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Study protocol for a randomised, double-blinded, placebo-controlled phase III trial examining the add-on efficacy, cost–utility and neurobiological effects of low-dose naltrexone (LDN) in patients with fibromyalgia (INNOVA study)

Ariadna Colomer-Carbonell,[1,2] Juan P Sanabria-Mazo,[1,2] Halbert Hernández-Negrín,[2,3] Xavier Borràs,[2] Carlos Suso-Ribera,[4,5] Azucena García-Palacios,[4,5] Jordi Muchart,[6] Josep Munuera,[6] Francesco D'Amico,[7] Michael Maes,[8] Jarred W Younger,[9] Albert Feliu-Soler,[10] Antoni Rozadilla-Sacanell,[11] Juan V Luciano[1,10]

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AC-C, JPS-M and HH-N are joint first authors.
AF-S, AR-S and JVL are joint senior authors.

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For numbered affiliations see end of article.

Correspondence to
Dr Juan V Luciano; juanvicente.luciano@uab.cat

ABSTRACT

Introduction There is evidence that low-dose naltrexone (LDN; <5.0 mg/day) reduces pain and improves the quality of life of people with fibromyalgia syndrome (FMS). However, no randomised controlled trials with long-term follow-ups have been carried out. The INNOVA study will evaluate the add-on efficacy, safety, cost–utility and neurobiological effects of LDN for reducing pain in patients with FMS, with a 1-year follow-up.

Methods and analysis A single-site, prospective, randomised, double-blinded, placebo-controlled, parallel design phase III trial will be performed. Eligibility criteria include being adult, having a diagnosis of FMS and experiencing pain of 4 or higher on a 10-point numerical rating scale. Participants will be randomised to a LDN intervention group (4.5 mg/day) or to a placebo control group. Clinical assessments will be performed at baseline (T0), 3 months (T1), 6 months (T2) and 12 months (T3). The primary endpoint will be pain intensity. A sample size of 60 patients per study arm (120 in total), as calculated prior to recruitment for sufficient power, will be monitored between January 2022 and August 2024. Assessment will also include daily ecological momentary evaluations of FMS-related symptoms (eg, pain intensity, fatigue and sleep disturbance), and side effects via ecological momentary assessment through the Pain Monitor app during the first 3 months. Costs and quality-adjusted life years will be also calculated. Half of the participants in each arm will be scanned with MRI at T0 and T1 for changes in brain metabolites related to neuroinflammation and central sensitisation. Inflammatory biomarkers in serum will also be measured.

Ethics and dissemination This study has been approved by the Ethics Committee of the Fundació Sant Joan de Déu. The results will be actively disseminated through peer-reviewed journals, conference presentations, social media and community engagement activities.

Trial registration number NCT04739995.

Strengths and limitations of this study

- This is thought to be the first randomised, double-blinded, placebo-controlled phase III trial to assess the efficacy, safety, cost–utility and neurobiological effects of low-dose naltrexone (LDN) for reducing pain in patients with fibromyalgia syndrome.
- The INNOVA protocol combines mobile-technology-based ecological momentary assessment and assessment with classical legacy measures to obtain more precise information on the dynamics of the assessed primary and secondary outcomes.
- This study will include immune and neuroimaging biomarkers in order to explore the neurobiological underpinnings of LDN.
- Challenges of the randomised controlled trial include the long follow-up period (1 year) and potential measurement burden that takes the risk of high dropout rate.

INTRODUCTION

Fibromyalgia: definition, prevalence and pharmaceutical indications

Fibromyalgia syndrome (FMS) is a chronic condition of unknown origin that is characterised by generalised musculoskeletal pain, fatigue, stiffness, cognitive problems, sleep disturbances and malaise.[1 2] This syndrome is highly prevalent in the general population

(2.7% worldwide).[3] Around 6% of adult patients who visit their general practitioner, and between 10% and 20% of those who visit rheumatology services, have FMS.[2] In 2007, the U.S. Food and Drug Administration approved pregabalin as the first drug indicated for the treatment of FMS, and later approved duloxetine and milnacipran for this indication. However, the European regulatory authorities rejected the indication of these three drugs in the treatment of FMS given the small effect sizes in various studies and the associated adverse effects.[4–6]

