discovered that disulfiram is very effective in the lab setting at killing the microbes that cause Lyme disease. Disulfiram is more commonly known as “Antabuse”. It is an FDA-approved compound used to assist alcoholics in resisting alcohol consumption. Most remarkable is that disulfiram was effective at killing not only the actively replicating Lyme bacteria (ie, the ones that are typically killed by several antibiotics) but also the relatively dormant or quiescent Lyme bacteria (these are called “drug-tolerant persisters”) – these latter spirochetes are the ones that may account for the development of chronic Lyme disease symptoms.

Our initial pilot study will focus on patients with persistent symptoms despite having received the standard antibiotic therapy (or more) for Lyme disease. Because no one has yet studied the safety of disulfiram for

patients with a history of Lyme disease and because we do not know the optimal treatment duration for disulfiram, our initial effort will have the primary aims of assessing safety and determining whether a longer course of daily treatment is more effective than a shorter course of daily treatment.

We propose therefore a small 14-week randomized placebo-controlled pilot study enrolling 24 patients with persistent symptoms despite prior antibiotic treatment for Lyme disease (known as Post-treatment Lyme Disease Syndrome or "chronic Lyme"). Among the 24 disulfiram-treated patients, half will get 54 days of disulfiram treatment over the course of 8 weeks and the other half will get a shorter duration of disulfiram for 26 days given over the course of 4 weeks. After week 8, patients will be off pills for 2 weeks for the primary week 10 evaluation and then for another 4 weeks for the week 14 follow-up evaluation. This will be a double-blinded study; neither clinician nor patient will know which treatment group the patient is assigned to.

With this initial study, we will be able to evaluate the side effects, tolerability and initial signs of effectiveness of disulfiram in reducing symptoms among the 24 patients assessed. The results of this study will guide us regarding the safety of disulfiram among patients with Lyme disease and whether a definitive randomized trial should be conducted; it will also inform us regarding which treatment schedule is optimal.

Background, Significance and Rationale

Background, Significance and Rationale

About 10-20% of patients treated with standard antibiotic therapy suffer from persistent relapsing-remitting symptoms. Persistent infection may account for the persistent symptoms in some of these patients, as persistent infection after antibiotic treatment has been well-documented in several animal models of Lyme disease. Clearly, a more effective antibiotic is needed

A recent laboratory-based research study discovered that disulfiram, an FDA-approved compound used to assist alcoholics in resisting alcohol consumption, was one of the more potent compounds in killing Borrelia burgdorferi (Bb - the microbe that causes Lyme disease) (Potheni 2016; Lewis 2017). Disulfiram was shown to be more effective than 1,000s of other FDA-approved compounds that were tested, even when compared to standard antibiotics for Lyme disease such as doxycycline and amoxicillin. Disulfiram administered for just 2 days was shown to be effective at inhibiting the growth of not only the actively replicating Borrelia (ie, the ones that are typically killed by several antibiotics) but also the relatively dormant Borrelia (these are called “drug- tolerant persisters”) – these latter spirochetes have been hypothesized as one possible cause for the development of chronic or relapsing symptoms. Other reports indicate that the metabolites of disulfiram inhibit the growth of a number of other bacterial species as well, including Pseudomonas aeruginosa and Staph aureus (Zaldivar-Machorro 2011, Long 2017). In addition to its ability to eradicate drug-tolerant persister Borrelia, disulfiram has the advantage of excellent tissue penetration – it crosses the blood-brain barrier easily. Because of excellent tissue penetration, it may be a more effective agent than many other antibiotics in killing Borrelia spirochetes in humans.

As a next step in assessing disulfiram, disulfiram was studied in a mouse model of Lyme disease; disulfiram was given for 5 days to 13 infected mice and found to be ineffective at eradicating Borrelia spirochetes in this mouse model. Dr. Kim Lewis, the lead investigator on these laboratory and mouse model studies, considers it reasonable that disulfiram may still work in the human as "the metabolic rate of the mouse is 10x faster than the human." Dr. Lewis is Director of the Drug Discovery Center at Northeastern University and University Professor of Biochemistry. His hypothesis is that the rapid metabolism of the mouse denatured the disulfiram to such an extent that the blood concentration was too low to be effective. A second hypothesis for the failure of disulfiram in the mouse model is that the duration of treatment may have been too short. To our knowledge, all published studies investigating antibiotic efficacy in the mouse model have used between 10 and 30 days of antimicrobial treatment; the Lewis lab mouse study only used 5 days of disulfiram.

Most recently, an internal medicine colleague of ours in private practice has given disulfiram to 3 of his chronically ill patients and reported remarkable improvement. To report these results, he has submitted a manuscript to a peer-reviewed journal for consideration of publication. He had previously treated these patients for years with various courses of antibiotics for Lyme disease without much success. In the past 2 years, each was taken off standard antibiotics and then given disulfiram, reaching a 500 mg/day dose for 6-12 weeks; the improvement was remarkable, far beyond what had been achieved with many courses of antibiotic therapy previously.

Given the report from this physician and given that disulfiram has impressive tissue penetration and has been shown in the laboratory setting to be highly effective in killing Borrelia spirochetes, it is our intent to conduct a preliminary study to assess safety and to conduct a duration of treatment study to assess whether disulfiram leads to improvement in some of the core symptoms of post-treatment Lyme disease.

Significance

Disulfiram is a well-known drug in psychiatry. Not without side effects or risk, it is nevertheless considered to be a useful treatment option for patients wishing to maintain alcohol abstinence. The only treatment approach that has been studied for patients with PTLS is repeated antibiotic therapy with IV ceftriaxone (with or without doxycycline) (Klempner 2001; Krupp 2003; Fallon 2008); this treatment option is not widely recommended given that the IV route requiring a PICC or Mid-line is associated with serious risk (sepsis, thrombi) and given that the results of the clinical trials have been equivocal, with some showing benefit and others no benefit.

If this pilot study indicates that disulfiram is well-tolerated among patients with post-treatment Lyme disease and if the dose-finding study suggests disulfiram is effective, we will then conduct a placebo-controlled study to confirms efficacy. If the next study after that shows that disulfiram is even better than standard antibiotic treatment in leading to sustained improvement, then this would be a major treatment advance for patients with post-treatment Lyme disease. Given that disulfiram is not a "broad-spectrum antibiotic" it would be expected to have a smaller impact on the gut microbiome than standard antibiotic therapy which would make it much more appealing to patients and to infectious disease doctors; (we will assess gut microbiome changes in this study with the different dosing duration of disulfiram).

Rationale

We have chosen not to start by conducting a larger efficacy study comparing disulfiram to placebo for two reasons: a) we would like to assess how well disulfiram is tolerated; b) we would like preliminary data to determine the magnitude of effect and to test out our different primary and secondary outcome measures; c) we are uncertain as to the optimal duration (26 days vs 54 days). A shorter duration of exposure to disulfiram would be expected to reduce the risk to the patient of disulfiram treatment.

For this study, we will consider a negative finding in each active treatment group to be a result at 10 weeks indicating that 30% or fewer patients are rated as responders on either of the primary outcome measures of fatigue (FSS-9) or quality of life experience (Q-LES-Q). Secondary outcome measures include functional status (PROMIS-29 and SF-36), general symptoms (GSQ-30), pain (from PROMIS 29 domain), cognitive symptoms (computer battery), and mood (BDI, STAI).

If one of the two active treatment regimens offers more promise than the other and if the percentage of responders is greater than the anticipated 20-30% responder rate typically seen with placebo, we would then choose that option for the next larger and definitive placebo-controlled study. The sample size in this study is likely too small to show statistically significant differences between the groups.

This initial duration-finding study focuses on patients with persistent symptoms despite having received the standard antibiotic therapy for Lyme disease. While it would be reasonable from a scientific perspective to examine whether this particular treatment would be effective at the time of early Lyme disease, it would be considered unethical without additional data to experiment on patients by randomizing them to something other than what is already known to be helpful for most patients with early Lyme disease (e.g., about 80% of patients respond well to doxycycline or amoxicillin treatment of the Lyme rash).

For our proposed initial study, therefore, our focus of attention will be on patients who have already tried the standard course of treatment but who relapsed or not responded adequately; these patients are urgently in need of a cure for their disabling relapsing symptoms. Currently there is no evidence-based treatment for these patients.

Specific Aims and Hypotheses

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There are two primary aims. First, we will assess the safety and side effect profile of disulfiram among patients with post-treatment Lyme symptoms. Second, we will investigate whether treatment with disulfiram results in a meaningful reduction in fatigue and improvement in the quality of life among patients with Post-treatment Lyme Disease. Fatigue will be assessed by the Fatigue Severity Scale (FSS) and quality of life will be assessed with the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q).

There are several secondary goals.
1. We will examine whether there is a difference in the proportion of responders on the fatigue scale among the 2 different dosing regimens (54 days over 8 weeks vs. 26 days over 4 weeks followed by placebo). We will assess both the percentage of responders and magnitude of the effect.
2. We will examine whether there is an improvement on the secondary outcome measures.
3. We will examine the side effect profile and drop-out rate associated with different treatment schedules of disulfiram.
4. We will examine whether there are other self-report measures that are more sensitive in documenting change over time than the FSS and the Q-LES-Q. These other measures, for example, include the PROMIS 29 v2.0 profile questionnaire, the SF-36, and the General Symptom Questionnaire (GSQ-30).
5. We will examine whether tests of sensory function, autonomic function, and cognitive function change with treatment.
6. We will examine whether the urine antigen marker of Borrelia burgdorferi (as assessed by the Ceres Nanoscience Urine Nanotrap assay) is present at baseline and not present after treatment.
7. We will collect biological samples for future precision medicine studies to be stored in our repository.
8. We will collect fecal samples to be probed by investigators interested in studying microbiome changes in response to disulfiram.
9. We will also monitor patients' activity via the data generated by Fitbit- The rationale for the Fitbit is that our primary outcome is fatigue. People who are less fatigued may be engaging in more activity, such as doing more steps during the day. Moreover, activity monitoring using a device such as a Fitbit is being increasingly used in research studies as a measure of the change in response to treatment.

REMOTE PARTICIPATION CONSIDERATIONS:
Due to the challenges imposed with remote data collection, we will not address research aims addressing sensory and autonomic function (aim 5), or collection of biological specimens for our repository (aim 7). Capacity to address these aims is dependent on final numbers of in-person vs. remote study participation. In light of the current COVID-19 pandemic, no in-person procedures will be conducted at NYSPI and we are unable to estimate future in-person enrollments at this time.

Description of Subject Population

Sample #1

Specify subject population
Patients with Post-Treatment Lyme Disease Syndrome
Number of completers required to accomplish study aims
20
Projected number of subjects who will be enrolled to obtain required number of completers
24
Age range of subject population

18-65

Gender, Racial and Ethnic Breakdown
Based on prior studies of individuals with Lyme disease, we anticipate the following gender and racial/ethnic group representation:

Gender: 60% women, 40% men
Racial/ethnic: 90% Caucasian; 10% other

(The racial/ethnic mix reflects the demographics of heavily Lyme endemic areas which tend to be rural or suburban areas as opposed to urban cities)
Description of subject population

All participants will have a history of prior Lyme disease, a history of symptoms that persist or relapse after antibiotic therapy, at least moderate fatigue at enrollment (≥4 on the Fatigue Severity Scale), and a history of having received more than the recommended duration of antibiotic therapy for Lyme disease based on the Lyme Disease Treatment Guidelines (IDSA, 2006).

In order to maximize the likelihood of response, in our enrollment, we seek to enroll a majority of patients (at least half) who have received at least 8 weeks but no more than 6 months total of prior antibiotic therapy. If completing our enrollment numbers of patients with PTLS using this criterion proves infeasible then we will allow the other half of patients in this study to have had more than 6 months but no more than 24 months of prior antibiotic therapy for this bout of Lyme disease.

Recruitment Procedures

Describe settings where recruitment will occur

Recruitment will primarily occur at the NYS Psychiatric Institute, with initial screening conducted remotely by a research assistant.

Because doctors will have heard about our study (see below), patients may initially be told about the study by a health care provider.

How and by whom will subjects be approached and/or recruited?

A research assistant will be specifically assigned to this study.
She (or he) will reach out to all PTLS patients who have contacted us and/or responded to our mailers or posters. She will then conduct an initial telephone screening during which she will inform the individual about the study and answer questions. Eligible patients will be invited for the initial visit to confirm eligibility and obtain consent. If the participant is participating remotely or via the hybrid protocol, this

initial visit will be completed remotely. RAs will use a telephone screening form when talking to patients interested in the study (see uploaded document).

How will the study be advertised/publicized?

1. Our Lyme Center website and the Columbia Recruit Me website.
2. We will be mailing flyers to physicians who are known to treat many patients with Lyme disease to inform them about our study. Physicians can post these flyers in their office and can share the information about our study with potentially eligible patients and give our contact information to those who are interested.
3. Patients on our mailing list will be contacted by mail and email.
4. Patients from past studies who gave consent to be contacted if new studies emerged will be informed of this study.

Do you have ads/recruitment material requiring review at this time?
Yes
Does this study involve a clinical trial?
Yes
Please provide the NCT Registration Number
NCT03891667

Concurrent Research Studies

Will subjects in this study participate in or be recruited from other studies?
Yes
Describe concurrent research involvement
If a patient who is enrolled in our Lyme Diagnostic Study (IRB# 6805) is identified as having persistent post-treatment Lyme symptoms that have lasted more than six months, he/she will be informed about this study.

Inclusion/Exclusion Criteria

Name the subject group/sub sample
Patients with Post-Treatment Lyme Disease Symptoms
Create or insert table to describe the inclusion criteria and methods to ascertain them

1. History of Lyme Disease diagnosis meeting CDC surveillance case criteria within the prior 16 years
This requires:

-For erythema migrans (EM) rash, this has to be health-care provider diagnosed

-For later stages of Lyme disease, this requires a diagnosis of LD by a health-care provider and laboratory testing that confirms a positive result historically.

Ascertainment: photo of rash, provider's note, or a provider's note years later reporting the initial Lyme disease, and/or positive lab test results.

2. History of treatment for Lyme disease within the last 16 years
-Documentation of prior antibiotic treatment for Lyme Disease of at least 5 weeks within the last 16 years; this meets or exceeds the Infectious Diseases Society of America (IDSA) recommended standards.
(We aim to recruit as many patients who have received between 5 weeks and 6 months of prior antibiotic therapy for this episode of illness; for this study, at least half of the sample will need to meet this criterion. Duration of prior treatment for the remaining portion of the study sample will have no upper limit for this episode of illness).
Ascertainment: Self-Report of patient and provision of at least one piece of external confirmatory historical documentation; for example, a provider's note years later reporting the initial or later Lyme treatment or pharmacy record.

3. Partial Prior Response. History of at least partial response to prior antibiotic therapy for Lyme disease.
Ascertainment: self-report

4. Antibiotic-free interval:
a) If antibiotics known to be effective for Lyme disease has been taken for 5 days or more in the recent past, the participant must agree to delay entering this study for at least 8 weeks prior to study randomization;
b) If antibiotics not effective against Lyme disease have been prescribed for other purposes, the participant must agree to wait 2 weeks before study randomization,
c) All participants must agree to be off antibiotics during the course of the study, regardless of length of antibiotic treatment.

Ascertainment: Self-report
Additionally, study clinician will confirm with the patients that the decision to stop antibiotics should only be made after the patient has consulted with their prescribing physician.

5. Current moderate to severe fatigue. The following criteria need to be met:
a) at least moderate intensity at study screening and at intake (a score of 4 or more on the Fatigue Severity Scale)
b) triggered or perpetuated by Lyme disease and persisting for at least 6 months after treatment
c) is not better attributed to another independent medical or psychiatric condition
d) current episode of Lyme disease-related fatigue is relatively persistent and has not had an intervening interval of 8 months without fatigue since diagnosis of Lyme disease.

6. Current post-Lyme symptoms impairs the patient's quality of life (self-report)

7. Keeping other current treatments stable
Patients can stay on other non-antibiotic medications as long as these medications have been stable for the 3 months prior to study onset and the dosage regimen does not change during the course of this study (unless the latter is medically or psychiatrically indicated).

8. Between the ages 18-65 (Patient Report)

9. Ability to read and speak English (Patient Report)

10. Willingness to wear an activity monitor (e.g., Fitbit which we will provide) (Patient Report)

Create or insert table to describe the exclusion criteria and methods to ascertain them

1. History of cardiovascular disease (e.g., coronary artery disease or heart failure). Ascertainment: Patient Report, EKG at Intake.
a) Remote **and hybrid** participants: Results provided of an abnormal EKG done within 6 months prior to starting the study or failure to provide an EKG done within 6 months prior to starting the study.

2. History of seizure disorder, abnormal EEGs, traumatic brain injury, renal disease (e.g. nephritis), diabetes mellitus, hypothyroidism and/or psychosis. History of active liver disease, including chronic active hepatitis, viral hepatitis (hepatitis B, C and CMV), cholestatic jaundice of any etiology, cirrhosis, toxic hepatitis, or cholestatic hepatitis or jaundice with bilirubin greater than 2.0 X upper institutional limit. Given that disulfiram may exacerbate these pre-existing conditions, patients with these conditions will be excluded. Also excluded will be individuals with a documented history of large fiber neuropathy based on EMG and/or Nerve Conduction Studies. Ascertainment: self-report, MINI and LFTs (AST & ALT) & Bilirubin not greater than 2 times upper limit at intake.

3. History of Substance Use Disorder (e.g., alcohol abuse, multi-drug dependence) within the past 2 years Ascertainment: self-report and MINI interview

4. History in the last 6 months of heavy alcohol use which is defined as binge drinking more than 5 days in a one-month period. A binge-drinking episode refers to the consumption of 5 or more drinks for men or 4 or more drinks for women in a 2-hour period
Ascertainment: alcohol use questions in the screening questionnaire (self-report).

5. Evidence of current active tick-borne illness other than Lyme disease Ascertainment: self-report and review of provided medical records
(Note: patients with evidence of positive antibodies for another TBI will be eligible unless there is evidence that this other TBI is currently active (eg., elevated LFTS (AST & ALT not greater than 2 times upper limit), low platelets, low WBC, high fevers)

6. Unwillingness to confirm that he/she will abstain from alcohol and products that may contain alcohol (including sauces, cough syrup, vinegar, backrub products, aftershave lotions) during the month prior to randomization, during the course of this study, and for 6 weeks after the last dose of study medication. (Patient Report and Urinalysis).

7. Inability to confirm abstinence from cannabis or CBD or THC-containing products
Ascertainment: urinalysis at intake and at weeks 2 and 6 and patient report.