Pathogenesis of FMS

Although the aetiological factors of FMS are not known, the primary hypothesis of the pathogenesis of this syndrome highlights the role of the central nervous system in the amplification of pain perception as well as in the development of comorbid symptoms such as sleep-related problems, fatigue, cognitive difficulties and emotional distress.[1 7 8] Structural brain alterations have also been found in patients with FMS. For example, lower volumes of grey matter have been observed in areas associated with the processing of stress (eg, parahippocampal gyrus) and pain (eg, anterior cingulate cortex, insula, prefrontal cortex, and primary and secondary somatosensory cortices).[7] Functional MRI alterations have been associated with self-reported pain intensity. Brain activity exhibited greater connectivity between different pain-processing areas (eg, insula and secondary somatosensory cortex), the default-model network in persons with FMS, as well as in the association between these areas and the pain levels reported by patients and the right executive attention network.[9]

Altered functional connectivity has also been reported among various pain-inhibiting areas.[10] Some studies have reported reduced levels of neurotransmitters involved in the regulation of the descending analgesic response (serotonin and norepinephrine) and increased levels of glutamate (Glu) and substance P in people with FMS.[11–14] For example, high levels of Glu have been reported in the posterior insula, posterior cingulate cortex and prefrontal ventrolateral cortex of patients with FMS when compared with healthy controls.[15–19]

Activation of the microglia could be a contributing factor to the alteration of Glu neurotransmission in FMS.[20 21] The microglia is normally found in a state of rest but it is activated by a wide range of stimuli such as cell death, peripheral inflammation, chronic stress and infections.[22] Once activated, microglia release pro-inflammatory agents such as cytokines, excitatory amino acids and nitric oxide.[23] These inflammatory factors across multiple neural pathways can induce hyperalgesia, fatigue, depression and other symptoms which are known collectively as 'cytokine induced sickness behavior'.[24 25] Microglia activation might trigger a series of actions that lead to an increase in Glu that ultimately results in synaptic dysfunction.[26] A recent study using positron emission tomography[27] of translocator protein revealed a widespread cortical glial activation in patients with FMS, which gives support to the role of neuroinflammation in the aetiology of FMS. In addition, there is evidence that chronic stress facilitates the 'priming' and exaggerated activation of the microglia.[28]

Although FMS is not considered a classic inflammatory disease, there is extensive evidence that immune pathways play a significant role in the pathogenesis and maintenance of the syndrome. Cytokines play a key role in inflammatory response and in boosting the nociceptive response due to their sensitisation actions, both on a peripheral and central level.[29–32] Thus, there is evidence that FMS involves an imbalance in pro-inflammatory [eg, interleukin (IL)-1, IL-6, IL-17A and the tumour necrosis factor α (TNF-α)] and anti-inflammatory (eg, IL-4 and IL-10) levels of cytokines that could lead to a low-intensity, chronic state of inflammation. Bäckryd *et al*[30] identified both neuroinflammation and systemic inflammation by evaluating levels of a broad panel of cytokines and chemokines in cerebrospinal fluid and plasma.

Low-dose naltrexone (LDN): a promising treatment for FMS

Naltrexone is an opioid antagonist medication used to treat opioid and alcohol dependency. The drug blocks mu-opioid receptors, the delta-opioid receptors and, to a lesser extent, the kappa-opioid receptors. There is promising evidence to suggest that naltrexone administered in low doses (ie, LDN; <5 mg/day) is effective in the management of some pathologies which present with altered immune pathways, such as Crohn's disease, multiple sclerosis or FMS.[33 34] The immune-regulatory effect of LDN seems to be driven through the inhibition of the Toll-like receptor 4 (TLR-4) activity expressed in the membrane of various immune system cells (eg, microglia and macrophages).[33] Moreover, due to a 'rebound effect', LDN could exert an analgesic effect that strengthens the endogenous opioid pain inhibitory system. According to this hypothesis, the low-intensity and intermittent blockade of the opioid receptors generated by LDN induces a compensatory mechanism that facilitates an increase in the production of endogenous opioids and greater sensitivity of the system to their effects.[33 34]

To date, the effects of LDN in patients with FMS have only been evaluated through crossover pilot studies that have yielded preliminary results. In the first study conducted with LDN in FMS, significant reductions in pain, stress and fatigue levels were observed.[35] In a subsequent study, significant improvements in daily pain, satisfaction with life and mood were also observed.[36] In another crossover investigation, the pre and post changes in the levels of plasma cytokines were evaluated over 8 weeks. Significant reductions in a wide range of immune biomarkers were obtained (eg, IL-1β, sIL-1ra, IL-4, IL-6, IL-10, IL-17A and TNF-α), together with a reduction in the pain levels and the severity of FMS symptoms.[37]

While acknowledging the contribution of past studies into the field, these have included small sample sizes (n=8–31 participants) and crossover designs. Therefore, a single-site, prospective, randomised, double-blinded, placebo-controlled study (RCT) with a sufficiently powered sample is presented here to conduct a methodologically robust investigation into the role of LDN in FMS. Specifically, the main objective of the INNOVA study is to evaluate the efficacy, safety and cost–utility, and neurobiological effects of LDN to reduce pain in FMS. There is currently no gold standard pharmacological treatment for pain reduction in persons with FMS. Therefore, in the present study, placebo will be used instead of another drug in the control group.