8. Women who are breastfeeding, pregnant, or at risk of becoming pregnant during the course of the study.
Ascertainment: a) current pregnancy will be assessed by self-report and by a pregnancy test given to all women post-menarche and pre-menopausal onsite or for remote patients, at their initial testing visit); b) breastfeeding will be assessed by self-report; and c) if pregnancy is a risk, patients will be excluded if they plan to become pregnant during the course of this study or indicate an unwillingness to use an effective birth control method – these include double barrier methods (condom plus spermicide, or diaphragm plus spermicide), birth control, and abstinence.

9. Patients who are taking or plan to take warfarin, metronidazole, paraldehyde, phenytoin, theophylline, oral anticoagulants, or isoniazid (Patient report)

10. A concurrent or recent illness that may better account for current fatigue (Review of history)

11. Unwillingness to not take any new non-emergency medications during the course of this study without first reviewing with the study research physician (Patient Report)

12. History of rubber-contact dermatitis or allergy to disulfiram or thiuram derivatives (patient report)

13. Prior history of serious adverse reaction to disulfiram (Patient Report)

14. Cognitive Impairment for patients over 60.
Patient's with scores of less than 24 on the Mini-Mental Status Exam will not be eligible for this study.

15. Suicidal acts in the last 6 months (Screening Form) or current suicidal thoughts with intent or plan (assessed at intake by the study clinician and by the MINI). History of bipolar disorder (MINI).

16. Remote participants only: Unwillingness to provide a local physician who will provide secondary monitoring and collaborate to complete physical exams as part of study (patient report, screening form)

17. Remote **and hybrid** participants: Unwillingness to attend all required safety testing at his/her local Quest testing center (patient report, screening form).

Inclusion/Exclusion Criteria #2

Name the subject group/sub sample
Highly Probable
Create or insert table to describe the inclusion criteria and methods to ascertain them
1. Meets criteria for any one of the 4 follow categories of Highly Probable past Lyme Disease:

a. Health-care provider diagnosed Lyme disease in an individual exposed to a Lyme endemic area for which the HCP started antibiotic treatment for typical acute or disseminated Lyme disease (e.g., erythema migrans rash, arthritis, neurologic signs, or carditis)

or

b. EM rash after exposure to a Lyme endemic area that by history was not typical but highly suggestive and led a HCP to prescribe antibiotics for probable Lyme disease infection.

or

c. Multi-system symptoms (not better explained by another diagnosis) after exposure to a Lyme endemic area and current or past positive IgG Western blot or Lyme C6 ELISA or a Lyme PCR. Documentation of blood test is required.

or

d. A history of an acute viral-like illness after exposure to a Lyme endemic area followed within 16 weeks of symptom onset by a positive Lyme test that led the clinician to prescribe antibiotic treatment. (This criterion is partly based on the results from Steere and Sikand (NEJM 2003) in which they found that 18% of patients will present with only viral like symptoms (e.g., headache, arthralgia, fever) and none of the typical signs (ie, not showing signs such as EM rash or arthritis or facial palsy).

Ascertainment: photo of rash, provider's note, a provider's note years later reporting the initial Lyme disease, and/or positive lab test results (including the Lyme C6 Peptide ELISA), documentation of prior treatment for Lyme disease based on subsequent clinical notes, pharmacy records, and/or other sources.

2. History of treatment for Lyme disease within the last 16 years
-Documentation of prior antibiotic treatment for Lyme Disease of at least 5 weeks within the last 16 years; this meets or exceeds the Infectious Diseases Society of America (IDSA) recommended standards.
(We aim to recruit as many patients who have received between 5 weeks and 6 months of prior antibiotic therapy for this episode of illness; for this study, at least half of the sample will need to meet this criterion. Duration of prior treatment for the remaining portion of the study sample will have no upper limit for this episode of illness).

Ascertainment: Self-Report of patient and provision of at least one piece of external confirmatory historical documentation; for example, a provider's note years later reporting the initial or later Lyme treatment or pharmacy record.

3. Partial Prior Response. History of at least partial response to prior antibiotic therapy for Lyme disease.
Ascertainment: self-report

4. Antibiotic-free interval:
a) If antibiotics known to be effective for Lyme disease has been taken for 5 days or more in the recent past, the participant must agree to delay entering this study for at least 8 weeks prior to study randomization;

b) If antibiotics not effective against Lyme disease have been prescribed for other purposes, the participant must agree to wait 2 weeks before study randomization,
c) All participants must agree to be off antibiotics during the course of the study, regardless of length of antibiotic treatment.

Additionally, study clinician will confirm with the patients that the decision to stop antibiotics should only be made after the patient has consulted with their prescribing physician.

5. Current moderate to severe fatigue - The following criteria need to be met:
a) at least moderate intensity at study screening and at intake (a score of 4 or more on the Fatigue Severity Scale)
b) triggered or perpetuated by Lyme disease and persisting for at least 6 months after treatment
c) is not better attributed to another independent medical or psychiatric condition
d) current episode of Lyme disease-related fatigue is relatively persistent and has not had an intervening interval of 8 months without fatigue since diagnosis of Lyme disease.

6. Current post-Lyme symptoms impairs the patient's quality of life
Ascertainment: self-report

7. Keeping other current treatments stable -
Patients can stay on other non-antibiotic medications as long as these medications have been stable for the 3 months prior to study onset and the dosage regimen does not change during the course of this study (unless the latter is medically or psychiatrically indicated).

8. Between the ages 18-65 (Patient Report)

9. Ability to read and speak English (Patient Report)

10. Willingness to wear an activity monitor (e.g., Fitbit which we will provide) (Patient Report)

Create or insert table to describe the exclusion criteria and methods to ascertain them
1. History of cardiovascular disease (e.g., coronary artery disease or heart failure). Ascertainment: Patient Report, EKG at Intake.
a) Remote **and hybrid** participants: Results provided of an abnormal EKG done within 6 months prior to starting the study or failure to provide an EKG done within 6 months prior to starting the study.

2. History of seizure disorder, abnormal EEGs, traumatic brain injury, renal disease (e.g. nephritis), diabetes mellitus, hypothyroidism and/or psychosis. History of active liver disease, including chronic active hepatitis, viral hepatitis (hepatitis B, C and CMV), cholestatic jaundice of any etiology, cirrhosis, toxic hepatitis, or cholestatic hepatitis or jaundice with bilirubin greater than 2.0 X upper institutional limit. Given that disulfiram may exacerbate these pre-existing conditions, patients with these conditions will be excluded. Also excluded will be individuals with a documented history of large fiber neuropathy based on EMG and/or Nerve Conduction Studies. Ascertainment: self-report, MINI and LFTs (AST & ALT) & Bilirubin not greater than 2 times upper limit at intake.

3. History of Substance Use Disorder (e.g., alcohol abuse, multi-drug dependence) within the past 2 years
Ascertainment: self-report and MINI interview

4. History in the last 6 months of heavy alcohol use which is defined as binge drinking more than 5 days in a one-month period. A binge-drinking episode refers to the consumption of 5 or more drinks for men or 4 or more drinks for women in a 2-hour period
Ascertainment: alcohol use questions in the screening questionnaire (self-report).

5. Evidence of current active tick-borne illness other than Lyme disease Ascertainment: self-report and review of provided medical records
(Note: patients with evidence of positive antibodies for another TBI will be eligible unless there is evidence that this other TBI is currently active (eg., elevated LFTS (AST & ALT not greater than 2 times upper limit), low platelets, low WBC, high fevers)

6. Unwillingness to confirm that he/she will abstain from alcohol and products that may contain alcohol (including sauces, cough syrup, vinegar, backrub products, aftershave lotions) during the month prior to randomization, during the course of this study, and for 6 weeks after the last dose of study medication. (Patient Report and Urinalysis).

7. Inability to confirm abstinence from cannabis or CBD or THC-containing products
Ascertainment: urinalysis at intake and at weeks 2 and 6 and patient report.

8. Women who are breastfeeding, pregnant, or at risk of becoming pregnant during the course of the study.
Ascertainment: a) current pregnancy will be assessed by self-report and by a pregnancy test given to all women post-menarche and pre-menopausal onsite or for remote patients, at their initial testing site visit); b) breastfeeding will be assessed by self-report; and c) if pregnancy is a risk, patients will be excluded if they plan to become pregnant during the course of this study or indicate an unwillingness to use an effective birth control method – these include double barrier methods (condom plus spermicide, or diaphragm plus spermicide), birth control, and abstinence.

9. Patients who are taking or plan to take warfarin, metronidazole, paraldehyde, phenytoin, theophylline, oral anticoagulants, or isoniazid (Patient report)

10. A concurrent or recent illness that may better account for current fatigue (Review of history)

11. Unwillingness to not take any new non-emergency medications during the course of this study without first reviewing with the study research physician (Patient Report)

12. History of rubber-contact dermatitis or allergy to disulfiram or thiuram derivatives (patient report)

13. Prior history of serious adverse reaction to disulfiram (Patient Report)

14. Cognitive Impairment for patients over 60.
Patient's with scores of less than 24 on the Mini-Mental Status Exam will not be eligible for this study.

15. Suicidal acts in the last 6 months (Screening Form) or current suicidal thoughts with intent or plan (assessed at intake by the study clinician and by the MINI). History of bipolar disorder (MINI).

16. Remote participants only: Unwillingness to provide a local physician who will provide secondary monitoring and collaborate to complete physical exams as part of study (patient report, screening form)

17. Remote **and hybrid** participants: Unwillingness to attend all required safety testing at his/her local Quest testing center (patient report, screening form).

Waiver of Consent/Authorization

Indicate if you are requesting any of the following consent waivers
Waiver of consent for use of records that include protected health information (a HIPAA waiver of Authorization)
No
Waiver or alteration of consent
No
Waiver of documentation of consent
No
Waiver of parental consent
No

Consent Procedures

Is eligibility screening for this study conducted under a different IRB protocol?
No
Describe procedures used to obtain consent during the screening process
A research assistant will review with the potential study participant his/her history as it pertains to the specific inclusion/exclusion criteria of the study. During the phone screening, the study will be explained to the potentially eligible participants. The potential study participant will be informed that cannabis and/or alcohol use is strictly prohibited throughout the duration of this study. Those who are interested in the remote or hybrid study protocols will be notified that the consent forms will be provided prior to his/her initial telehealth study evaluation and will be reviewed with the study clinician and signed at the time of the initial evaluation. Those who are interested in the in-person study will be notified that the formal written consent will be provided for his/her review at the time of the in-person evaluation at the NYS psychiatric Institute.
Describe Study Consent Procedures

During the initial in-person or telehealth evaluation, the nature of the research protocol, including potential risks and benefits, will be explained verbally to all potential subjects by an experienced member of the study team who is knowledgeable about all aspects of the study. All remote and hybrid participants will receive the consent forms via email before or at the start of their initial telehealth evaluation.

The clinicians conducting the consent procedure will have a frank discussion with the potential participant about the serious risks associated with the use of cannabis and/or alcohol while taking disulfiram. This discussion will be documented, including the participant's plan for not using these substances during the duration of the study.

For individuals who are interested in completing the study remotely or via the hybrid protocol, the clinician obtaining consent will have a frank discussion regarding the risks of travel during COVID-19 when attending the Quest lab visits, NYSPI, and/or their local clinician's office. Discussion points will include maintaining social distance, avoiding crowds, and wearing masks in public spaces. They will be encouraged to stay informed about public health recommendations and guidelines regarding COVID-19, such as those issued by the Centers for Disease Control (CDC.gov) and local government guidelines and directives. Prospective participants will be advised that if they have any questions or concerns regarding their safety, they will be able to reschedule appointments. The clinician will also discuss the use of technology HIPAA-compliant platforms, and review any concerns the participant has including access to private space and accessible technology and internet connectivity.

Participants will be asked to read the study Consent Form and HIPPA Form. The person obtaining consent will answer any questions the subject may have. Once he/she feels confident the subject understands the study description, he/she will obtain informed consent from the subject by having him/her sign the consent form. Remote participants will sign and return the consent forms by scanning and returning them via a secure platform. Participants will be verbally reminded of the key points of the consent form and procedures of the study at the beginning of each study visit.

Indicate which of the following are employed as a part of screening or main study consent procedures
✓ Consent Form

Persons designated to discuss and document consent

Select the names of persons designated to obtain consent/assent
Delaney, Shannon, MD
Fallon, Brian, MD
McClellan, Denise
Type in the name(s) not found in the above list

Study Procedures

Describe the procedures required for this study

Screening/Intake Procedures

Telephone Screen- (30 mins)
Attached screening form will be completed over the phone by an RA. This will be used to collect basic

information about Lyme exposure and history of Lyme-like symptoms and treatment and of substance abuse history. Potentially eligible individuals will be invited to participate in the research study with the option for in-person, remote, or hybrid participation. If during the screening process, an individual should disclose a history of suicidal acts in the last 6 months, the study RA will inform the study clinician. The study clinician will then contact the person who had been screened to assess the patient and to make recommendations regarding additional psychiatric assessment or care as deemed advisable by the study clinician. Given that a history of suicidal acts is an exclusion item for eligibility, the clinician will inform the participant that the best clinical option is personalized treatment with a local mental health care provider as he/she would not be eligible for this study.

Participants who have been deemed eligible to participate in the remote or hybrid protocols after the screening process will be scheduled for their telehealth visits (described below). Once the intake has been scheduled, the RA will send a Medical History Form to the participants via email. In-person participants will be requested to bring the completed form to their intake visit. Remote and hybrid participants will be asked to return the completed forms via a secure method before their intake visit. The form will not only help in reviewing eligibility one final time, but will also help the study clinician organize their clinical notes while reducing the assessment time for the clinician and the participant alike. This form will be included in the participants' clinical folder. In the event, the participant is deemed ineligible the form will be returned to them.

IN-PERSON INTAKE AND STUDY VISITS- (please see attached document for visit breakdown)

Informed Consent and HIPPA Forms
On the intake day of the study, the nature of the research evaluation protocol, including potential risks and benefits, will be explained verbally to all potential subjects by an experienced member of the study team who is knowledgeable about all aspects of the evaluation process. Participants will be asked to also read the study Consent and HIPPA Forms. The person obtaining consent will answer any questions the subject may have. Once he/she feels confident the subject understands the evaluation description, he/she will obtain informed consent from the subject by having him/her sign the consent form. Participants will be verbally reminded of the key points of the consent form and procedures of the evaluation at the beginning of each study visit.

The study clinician will have a detailed and frank discussion about participants' cannabis and alcohol use and the risks of using these substances while taking disulfiram. The study clinician will also inquire if the patient is either vegan or lactose intolerant. If the patient reports being either of the two, then the pharmacy will be informed about the specific dietary restriction immediately following the intake visit. Documentation of this discussion and participants plan for not using these substances will be made in the consent procedure note.

Physical examination, sensory testing and collection of biological samples
A medical history and physical examination will be conducted, including sensory testing (pain, sound, vibration, sweat gland function). The Neuropathy Total Symptom Scale- 6 and the Total Neuropathy Scale will be administered by the clinician during the neurologic assessment at intake and at week 8. EKG will be conducted by one of the study RAs and read by one of the study clinicians in order to confirm the participants' inclusion/exclusion criteria during the intake visit.

The following tests will be performed during the study:

• CBC, Chemistry Screen, TFT (Tests performed at Nathan Klein Clinic- CBC and Chem screen with LFTS will be conducted at intake, baseline, wk 1 (post tx), 2, 4, 6, 8, and 10, study while TFTs will be done only at intake, Tox Screen will be done at Intake and Wks 2 and 6)
• Lyme, Babesia Microti (Tests performed only at intake)
• Lyme Urine Proteome Test (Test performed by the Center for Applied Proteomics and Molecular Medicine at George Mason University.- done at intake and Week 10)
• Fecal matter samples collected at intake, week 4, week 8 and at week 10 will be sent to our collaborator Dr. Kim Lewis at Northeastern University
• All females who are post-menarche and pre-menopausal will be required to take a urine pregnancy test at the time of the intake (Test performed at NYSPI)
• EKG (Test performed at NYSPI- done at intake)
• Storage for biorepository for analysis at the end of the study. This will include Blood (serum, plasma, whole blood) and urine collected at baseline, week 4, week 8, and week 10). (More information is provided in the blood and other biological samples subsection)

While some of these samples will be sent to known collaborators, others will be stored in anticipation of future collaborations. The known collaborators for stored samples include samples to: a) the Center for Applied Proteomics at George Mason University; b) Dr. Armin Alaedini at Columbia for inflammatory and immune markers; c) Dr. Rafal Tokarz at Columbia for coinfection markers; and d) Drs. Charlie Brown (University of Missouri) and Dr. Edward Dennis at (UCSD) for lipidomic markers.

REMOTE INTAKE AND STUDY VISITS- (please see attached study overview visit checklist document for visit breakdown)

Informed Consent and HIPPA Forms
On the day of the intake visit, the nature of the research evaluation protocol, including potential risks and benefits, will be explained verbally via a secure telehealth platform to all potential subjects by an experienced member of the study team who is knowledgeable about all aspects of the evaluation process. Participants will be asked to also read the study Consent and HIPPA Forms. The person obtaining consent will answer any questions the subject may have. Once he/she feels confident the subject understands the evaluation description, he/she will obtain informed consent from the subject by having him/her sign the consent form and scanning and returning them via a secure platform. Participants will be verbally reminded of the key points of the consent form and procedures of the evaluation at the beginning of each study visit.

The study clinician will have a detailed and frank discussion about participants' cannabis and alcohol use and the risks of using these substances while taking disulfiram. The study clinician will also inquire if the patient is either vegan or lactose intolerant. If the patient reports being either of the two, then the pharmacy will be informed about the specific dietary restriction immediately following the intake visit. Documentation of this discussion and participants plan for not using these substances will be made in the consent procedure note.

Physical examination

A medical history will be conducted via telehealth by a study clinician and a physical examination will be conducted by each participant's local physician. The Neuropathy Total Symptom Scale- 6 and the Total Neuropathy Scale will be administered by the local clinician during the neurologic assessment at intake and at week 8. The results of these assessments and any visit notes will be securely faxed from the local physician's office to the study clinician.

Remote participants will be required to visit their local Quest Diagnostic testing site for the following tests that will be performed during the study:

• CBC, Chemistry Screen, TFT (Tests performed at Quest Diagnostic- CBC and Chem screen with LFTS will be conducted at intake, Weeks **2,** 4, 6, and 10, study while TFTs will be done only at intake, Tox Screen will be done at Intake and Week 6)
• Lyme, Babesia Microti (Tests performed only at intake)
• Lyme Urine Proteome Test (Test performed by the Center for Applied Proteomics and Molecular Medicine at George Mason University.- samples collected at home and sent to collaborating lab at intake and Week 10)
• Fecal matter samples collected at home at intake, week 4, week 8 and at week 10 will be sent to our collaborator Dr. Kim Lewis at Northeastern University
• All females who are post-menarche and pre-menopausal will be required to take a urine pregnancy test at the time of the intake (Test performed at Quest Diagnostic)

The results of these laboratory tests will be accessible to the study clinicians via a HIPPA compliant, secure EHR portal provided by Quest Diagnostics.