METHODS AND ANALYSIS

Trial design

The randomised controlled trial (RCT) protocol has been developed following the Standard Protocol Items: Recommendations for Interventional Trials.[38] In addition, the RCT was approved by European Union Drug Regulating Authorities Clinical Trials (EudraCT; 2021-002534-16). For reporting purposes, we will follow the guidelines of the Consolidated Standards of Reporting Trials[39] and the Consolidated Health Economic Evaluation Reporting Standards statement.[40] INNOVA is a 12-month double-blind RCT with two arms: LDN versus placebo. LDN will be considered an add-on treatment to the usual care provided in the Spanish National Health System for FMS. For transparency and analytical reproducibility purposes, the dataset and data coding will be deposited in the Open Science Framework.

Sample size

There are no previous RCTs about the efficacy of LDN for FMS; therefore, we estimated the sample size taking into account a previous LDN crossover study[36] that had used self-reported pain as main outcome (the effect size was d=0.99). Thus, with a sample of 60 participants per arm, we aim to detect between-group differences with a significance level of 5% and a power of 80%. Allowing for a potential attrition rate of 20%, our final sample size is 60 participants per group. For the analysis of biomarkers (involving 50% of the sample), an initial sample size of 30 patients per arm is considered sufficient according to previous studies.[37 41]

Eligibility criteria

General selection criteria

All participants will meet the following inclusion criteria: women between 18 and 70 years; diagnoses of FMS according to American College of Rheumatology (ACR) 2016 criteria[42] by a rheumatologist; pain intensity ranked ≥4 out of 10 on a 10-point numerical rating scale in the past week; fluent in Spanish; provision of written informed consent; stable pharmacological treatment in the last 2 months; and having a smartphone with android operating system for ecological momentary assessment (EMA). Potential participants will be excluded according to the following exclusion criteria: treatment with naltrexone, opioids, anticoagulants or central antihypertensives in the last 3 months; diagnosis of severe medical/psychiatric disorders (eg, cancer, haematological diseases, abnormal hepatic/liver function, renal failure, suicide ideation, psychotic disorder); pregnant (or planning to become pregnant during the study period) or breast feeding; known allergy to naltrexone, naloxone or excipients; currently participating in other RCTs; ongoing litigation related to FMS.

Additional selection criteria for the biomarkers and neuroimaging substudy (50% of patients in each study arm)

All participants will meet the following inclusion criteria: right-handed (for the neuroimaging tests); and no comorbid rheumatologic conditions (eg, rheumatoid arthritis, lupus). Potential participants will be excluded according to the following exclusion criteria: fever (>38°C); infection in the last 2 weeks; vaccination in the last month; taking cortisone or anticytokine therapy; needle phobia or claustrophobia, metal implants or pacemakers; body mass index ≥36 kg/m^2; smoking over 5 cigarettes/day; presence of acute pain (eg, headache or back pain) unrelated to FMS on the day of the scan.

Recruitment strategy, procedure and randomisation

Patients diagnosed with FMS with an appointment at the Rheumatology Service of Parc Sanitari Sant Joan de Déu (St. Boi de Llobregat, Spain) will be invited to participate in the study and will be asked to attend a screening evaluation with a research assistant and a clinician. Once the informed consent is obtained, the clinician will review the study selection criteria to confirm eligibility. The week after, a face-to-face assessment (T0) including clinical history and variables related to the use of services will be conducted with those patients meeting all the eligibility criteria. Only the participants that are included in the biomarkers substudy will require an additional blood extraction and neuroimaging scan, which will be performed in the following 3–5 days. Participants will be given a sealed envelope with an identifying code which they will have to take to the pharmacy service. There, they will be given the dose of the corresponding drug (according to the randomisation) for the first 3 months (90 tablets). As shown in the patients' flow chart (figure 1), further in-person evaluations will be performed at 3 months (T1), 6 months (T2) and 12 months (T3). Neurobiological variables will be obtained at T1 using the same protocol as in the baseline assessment (T0).

Participants will be asked to abstain from taking any analgesic or anti-inflammatory drug in the 72 hours prior to the blood extractions/scans. All patients, including those who do not participate in the biomarker substudy, shall be subjected to a blood test at baseline. Participants will return to the pharmacy service every 3 months and will be given the assigned amount of LDN/placebo for the following 3 months (approximately 90 tablets). Unconsumed tablets will be returned for treatment adherence monitoring. The randomisation to conditions will be conducted by a biostatistician from the Clinical Trials

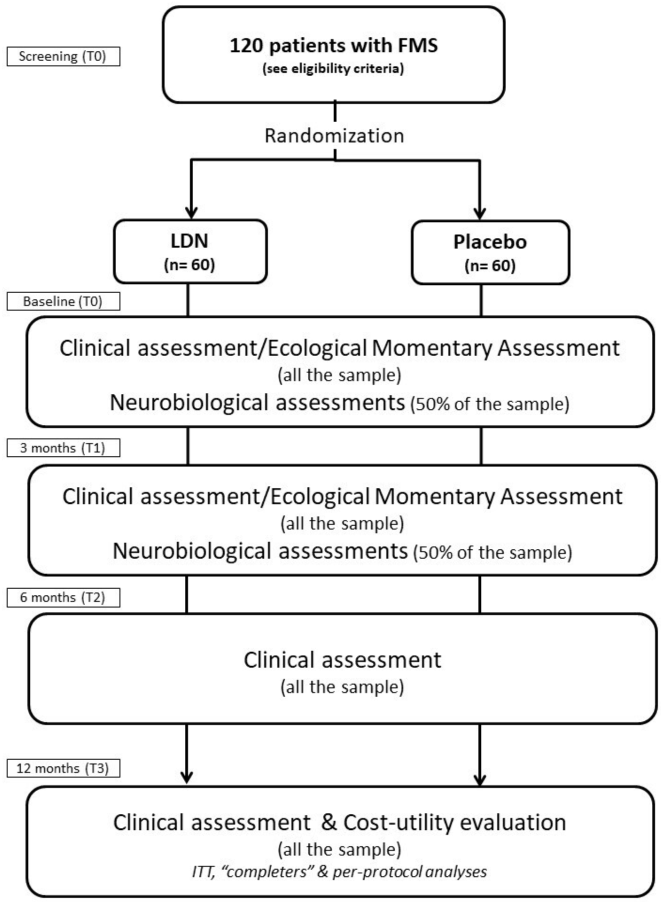

Figure 1 Flow chart of the INNOVA study based on the Consolidated Standards of Reporting Trials guidelines. FMS, fibromyalgia syndrome; ITT, intention-to-treat; LDN, low-dose naltrexone.

Unit of Fundació Sant Joan de Déu who has no involvement in the eligibility screening, enrolment and treatment processes. The computer-generated randomisation will apply a permuted block design to ensure that the study arms are balanced taking the biomarkers substudy eligibility criteria into account. As this is a double-blind RCT, neither the patient nor the evaluator or the clinician will know to which treatment arm each patient has been assigned. Only the clinical trial pharmacist who stores and delivers capsules, but is not involved in patient care, will know the allocation.

Data management, central monitoring and audit

The clinical data entry, data management and central monitoring will be performed with REDCap. An independent Clinical Research Organization (CRO) will be responsible for overseeing the intrastudy data sharing and storing process. Any modifications in the study protocol will be communicated to the CRO.

Treatments

Low-dose naltrexone

The intervention group will take one 4.5 mg naltrexone tablet (lactose-free) daily for 12 months before going to sleep.

Placebo

The control group will take the placebo daily for 12 months (a film-coated tablet identical to the LDN and filled with a lactose-free filler). For the control arm, the same guidelines will be followed.

In order to maintain the external validity of the study and for ethical reasons, the study participants' active treatments will be unchanged by this clinical trial. In Spain, chronic pain management is mainly managed by general practitioners in regular consultations. These generally consist of face-to-face appointments with a duration of 5–10 min in which the clinicians monitor the physical and, ideally, the emotional status of the patient. General practitioners usually provide advice prescribe pharmacotherapy (pain killers, hypnotics, antidepressants, etc) or refer patients to pain units in tertiary hospitals when more specialised pain management procedures are required. The frequency of consultations is based on the type of disease and its severity. In this study, usual care will be the same as in routine daily practice, without any modifications. In addition, participants will be allowed to withdraw from this study for any reason at any time without detriment to the provision or quality of their usual care. If a severe adverse event (AE) occurs, unblinding will be possible and study participation will be discontinued. If the adverse effects are tolerable, the treatment will be administered until the end of the study. All these events will be recorded and reported at the end of the study.