HYBRID INTAKE, BASELINE, AND STUDY VISITS- (please see attached study overview visit checklist document for visit breakdown)

Informed Consent and HIPPA Forms
On the day of the intake visit, the nature of the research evaluation protocol, including potential risks and benefits, will be explained verbally via a secure telehealth platform to all potential subjects by an experienced member of the study team who is knowledgeable about all aspects of the evaluation process. Participants will be asked to also read the study Consent and HIPPA Forms. The person obtaining consent will answer any questions the subject may have. Once he/she feels confident the subject understands the evaluation description, he/she will obtain informed consent from the subject by having him/her sign the consent form and scanning and returning them via a secure platform. Participants will be verbally reminded of the key points of the consent form and procedures of the evaluation at the beginning of each study visit.

The study clinician will have a detailed and frank discussion about participants' cannabis and alcohol use and the risks of using these substances while taking disulfiram. The study clinician will also inquire if the patient is either vegan or lactose intolerant. If the patient reports being either of the two, then the pharmacy will be informed about the specific dietary restriction immediately following the intake visit. Documentation of this discussion and participants plan for not using these substances will be made in the consent procedure note.

Physical examination

A medical history and physical examination will be conducted at the baseline visit prior to initiation of the study medication. The Neuropathy Total Symptom Scale- 6 and the Total Neuropathy Scale will be administered by the clinician during the neurologic assessment at baseline and at week 10.

Hybrid participants will be required to visit their local Quest Diagnostic testing site for the following tests that will be performed during the study:

• CBC, Chemistry Screen, TFT (Tests performed at Quest Diagnostic- CBC and Chem screen with LFTS will be conducted at intake, Weeks 2, 4, 6, and 10, study while TFTs will be done only at intake, Tox Screen will be done at Intake and Week 6)
• Lyme, Babesia Microti (Tests performed only at intake)
• Lyme Urine Proteome Test (Test performed by the Center for Applied Proteomics and Molecular Medicine at George Mason University.- samples collected at home and sent to collaborating lab at intake and Week 10)
• Fecal matter samples collected at home at intake, week 4, week 8 and at week 10 will be sent to our collaborator Dr. Kim Lewis at Northeastern University
• All females who are post-menarche and pre-menopausal will be required to take a urine pregnancy test at the time of the intake (Test performed at Quest Diagnostic)
• Storage for biorepository for analysis at the end of the study. This will include Blood (serum, plasma, whole blood) and urine collected at baseline and week 10). (More information is provided in the blood and other biological samples subsection)

The results of laboratory tests done through Quest will be accessible to the study clinicians via a HIPPA compliant, secure EHR portal provided by Quest Diagnostics.

While some of these samples will be sent to known collaborators, others will be stored in anticipation of future collaborations. The known collaborators for stored samples include samples to: a) the Center for Applied Proteomics at George Mason University; b) Dr. Armin Alaedini at Columbia for inflammatory and immune markers; c) Dr. Rafal Tokarz at Columbia for coinfection markers; and d) Drs. Charlie Brown (University of Missouri) and Dr. Edward Dennis at (UCSD) for lipidomic markers.

All Participants (Remote, Hybrid and In-Person) will also complete the following as part of study visits:

Medical history and psychiatric diagnostic Interview MINI
At intake, all subjects will undergo structured diagnostic interviews in-person or via telehealth, which include questions about their current and psychiatric history using MINI. A medical history will be obtained at intake using the Self-Administered Comorbidity Questionnaire (SCQ) and by the study clinician during the clinician interview.

Self-report questionnaires
Participants will have in-person or telehealth assessments at baseline and at weeks 1, 2, 4, 6, 8, 10. Participants will complete self-report questionnaires every 2 weeks at each assessment throughout the study and at Week 14.

These self-report questionnaires and research data will be collected electronically via REDCap (Research Electronic Data Capture), hosted by New York State Psychiatric Institute. REDCap is a secure web application for building and managing online surveys and databases that complies with HIPAA requirements for a secure database.

For in-person participants who opt to complete paper versions of the questionnaires, this data will be stored in locked files and will be kept confidential to the extent permitted by law. Research binders will be available only to research staff and Federal, State and Institutional personnel as part of routine audits. Paper versions of self-report questionnaires will be labeled with a research number assigned to the patient, not the patient's name.

Wearing of activity monitor
All participants will be provided with an activity monitor (e.g., Fitbit) to keep track of sleep and of the number of steps taken each day. Participants will wear this device for 2 weeks prior to randomization and throughout the 14 weeks of the study. We will also inform the participants that they will need to share the data from their devices periodically during their study visits.

Phone-calls at end of Weeks 3, 5,7, 9 and 12 (10-20 mins)
The follow-up phone calls will be done by one of the study clinicians and will focus on inquiring about the following-
• If the participant is experiencing side-effects related to disulfiram
• If the participant is adhering to the study treatment
• If the participant has used any kind of substance like alcohol, cannabis etc.
• If the participant has started any new medications

Treatment Phase

Patients will be randomly assigned to one of two groups.

Both groups (the 4 week duration and the 8 week duration groups) will share the same protocol for the first 4 weeks as follows:

Week 1 Disulfiram 250 every other day
Week 2 Disulfiram 250 daily.
Week 3 Disulfiram 250 alternating with 500
Week 4 Disulfiram 500 daily.

Week 5-8 Continue with 500 daily (2 pills daily of disulfiram or placebo) or lower if needed based on side effects. (Note: the last 4 weeks of the study are double-blind)

(The long duration group will increase to two pills daily (500 mg) or the highest dosing regimen they can tolerate without significant side effects, while the short duration group during the last 4 weeks of the treatment period will be given placebo pills).

In-person patients will be seen in the clinic at least every 2 weeks to week 10 and at week -14 for a follow-up. Remote and Hybrid patients will be seen in via scheduled telehealth sessions at least every 2 weeks up to week 10 and at week -14 for follow-up. Additionally, when not seen in person or via telehealth, patients will be followed up weekly over the phone to week 12.
Remote and Hybrid patients will be sent a digital blood pressure cuff prior to the Intake visit for safety-related monitoring. At each telehealth evaluation, the participant will be asked to take and report pulse and blood pressure to the NYSPI clinician. These blood pressure values will be documented by the NYSPI clinician to allow for the observation of any critical changes throughout treatment.

In-person and hybrid patients will be asked to take their first dose of medication during the baseline visit and will be monitored on site at NYSPI for 1/2 hour to ensure that they are not experiencing any serious side-effects of the medication. If during this time, the patient experiences signs of a mild allergic reaction, the patient will be given 50 mg of diphenydramine orally; observation will continue until the patient is free of allergic symptoms for at least 1/2 hour. Should the patient experience signs of an emerging, more severe allergic reaction, a medical emergency will be called (x5555) and the patient will be transferred to the ER if needed (e.g., symptoms are consistent with anaphylaxis). **Some hybrid patients will receive their second 4 weeks of treatment in the mail directly from the NYS Psychiatric Institute's Pharmacy. Some hybrid patients will receive both the first month and second month of treatment at their initial study visit in medication vials labeled "Bottle 1" and Bottle 2". The study clinician will initiate treatment with the patients at that appointment with "Bottle 1". They will also provide clear instructions not to open or use "Bottle 2" until instructed to do so after week 4.**

Remote patients will receive their medication in the mail directly from the NYS Psychiatric Institute's Pharmacy. The NYSPI pharmacist will send the medication directly to the participant with detailed instructions that they are not to begin taking the medication until they meet with the study clinician at their baseline telehealth visit. At the baseline telehealth visit, the study clinician will ask patients to open the sealed packaging enclosing their medication. Subsequently, they will be asked to take their first dose of medication and will be monitored via telehealth for 1/2 hour to ensure that they are not experiencing any serious side-effects of the medication. If during this time, the patient experiences signs of a mild allergic reaction, the patient will be instructed to take 50 mg of diphenydramine orally; observation will continue until the patient is free of allergic symptoms for at least 1/2 hour. Should the patient experience signs of an emerging more severe allergic reaction, the patient will be instructed to visit their local physician or ER if needed (e.g., symptoms are consistent with anaphylaxis). As part of the consent process, the participant has agreed that a family member or friend will be present when taking the initial study medication. The family member or friend provides an additional layer of safety (on top of the NYSPI clinician monitoring remotely) should the participant start to experience an initial adverse reaction (e.g., an allergic reaction).

To monitor adherence to treatment, all patients will be given a pill log to document the pill taking.

While all patients will be started on the schedule of dose escalation as stated above and our study aims for patients to keep this schedule, if an individual patient has trouble tolerating disulfiram the clinician can adjust the dose based on patient tolerance.

Assessment of Outcome

The outcome will be assessed across groups and within groups. Data will be evaluated both as categorical and continuous measures. A reduction from baseline on the FSS of ≥0.7 points is considered clinically meaningful.