Study measures

All participants will be assessed with a computer-administered battery of measures using the REDCap software (see table 1).

Measures for sociodemographic characteristics, clinical features and screening

A *sociodemographic questionnaire* will be used to obtain information about the following variables: gender, date of birth, marital status, living arrangements, educational level, income level and employment status.

The *Clinical data* interview will be used to collect information about history and duration of FMS symptoms, as well as family history of medical/mental illness. Information regarding comorbidity with other diagnosed physical-psychiatric conditions and the type and dose of current drugs will be checked from medical records.

The *Fibromyalgia Survey Diagnostic Criteria*[43 44] is a 6-item self-report measure of the core FMS symptoms according to the latest revision of the ACR 2016 criteria.[42] It includes two subscales: the Widespread Pain Index, which is used to identify the presence of pain in 19 body areas in the last week, and the Symptom Severity Scale, in which the three major FMS symptoms (fatigue, 'fibrofog' and waking up tired) are assessed along with three additional symptoms (pain in the lower stomach, depression and headache). A total score is obtained by adding the two subscales. This total score ranges from 0 to 31, where higher values indicate greater FMS severity.

Measures	T0 (baseline)	T1 (3-m)	T2 (6-m)	T3 (12-m)
Sociodemographic, clinical and screening measures				
Sociodemographic data	X			
Clinical data (years of evolution, comorbidities, etc)	X			
FSDC screening and secondary outcome measure (fibromyalginess)	X	X	X	X
Primary outcome measure				
NRS (pain intensity)	X	X	X	X
Secondary outcome measures				
FIQR (functional impairment)	X	X	X	X
DASS-21 (anxiety, depression, and stress)	X	X	X	X
MISCI (subjective cognitive impairment)	X	X	X	X
WHODAS 2.0 (disability)	X	X	X	X
GAD-7 (general anxiety/worry)	X	X	X	X
Other measures				
EQ-5D-5L (quality of life)	X			X
CSRI (medication consumption and service receipt)	X			X
PGIC and PSIC (impression of change)		X	X	X
ACTTION checklist (adverse events throughout the trial)	X	X	X	X
Pain Monitor app (EMA)	X	X		
Physiological variables				
Immune biomarkers	X	X		
Neuroimaging	X	X		

Table 1 Time points for data collection

ACTTION checklist, Analgesic, Anesthesic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks; CSRI, Client Service Receipt Inventory; DASS-21, Depression Anxiety Stress Scales-21; EMA, ecological momentary assessment; EQ-5D-5L, EuroQoL 5 Dimension 5 Level; FIQR, Fibromyalgia Impact Questionnaire Revised; FSDC, Fibromyalgia Survey Diagnostic Criteria; GAD-7, Generalised Anxiety Disorder 7-Item Scale; MISCI, Multidimensional Inventory of Subjective Cognitive Impairment; NRS, Numerical Pain Rating Scale; PGIC and PSIC, Patient Global Impression of Change and Pain Specific Impression of Change; WHODAS 2.0, 12-item interviewer administered version of the WHO Disability Assessment Schedule 2.0.

Primary outcome measure

The *Numeric Rating Scale*[45] is a unidimensional measure of pain intensity mainly used for adults. The most frequently used version is an 11-point numeric scale (a horizontal bar or line) scored from 0 ('no pain') to 10 ('worst pain imaginable'). Time frames vary between studies. In the present study, respondents will be asked to report average pain intensity over the last week.

Secondary outcome measures

The *Revised Fibromyalgia Impact Questionnaire* (FIQR)[46] includes 21 items that are answered on a 0 to 10 numerical scale in which higher scores indicate greater functional impairment. The questionnaire asks about the previous 7 days. The items are distributed into three domains: physical impairment, overall impact and severity of symptoms (ie, pain, energy, stiffness, sleep quality, depression, memory issues, anxiety, pain to the touch, balance problems and increased sensitivity to noises, lights, smells or temperatures). A total score is obtained by summing the three subscale scores. This can range from 0 to 100. Higher scores indicate greater impairment. The Spanish version of the FIQR has obtained high internal consistency estimates (α=0.91–0.95), adequate test–retest reliability indices (r=0.82) and good construct validity.[47]

The *Depression Anxiety Stress Scales-21* (DASS-21)[48] is a self-report scale developed to discriminate between features of depression (anhedonia/low positive affect), anxiety (physical arousal) and stress (psychological tension/agitation) in clinical and non-clinical samples. The DASS has been validated in patients with FMS.[49] Responders are required to indicate the presence of a symptom over the previous week. Each item is scored from 0 ('did not apply to me at all over the last week') to 3 ('applied to me very much or most of the time over the past week'). There are seven items on each of the three subscales: depression, anxiety and stress. Therefore, total scores in each scale can range from 0 to 21. Higher scores indicate more severe levels of depression, anxiety and stress. The Spanish version showed adequate internal consistency for depression (α=0.84), anxiety (α=0.70) and stress (α=0.82).[50]

The *Multidimensional Inventory of Subjective Cognitive Impairment* (MISCI)[51] is a 10-item self-report measure of subjective cognitive dysfunction (ie, fibrofog) in FMS. Each item is scored from 1 ('never') to 5 ('very often') and the total score ranges from 10 to 50. Lower scores indicate higher cognitive dysfunction. The MISCI showed excellent internal reliability, low ceiling/floor effects and good convergent validity with a similar measure. The Spanish version of the MISCI had sound psychometric properties (α=0.91 and intraclass correlation coefficient, ICC=0.88).[52]

The *WHO Disability Assessment Schedule 2.0* (WHODAS 2.0)[53] is a 12-item self-report measure of the level of difficulty experienced taking into consideration how they usually do the activity. This includes the use of any devices to assist them and/or the help of a person. In each item, individuals estimate the magnitude of the disability during the previous 30 days using a 5-point scale scored from 1 (none) to 5 (extreme/cannot do). The total score ranges from 0 to 100. Higher scores reflect greater disability. The 12-item WHODAS 2.0 has sound psychometric properties in patients with FMS.[54]

The *Generalized Anxiety Disorder 7-Item Scale* (GAD-7)[55] is a 7-item self-report measure of pathological worry. Each item is scored from 0 ('not at all') to 3 ('nearly every day'). The total score ranges from 0 to 21, where higher scores reflecting greater anxiety symptoms. The GAD-7 has sound psychometric properties (α=0.92 and ICC=0.83) in patients with FMS in previous studies.[56]

Other measures

The *ACTTION AE* is a *reporting checklist* used to measure safety and benefit-risk of a clinical trial.[57] The Safety and Benefit-Risk Reporting and Evaluation Working Group of the Analgesic, Anaesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION; http://www.acttion.org) public–private partnership with the FDA developed an AE reporting checklist that will be used in the present study.

The *EuroQoL* (version EQ-5D-5L)[58] is a health-related quality of life questionnaire that consists of two parts. In the first one, the individual's difficulties concerning mobility, self-care, pain/discomfort and anxiety/depression are evaluated. In the second part, the perceived health is assessed by means of a Visual Analogue Scale ranging from 0 to 100. The EQ-5D-5L scores will be used to calculate the quality-adjusted life years (QALYs) during the follow-up period by adjusting the duration of time affected by the health outcome by the value of the utility.

The *Client Service Receipt Inventory* (CSRI)[59] is a self-report tool used to collect retrospective data on medication consumption and service receipt. Patients are asked to bring their daily medication prescriptions and information about pain-related drugs (analgesics, anti-inflammatories, opioids, muscle relaxants, antidepressants, etc) is recorded. This includes the name of the drug, the dosage, total number of prescription days and daily dosage consumed. Concerning service receipt, patients are asked about the total appointments for accident and emergency services, total number of general inpatient hospital admissions, number of diagnostic tests administered and total appointments with healthcare professionals for pain management (family physicians, nurses, social workers, psychologists, psychiatrists, group psychotherapy and other community healthcare professionals). The CSRI will be administered on two occasions: at baseline and at 12-month follow-up, both referring to the previous 12 months. Medical records will be checked to verify the accuracy of the collected data.

The *Patient Global Impression of Change* measures meaningful change in overall status and the *Pain Specific Impression of Change*[60] measures the perception of pain improvement. The most frequently used scale is a 7-point numerical scale scored from 1= 'much better') to 7= 'much worse').