Assessment of Outcome among individuals with early discontinuation

Should a patient need to be discontinued from the study before week 10, he/she will be asked to return to NYSPI or to complete a telehealth evaluation and an assessment with their local physician (if participating remotely) to complete the major week 8/10 assessments so that his/her progress can continued to be evaluated by the study clinician. Since we do not know the optimal duration of disulfiram (ie, shorter courses may be effective) and because improvement may occur during the weeks after discontinuation, we will ask patients to return at week 10 (or to complete telehealth and local evaluations) but also to complete self-reports assessments and telephone follow-up at home at weeks 2, 6, 8, and 14.

Should a patient who drops from treatment early plan to start a new treatment that might impact clinical ratings, we will ask the patient to complete the full set of week 10 assessments early so that these can be used in the final data analysis; that patient will then be discontinued from both the treatment and assessment phase of the study. The patient will also be asked to return all study medication which we will then return to the NYSPI pharmacy.

During COVID-19 pandemic: I attest to follow the COVID-19 Safety Guidelines for Columbia Psychiatry and NYSPI Re-Entry outlined in the NYSPI Director's June 1st memo, which include but are not limited to:

• Infection Control/PPE – Guidelines
• Research participants will only come on-site if absolutely necessary for study procedures.
• No volunteers/externs on-site during Stage 1.
• Clinical research teams will screen their participants for COVID symptoms (night before and day of onsite visit, documenting this in the chart), and escort them in and out of the building.
• COVID/COVID-like symptoms in participants will be reported to the IRB via PRISM as an SAE.

You can upload charts or diagrams if any

Criteria for Early Discontinuation

Criteria for Early Discontinuation

Patients will be monitored for global clinical change (CGI Change - clinician rating) and for side-effects of the medications (Saftee) during the clinic visits or telehealth visits and weekly phone check-ups.

• A patient will be discontinued from treatment early if he/she shows signs of liver toxicity on laboratory tests; an abnormal finding (e.g., Moderate or Severe ALT elevation > 2x ULN or AlkPhos > 1.5x ULN or Bili > 1.5x ULN) will lead to a discontinuation of the treatment, repeat of the lab test with close monitoring of the patient, and a referral for the patient to see their internist for further liver monitoring. If patients experience any mild ALT elevation or Alk Phos elevation (e.g., ALT >ULN but <2x ULN or ALK Phos >ULN <1.5x ULN), then the study clinician will keep their disulfiram dose the same and repeat testing in 2 weeks as long as their TB remains <1.5 ULN. Patients will be advised to immediately notify their study clinician of any early symptoms of hepatitis, such as fatigue, weakness, malaise, anorexia, nausea, vomiting, jaundice or dark urine; this will lead to a medical evaluation to rule out liver involvement.

• Patients will also be discontinued from the treatment component of the study early if they experience any new onset adverse neurological reactions thought to be due to the study treatment and which persists for at least 1 week (e.g., polyneuritis, peripheral neuropathy).

Clinically, early discontinuation from treatment will occur if:
a. a patient's self-report on the CGI Global Change scale indicates a score of "very much worse" for 2 consecutive weeks or "much worse" for 4 consecutive weeks.
b. a patient's score on the BDI item 9 suicide item is 2 or higher for 2 consecutive assessments. A BDI item 9 score of 2 or 3 will lead to an evaluation by a psychiatrist and closer monitoring which will include a reassessment one week later. If the worsening suicidal ideation continues, the patient will be withdrawn from the study and appropriate clinical care will be arranged.

Blood and other Biological Samples

Please create or insert a table describing the proposed collection of blood or other biological specimens

IN-PERSON PARTICIPANT SPECIMEN COLLECTION:
The following will be drawn or collected for in-person participants:

Intake
CBC, Chemistry Screen, TFT (Tests performed at NKI)
1. CBC- 1 4cc EDTA
2. TFTs and Chemistry Screen- 2, 8cc Red Top
3. Tox Screen and Pregnancy Test- 50 cc Urine

Lyme and Babesia test (Tests performed at MDL)
1. 2, 8.5cc Serum Tube

Stool collection kit is given to patient at intake visit. Patient is to collect stool sample at home and send to Dr. Lewis' lab at Northeastern- kits prior to the Baseline visit.

Baseline/Wk0

Lyme Proteome Test (Test performed at George Mason University)
1. 80cc Urine Sample

Storage for Biorepository-
1. 2, 8 cc Red top Serum Tube- stored in .25cc aliquots
2. 1, 8cc EDTA Plasma-tube - stored in .5cc aliquots
3. 1, 4cc EDTA Whole Blood - stored in .5cc aliquots

CBC, Chemistry Screen, LFT (Tests performed at NKI)
1. CBC- 1 4cc EDTA
2. TFTs and Chemistry Screen- 2, 8cc Red Top

Weeks 1, 2, 4, 6, 8
CBC and Chem screen (including LFTs). Urine Tox Screen at Wks 2 and Wk 6

Week 4 & 8
Storage for Biorepository-
1. 1, Serum from one 8cc Red Top Tube
2. 1, Plasma from one 6cc EDTA Plasma Tube
3. 50cc Urine Sample

Stool sample (collected at home and sent to Dr. Lewis' lab at Northeastern)

Week 10
CBC and Chem screen (including LFTs)
1. CBC- 1 4cc EDTA
2. TFTs and Chemistry Screen- 2 8cc Red Top

Lyme Proteome Test (Test performed at George Mason University)
1. 80cc Urine Sample

Storage for Biorepository-
1. 2, 8 cc Red Top Serum Tube- stored in .25cc aliquots
2. 1, 8cc EDTA Plasma-tube - stored in .5cc aliquots
3. 1, 4cc EDTA Whole Blood - stored in .5cc aliquots

Stool sample (collected at home and sent to Dr. Lewis' lab at Northeastern)

REMOTE PARTICIPANT SPECIMEN COLLECTION:
The following will be drawn or collected for remote participants:

Intake
CBC, Chemistry Screen, TFT (Tests performed at Quest Diagnostics)
1. CBC- 1 4cc EDTA
2. TFTs and Chemistry Screen- 2, 8cc Red Top

3. Tox Screen and Pregnancy Test- 50 cc Urine

Lyme and Babesia test (Tests performed at MDL)
1. 2, 8.5cc Serum Tube

Stool collection kit is mailed to patient after intake telehealth visit. Patient is to collect stool sample at home and send to Dr. Lewis' lab at Northeastern prior to the Baseline visit.

Baseline/Wk0
Lyme Proteome Test (Test performed at George Mason University)
1. 80cc Urine Sample (Participants will be mailed a urine collection kit. Urine sample is to be collected at home and sent to George Mason University collaborators)

Weeks 2, 4, & 6
CBC and Chem screen (including LFTs). Urine Tox Screen at Wk 6 only (Tests performed at Quest Diagnostics)

Week 4 & 8
Stool sample (collected at home and sent to Dr. Lewis' lab at Northeastern)

Week 10
CBC and Chem screen (including LFTs) - (Tests performed at Quest Diagnostics)
1. CBC- 1 4cc EDTA
2. TFTs and Chemistry Screen- 2 8cc Red Top

Lyme Proteome Test (Test performed at George Mason University)
1. 80cc Urine Sample (Urine sample is to be collected at home and sent to George Mason University collaborators)

Stool sample (collected at home and sent to Dr. Lewis' lab at Northeastern)

HYBRID PARTICIPANT SPECIMEN COLLECTION:
The following will be drawn or collected for remote participants:

Intake
CBC, Chemistry Screen, TFT (Tests performed at Quest Diagnostics)
1. CBC- 1 4cc EDTA
2. TFTs and Chemistry Screen- 2, 8cc Red Top
3. Tox Screen and Pregnancy Test- 50 cc Urine

Lyme and Babesia test (Tests performed at MDL)
1. 2, 8.5cc Serum Tube

Stool collection kit is mailed to patient after intake telehealth visit. Patient is to collect stool sample at home and send to Dr. Lewis' lab at Northeastern prior to the Baseline visit.

Baseline/Wk0
Storage for Biorepository- Collected at NYSPI
1. 2, 8 cc Red top Serum Tube- stored in .25cc aliquots
2. 1, 8cc EDTA Plasma-tube - stored in .5cc aliquots
3. 1, 4cc EDTA Whole Blood - stored in .5cc aliquots

Lyme Proteome Test (test performed at George Mason University)
1. 80cc Urine Sample - collected at NYSPI

Weeks 2, 4, & 6
CBC and Chem screen (including LFTs). Urine Tox Screen at Wk 6 only (Tests performed at Quest Diagnostics).
Stool sample at Wk 4 only (collected at home and sent to Dr. Lewis' lab at Northeastern)

Week 8
Stool sample (collected at home and sent to Dr. Lewis' lab at Northeastern)

Week 10
CBC and Chem screen (including LFTs) - (Tests performed at Quest Diagnostics)
1. CBC- 1 4cc EDTA
2. TFTs and Chemistry Screen- 2 8cc Red Top

Storage for Biorepository-
1. 2, 8 cc Red Top Serum Tube- stored in .25cc aliquots
2. 1, 8cc EDTA Plasma-tube - stored in .5cc aliquots
3. 1, 4cc EDTA Whole Blood - stored in .5cc aliquots
Lyme Proteome Test (Test performed at George Mason University)
1. 80cc Urine Sample - collected at NYSPI

Stool sample (collected at home and sent to Dr. Lewis' lab at Northeastern)

Assessment Instruments

Create a table or give a brief description of the instruments that will be used for assessment
Participants will complete the following questionnaires. Detailed information on what intervals these

questionnaires will be completed is attached below.