Ecological momentary assessment

Pain intensity and other pain-related variables (eg, depressive-anxious symptoms and activity level) can fluctuate during the day and across days depending on personal and environmental factors. Collecting self-reported data prospectively and closer in time to its occurrence substantially improves the accuracy, reliability and quality of data. EMA has been successfully performed in patients with a variety of physical and mental problems.[61 62] There is growing evidence indicating that well-designed smartphone apps can be easy to use and well-tolerated even in relatively old pain populations, with compliance rates as high as 85%.[61] In this RCT, we will use the Pain Monitor (Monitor de Dolor, by its Spanish name) app[63] to assess a wide range of variables (see items in table 2) twice a day (once in the morning and once in

Table 2 List of items administered via Pain Monitor app

Items	Morning	Evening
Pain intensity	X	X
Fatigue	X	X
Perceived control over pain	X	X
Depression	X	X
Anxiety	X	X
Stress	X	X
Sleep disturbance	X	
Activity level		X
Interference with leisure activities		X
Interference with work-related activities		X
Adverse effects		X
Rescue medications		X

The Pain Monitor app automatically informs patients when to respond (by default, at 11:00 and 19:00) using a push notification system, but patients can respond with a margin of 2 hours from given times. Collected data are stored on a secure server at the Jaume I University, Spain.

the evening, at convenient times along the week) during 120 days. The app and the data will be stored on different servers with different domain names and connected locally only (the server containing the data does not have Internet access). According to a recent meta-analysis,[64] EMA-completion rates are higher among elderly patients compared with younger patients. Considering that the majority of FMS patients in our study are not expected to be young and that the EMA item battery does not require a long response time (<1 min), it is expected not to place an excessive burden on participants.

Inflammatory biomarkers

After obtaining the blood sample, it will be allowed to coagulate for a minimum of 30 min at room temperature. It will then be centrifuged for 10 min at 1000g. The resulting serum will be stored at −80°C during the same morning of extraction until it is ready to be analysed. All samples (at T0 and T1) will be analysed in a single analytical batch to reduce interassay variability (approximately 15%). The serum levels of IL-1β, sIL-1ra, IL-4, IL-6, sIL-6r, sgp130, CXCL-8, IL-10, IL-17, TNF-α and high-sensitivity (hs) C reactive protein will be evaluated.[29] For the quantification of the cytokines, the Milliplex reagents from the company MerckMillipore will be used and analysed using a Luminex platform. The high sensitivity multiplex kit will be used: Human High Sensitivity T Cell, catalogue number: HSTCMAG28SPMX11, adapted to the aforementioned cytokines. The hs-PCR will be quantified using turbidimetry in an Olympus AU5400 auto-analyser. These biomarkers will only be evaluated at baseline (T0) and 3 months (T1) for the following reasons: (1) there is evidence of significant inflammatory changes at 8 weeks with LDN[37]; (2) this results in lower risk of dropout (vs evaluating them at 6 or 12 months); (3) conducting at least two measures allows to use the change between baseline and 3 months as a mediator of long-term clinical changes; and (4) budget constraints.

Neuroimaging

The scans (protocol duration: approximately 30 min) will be performed in a Phillips Ingenia 3T MRI scanner with a 32-channel head coil at Hospital Sant Joan de Déu (Esplugues de Llobregat, Spain). To examine cingulate, insular, amygdalar, occipital, angular, parahippocampal and prefrontal grey matter volume, we will use voxel-based morphometry (VBM). We will also use surface-based morphometry (with FreeSurfer calculation of cortical thickness, surface area and local gyrification index) for examining cortical abnormalities. Additionally, Glu, glutamine, myo-inositol, N-acetylaspartate, choline and creatine (and creatinine ratios) levels will be analysed using magnetic resonance spectroscopy. Specifically, we will conduct the following processing for the regions of interest according to the corresponding hypotheses. For VBM, we will apply a bias field correction, tissue segmentation with SPM12 plus normalisation with Diffeomorphic Anatomic Registration Through Exponentiated Lie algebra (**DARTEL**). We will use both unmodulated and modulated grey matter images to convey complementary volumetric information. We will use FreeSurfer ENIGMA pipelines to perform the VBM. In addition, we will quantify metabolites concentrations using LCModel (V.6.3-1J). We will only include high-quality spectra, defined as signal-to-noise ratio >15, Cramer-Rao lower bounds< 15% and full width at half-maximum of metabolites <0.07. The spectroscopy analysis will account for the effects of cerebrospinal fluid and grey matter within the voxel, and interindividual differences in cortical grey matter.