Overall Multi-Domain Assessment:
1. Promis 29
2. Patient-rated Clinical Global Improvement

Somatic Symptoms
1. General System Questionnaire- 30 items
2. VAS - for "Fatigue"
3. Fatigue Severity Scale

Psychopathology:
1. Depression: Beck Depression Inventory II; (and PROMIS module)
2 Anxiety: STAI (and PROMIS module)
3. MINI-Neuropsychiatric Assessment

Cognition:
1. Keilp Cognitive Battery or Abbreviated Cognitive Battery for remote and hybrid participants
2. NeuroQoL-Short Form v2.0 Cognition
3. VAS- for "Brain Fog"
4. Mini Mental Status (for participants 60 and older)

Functional Status
1. SF-36
2. Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q SF)

Demographics & History
1. History of Medical and Tick-borne Illness, Medical Utilization
2. Demographics+ Identifying Information Form
3. Physical History Form x 2 (completed by the MD)
4. Stressful Life Events Scale
5. NTSS6, TSS
6. Cumulative Illness Rating Scale (CIRS)

Sensory and Neuro testing (These procedures will not be conducted at NYSPI at present due to COVID-19**)**
1. Sensitivity to sound, light, vibration, pressure (in-person only)
2. Heart rate variability (in-person only)
3. Sudomotor small fiber function (Sudoscan) (in-person only)

Side-effect Monitoring
1. SAFTEE

Please attach copies, unless standard instruments are used

Off label and investigational use of drugs/devices

Choose from the following that will be applicable to your study
✓ Drug
Select the number of drugs used in this study
1

Drug #1

Name of the drug
Disulfiram
Manufacturer and other information

Disulfiram is FDA approved to help individuals wishing to abstain from alcohol.
There are several manufacturers of disulfiram.

Approval Status
IND is approved
IND#
142979
Who holds the IND/IND sponsor?
IND is held by PI/CU Investigator
Fallon, Brian, MD

Research Related Delay to Treatment

Will research procedures result in a delay to treatment?
Yes
Maximum duration of delay to any treatment
We are asking patients not to start any new treatments during the course of this study and for 3 months prior. Therefore, the delay in starting any new treatment will be approximately 6.5 months.
Treatment is provided to all the participants. However, the participants who are randomized to the shorter dose regimen will receive 26 days of treatment compared to the participants who will get treatment for 54 days.
Maximum duration of delay to standard care or treatment of known efficacy
There is no treatment of known efficacy for patients with post-treatment Lyme disease.
Treatment to be provided at the end of the study

Patients will be offered the option of 3 months of symptom-based clinical treatment at the end of the study. The clinician visits at PI will be free. Patients will be given scripts of medication if needed, the cost of which will be covered by them or their insurance carrier.

Clinical Treatment Alternatives

Clinical treatment alternatives
The treatment of post-treatment Lyme disease symptoms is a matter of considerable uncertainty. Some health care providers offer repeated courses of antibiotics while other health care providers offer symptom-based therapies. Unfortunately too few studies have been conducted among patients with post-treatment Lyme disease to recommend specific treatments.

Risks/Discomforts/Inconveniences

Risks that could be encountered during the study period

Treatment with Disulfiram

1. Disulfiram-alcohol reaction. If patients consume alcohol or alcohol-containing products while on disulfiram, the patient may experience diaphoresis, palpitations, facial flushing, nausea, vertigo, hypotension, and tachycardia.

2. Disulfiram-related adverse effects.
a) Less serious side effects include headache, sleepiness, fatigue, and a metallic taste in the mouth.

b) More serious and rare side effects have been reported affect the following systems.
i. Dermatologic. Rare reports exist of exfoliative dermatitis, rash, and pruritis.

ii. Liver. Rare reports exist of hepatitis, hepatotoxicity, and hepatic failure; there have been cases of fatal fulminant hepatic failure despite discontinuation of medication (1 case in 30,000 patients treated per year) (Stokes, Abdifadid Stat Pearls Publishing, October 2017).

iii. Psychiatric. Rare reports exist of psychosis, confusional states, mutisim, head banging, memory impairment, and stupor.

iv. Neurologic. Neuropathy occurs in 1 case per 10,000 patients treated with disulfiram per year. Cases of seizures and optic neuritis attributed to disulfiram have been reported.

v. Cardiac. Cases of heart failure and death have been reported in patients with significant coronary artery disease or heart failure.

vi. Genitourinary. Impotence has also been reported.

3. Disulfiram interaction with other medications.
a). Disulfiram and cannabis increases the risk of psychosis.
b) Disulfiram and metronidazole can lead to confusion or psychosis (hallucinations/delusions).
c). Interaction with compounds that use the P450 enzyme system for metabolism has been reported and is likely to occur. These include (but are not limited to): amitriptyline, imipramine, phenytoin, chlordiazepoxide, diazepam, omeprazole, and acetaminophen. Other drug-drug interactions have been reported as well.

4. Disulfiram may exacerbate certain conditions such as diabetes mellitus, hypothyroidism, seizure disorder, cerebral damage, cardiac, liver and renal disease.

Self -Report Questionnaires
Psychological distress at completing the self-report questionnaires.

Blood Draw
There is the risk of discomfort and a possible bruise at the site of the needle insertion. There is also a small risk of infection which can be treated if that occurs.

Sensory Testing (These procedures will not be conducted at NYSPI at present due to COVID-19.)
Some participants might find the sensory testing mildly unpleasant. There is no significant risk to subjects associated with this kind of testing. The experimenter can stop the task at any time if the participant experiences discomfort and wants to discontinue the task.

Remote and hybrid participation during COVID-19 pandemic:
There are some risks associated with travel during the COVID-19 pandemic for participants completing study procedures remotely or via the hybrid protocol. The number of laboratory assessments and in-person assessments has been reduced to minimize risk. Nonetheless, for safety-related reasons, it will still be necessary for participants to attend some assessments in-person.

Describe procedures for minimizing risks

Treatment with Disulfiram

1. Disulfiram-alcohol reaction. Patients are required to be alcohol-free during this study and for at least 2 weeks prior to starting the study and for 6 weeks after receiving the last dose of study medication (I.e from weeks 8-14). The consent form will describe this reaction so that patients will be aware of the typical symptom profile should he/she inadvertently consume an alcohol-containing product; this will also be described in detail to the patient by the study clinician. Patients will also be advised to check labels of all consumed products to ensure there is no alcohol within the food preparation (e.g., sauces, vinegar, cough medication).

2. Patients will be monitored for side-effects of the medication during the clinic visits and weekly phone check-ups. The number of pills taken (either 2 or 1 or none) each day can be adjusted based on tolerability

and clinician's judgment. Intolerable side effects or clinically severe worsening that is sustained for 2 consecutive assessments will result in withdrawal from the study.

3. To reduce the risk of rare but serious adverse effects, patients will be excluded from enrollment in the study if there is:
a. Liver: evidence or history of liver disease or insufficiency
b. Psychiatric: a lifetime history of psychosis or of bipolar disorder or recent or current suicidality
c. Substance use: alcohol or substance abuse disorder within the past 2 years
d. Neurologic: a lifetime history of seizures or history of abnormal EEG
e. Cardiac: a current or lifetime history of coronary artery disease or heart failure.

As additional precaution against liver injury, patients will be monitored closely during the study, including blood tests at intake and after weeks 2, 4, 6, and 10. If the clinician notices mild ALT or Alk Phos elevation (e.g., ALT >ULN but <2x ULN or ALK Phos >ULN <1.5x ULN), then the patient will remain at the same dose and repeat testing in 2 weeks (as long as TB <1.5 ULN). If the clinician notices moderate or severe LFT elevation (e.g., ALT > 2x ULN or AlkPhos > 1.5x ULN or Bili > 1.5x ULN), then the patient will discontinue disulfiram, be monitored closely, and referred to their internist for further liver monitoring. The clinician will also monitor the patient for signs of hepatitis, such as fatigue, weakness, anorexia, nausea, vomiting, jaundice, malaise, and dark urine.

Because disulfiram may exacerbate certain conditions, patients will be excluded from participation who have a diagnosis of diabetes mellitus, hypothyroidism, seizure disorder, cerebral damage, cardiac, liver or renal disease

4. Drug interactions:
a. Patients will be warned not to take metronidazole or paraldehyde; as the latter is not available in the United States, we anticipate this to be an unlikely risk.
b. Patients will be advised to review all new medications (prescribed or over the counter) with his/her research clinician to ensure lack of drug interactions.

Self- Report Questionnaires
Patients will be told that they can skip questions if they are too distressing to complete.

Blood Draw (These procedures will be minimally conducted as needed at NYSPI due to COVID-19.)
Gloves will be used to reduce risk of infection and the skin is wiped with alcohol prior to the blood draw; if an infection occurs, it will be treated.

Sensory Testing (These procedures will not be conducted at NYSPI at present due to COVID-19.)
Some participants might find the sensory testing mildly unpleasant. There is no significant risk to subjects associated with this kind of testing. The experimenter can stop the task at any time if the participant experiences discomfort and wants to discontinue the task.

Remote and hybrid participation during COVID-19 pandemic:
The number of laboratory assessments and in-person assessments has been reduced to minimize risk. However, for safety-related reasons, participants will be required to attend some assessments in-person. To

minimize risks associated with travel, the clinician obtaining consent will have a frank discussion regarding the risks of travel when attending the local physician's office, visits to NYSPI, and all Quest lab visits. Discussion points will include maintaining social distance, wearing masks in public spaces, exercising caution when traveling in public, and following public health guidelines. Participants will be informed about implemented procedures at NYSPI to minimize COVID-19 exposure risk such as personal protective equipment (masks and face shields), frequent disinfecting of equipment, and social distancing when possible. Prospective participants will also be advised that if they have any concerns regarding their safety, they will be able to reschedule appointments.

Methods to Protect Confidentiality

Describe methods to protect confidentiality

New techniques and technologies are developed each year that when applied to blood samples can help facilitate new discoveries and biomarkers; that is one of the goals of Precision Medicine research. To enable us to take advantage of emerging technologies, we would like to keep participant samples for at least 10 years or as long as they are deemed useful for research purposes. However, participants have the right to request that their samples be destroyed at any time.

All of the patient’s medical records, laboratory reports, and research data will be stored in locked files and will be kept confidential to the extent permitted by law. Medical records, laboratory reports, research binders, and medical charts will be available only to research staff, local consulting physicians, and Federal, State and Institutional personnel as part of routine audits. There are legal advocacy organizations that have the authority under State law to access otherwise confidential subject records, but they cannot re-disclose this information without the patient’s consent. Any research data transmitted or stored electronically will use a number assigned to the patient, not the patient’s name. As a part of our remote protocol, local physicians will fax all assessment results and notes to the study clinicians via a HIPPA compliant fax. Quest diagnostics, who will perform local laboratory tests, have provided access to a HIPPA compliant secure EHR portal. Study clinicians will access participant laboratory results via that secure portal.

All the shared samples will be assigned a unique subject ID and no PHI will be shared with the collaborators. Samples will be shared after obtaining a Material Transfer Agreement (MTA).

Will the study be conducted under a certificate of confidentiality?
No

Direct Benefits to Subjects

Direct Benefits to Subjects
There is no direct benefit to the participants expected from participation in this research study. It is hoped,

however, that the knowledge gained from this study may lead to a significant public health benefit as we hope it will help establish the safety and suggest efficacy of disulfiram as a medication to treat chronic symptoms of Lyme disease. While we hypothesize that patients will experience a reduction in symptom burden as a result of participation in this study, we are not certain this will be the case. Therefore, at this point, we cannot state that there will be direct benefits to the subjects.

Compensation and/or Reimbursement

Will compensation or reimbursement for expenses be offered to subjects?
Yes
Please describe and indicate total amount and schedule of payment(s).
Include justification for compensation amounts and indicate if there are bonus payments.
Participants who live outside the NYC metro area and choose to participate in-person will be reimbursed for reasonable travel expenses up to $100 per visit. The amount is considered proportionate to the costs of rail travel for participants that live along the Northeast corridor and/or cover costs incurred for paid parking. For participants traveling from interstate, the reimbursement may be used to subsidize the cost of accommodation for each visit. Remote participants will not receive reimbursement. During the COVID-19 Pandemic, we will reimburse travel for participants within and outside the NYC metro area so that it may be more feasible for them to avoid public transportation. Hybrid participants will be reimbursed for reasonable travel expenses up to $200 per visit.

References

References

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Uploads

Upload copy(ies) of unbolded Consent Form(s)
Upload copy(ies) of bolded Consent Form(s)
Upload copy(ies) of recruitment materials/ads to be reviewed
Disulfiram_Facebook_Ad_Text_approved_2019-06-26.pdf
Email_template_to_clinicians_approved 2019-11-04.pdf
Lyme_Clinical_Trial_flyer_(002).pdf
Upload evidence of FDA IND approval(s)
FDA_IND_Letter_7766.pdf
7755_'Form_of_Notice_by_IND.IDE_Holder_03292019.pdf
Upload copy(ies) of the HIPAA form
HIPPA_Disulfiram_03-11-2021.pdf
Upload any additional documents that may be related to this study
7755_Request_for_Deidentified_Data_sharing_approved 2019-06-26.pdf
FDC_Foundation_Nov_2018.pdf
Consent Procedure Note.pdf
Disulfiram instructions_02.28.22.pdf
Disulfiram_Alcohol_Interaction_Information_Feb_2020.pdf
DSFLocalProviderPhysicalNeuroExamFINAL2.25.2021. docx..pdf
Hybrid Study Overview Visit Checklist.pdf
Medical_History_Form_approved_2019-07-31.pdf
Revised Remote Disulfiram Screening Form_2020-09-18_JP.pdf
Study Overview Visits Checklist_approved 2019-06-26.pdf
Consulting_Agreement_10-13-20 (1).pdf
'Dr._Fallon's_General_Symptom_Questionnaire_30_item_3_04_16_version.pdf
Amendment 3.16.22 Prot 7755_BAF_to_IRB_03.16.202 Amendment.pdf

Statistician	Data preparation and analysis is performed by a research scientist for the team.
Study Objectives	A study is a preliminary investigation regarding the relative benefit of 4 vs 8 weeks of treatment with disulfiram. With this initial study, the investigators will be able to evaluate the side effects, tolerability and initial signs of the effectiveness of disulfiram in reducing symptoms among the 24 patients assessed. The results of this study will guide the investigators regarding whether a larger definitive randomized trial should be conducted, and which treatment schedule is optimal.
Primary endpoint	Week 10 evaluation.
Study Design	A small 14-week randomized placebo-controlled pilot study enrolling 24 patients with persistent symptoms despite prior antibiotic treatment for Lyme disease (known as Post-treatment Lyme Disease Syndrome). Among the 24 disulfiram-treated patients, half will get 8 weeks of disulfiram and the other half will get a shorter duration of disulfiram for 4 weeks followed by 4 weeks of matching placebo. After week 8, patients will be off pills for 2 weeks for the primary week 10 evaluation and then for another 4 weeks for the week 14 follow-up evaluation. This will be a double-blinded study; neither physician nor patient will know which treatment group the patient is assigned to. For details see PSF.
General Study Population	See PSF respective section
Inclusion-Exclusion Criteria	See PSF respective section
Study Assessments	See PSF respective section
Sample size	24 as of 04/02/2019. The study was terminated in 2022 with a sample size of 11.
Randomization	This will be a double-blinded study; neither physician nor patient will know which treatment group the patient is assigned to. Randomization is performed at New York Psychiatric Institute pharmacy when medication is issued to an enrolled participant. Randomization is performed in blocked of 12. The study unblind will occur when the enrollment is completed, and all patients finish their follow-up assessments.
Primary aim#1	To assess the safety and side effect profile of disulfiram among patients with post treatment Lyme symptoms. This will be assessed by SAFTEE (systematically) as well as recording all unanticipated adverse events/serious adverse events.
Primary aim #2	To investigate whether treatment with disulfiram results in a meaningful reduction in fatigue and improvement in the quality of life among patients

	with Post- treatment Lyme Disease. Fatigue will be assessed by the Fatigue Severity Scale (FSS) and quality of life will be assessed with the Quality-of-Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q).
Secondary aims and Exploratory goals:	1. We will examine whether there is a difference in the proportion of responders on the fatigue scale among the 2 different dosing regimens (54 days over 8 weeks vs. 26 days over 4 weeks followed by placebo). We will assess both the percentage of responders and magnitude of the effect. 2. We will examine whether there is an improvement on the secondary outcome measures. 3. We will examine the side effect profile and drop-out rate associated with different treatment schedules of disulfiram. 4. We will examine whether there are other self-report measures that are more sensitive in documenting change over time than the FSS and the Q-LES-Q. These other measures, for example, include the PROMIS 29 v2.0 profile questionnaire, the SF-36, and the General Symptom Questionnaire (GSQ-30). 5. We will examine whether tests of sensory function, autonomic function, and cognitive function change with treatment. 6. We will examine whether the urine antigen marker of Borrelia burgdorferi (as assessed by the Ceres Nanoscience Urine Nanotrap assay) is present at baseline and not present after treatment. 7. We will collect biological samples for future precision medicine studies to be stored in our repository. 8. We will collect fecal samples to be probed by investigators interested in studying microbiome changes in response to disulfiram. 9. We will also monitor patients' activity via the data generated by Fitbit- The rationale for the Fitbit is that our primary outcome is fatigue. People who are less fatigued may be engaging in more activity, such as doing more steps during the day. Moreover, activity monitoring using a device such as a Fitbit is being increasingly used in research studies as a measure of the change in response to treatment.
Timing of Analysis	Analysis will be performed after the study is unblinded.
Analysis Population	We conduct intent to treat analysis which covers all enrolled patients who received a study drug and who participated in at least one post-baseline assessment.
Missing Data	Missing data is treated as missing at random
Interim Analyses and Data Monitoring	There is no interim analysis for the protocol.

Primary aim#1 analysis	Tables on all mortality rate, SAE and AE will be generated. To estimate safety, number of adverse events in active and sham treatment groups by the end of 10-week period will be computed and reported.
Primary aim#2 analysis	To investigate whether treatment with disulfiram results in a meaningful reduction in fatigue and improvement in the quality of life, a change in scores between the baseline and week 10 will be computed. We will calculate a number of participants who's change in score reached a minimal clinically significant difference (MCID) for each of the measures. MCID for Fatigue Severity Scale (FSS) and MCID for Quality-of-Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) is 6.8. A Log Odds ratio for 8-week and 4-week group will be computed along with the 95% confidence interval for this ratio. The 95% confidence interval provides considerably more information than testing a specific null hypothesis: it provides a range of plausible values for differences in these primary outcomes between treatment groups which can be used to inform research in larger studies.