Statistical analysis

The main analysis will compare the effect of LDN versus placebo on the primary outcome (pain intensity at T1). Data analyses will be performed following an intention-to-treat plan. Then, we will compute analysis of the primary outcome (at T2 and T3) and analysis of the secondary outcomes at T1, T2 and T3. Linear mixed models will be created using the restricted maximum likelihood method for the estimation of parameters. The effect sizes will be calculated according to Cohen's d. An interim analysis is planned at T1 once 50% of the total sample has been evaluated. A 5% significance level will be used in all two-tailed tests, applying the Benjamini-Hochberg correction for multiple comparisons. Additionally, to make the findings from our study clinically meaningful, the number needed to treat will be reported. For this analysis, we will dichotomise participants into responders or non-responders using two different cut-off criteria in compliance with the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations[45]: at least 50% pain relief over baseline (substantial benefit) or 30% or more pain relief (moderate benefit). For these analyses, we will use SPSS V.26 (IBM Corp).

Regarding EMA, a recent recommended approach is 'network analysis'. There has been burgeoning interest in conceptualising chronic pain as a network of interacting symptoms and psychobiological processes.[65] Network analysis will offer us a good chance to quantify and visualise relationships between pain intensity and pain-related variables (eg, depression, anxiety, fatigue, sleep disturbance). We will estimate temporal networks by means of vector autoregression techniques[66]; these 'temporal networks' would indicate potential causality with one or more variables preceding one or more variables in time. Network analysis will be performed with the free statistical software JASP.[67]

In economic evaluation, it is important to calculate the relationship between the costs of each treatment and its consequences in the form of QALYs, an index measure designed to assess both quantity of life (years) and health-related quality of life. A year lived with the maximum quality of life would be transformed into 1 QALY; a year lived with half the maximum quality of life would be transformed into 1/2 QALY. This relative value is called the incremental cost–utility ratio (ICUR) and it expresses the relationship between the costs and the effects of one option compared with another. The QALYs obtained in the 12 months after the treatment onset will be calculated by the area under the curve. The direct costs will be calculated by adding together the costs derived from the medication and the use of the health services. The cost of medications will be calculated by multiplying the price per milligram by the total daily dose consumed (in milligrams) and the number of days that the treatment is received. The cost arising from the use of the health services (primary care, specialist and accident and emergency consultations, and hospital admissions) will be obtained from the clinical electronic records (http://www.oblikue.com/en/esalud.html). The indirect costs will be calculated based on the days off work, which will be multiplied by the official minimum wage during the study period. The effect of the treatments will be estimated using ordinary least squares multivariate regression, adjusting for the baseline differences between groups. In order to manage uncertainty in the sampling distribution of the ICUR, non-parametric bootstrapping will be applied, with 1000 replications in each comparison. Cost–utility analyses will be conducted with STATA V.16.0 (StataCorp).

Patient and public involvement

Patients and the public will not be involved in the design, conduct, reporting or dissemination of our research.

ETHICS AND DISSEMINATION

All procedures performed in this study will be in accordance with the 1964 Helsinki declaration and its last amendments (7th revision, adopted by the 64th World Medical Association General Assembly, Fortaleza, Brazil). Signed informed consent will be obtained from all patients once they have been informed of the study procedures, potential risks, and their right to withdraw at any time from the RCT. The FSJD Ethics Committee Board evaluated and approved the study protocol in June 2021 (PIC-178-19). Only the principal investigators (AR-S and JVL) will have full access to the final trial dataset. Modifications in the study protocol will be reported to the FSJD Ethics Committee Board as well as the independent CRO.

Once the RCT is completed, we will publish our results in international peer-reviewed biomedical journals and present them at national and international conferences. Authorship will be assigned in accordance with the International Committee of Medical Journal Editors guidance. In addition, we will send participating patients a short report of our findings. A copy of the report will also be sent to Institute of Health Carlos III (main funding body). The principal investigators will organise an end-of-study seminar. The main objective of this activity will be to share the study findings with stakeholders to discuss how to maximise uptake of the findings in patient treatment and clinical practice, and to determine future research directions.

DISCUSSION

As far as we know, no RCT has been published about the efficacy, safety, cost–utility and neurobiological underpinnings of LDN in patients with FMS. This manuscript presents the design and rationale of a randomised, double-blinded, placebo-controlled phase III study, which is a powerful design to assess the efficacy of LDN. We have decided to administer 4.5 mg/day of LDN in this RCT because this dose seems to provide an optimal balance between significant analgesic efficacy and minimal side effects (nausea, sleep disturbance, nightmares, etc) according to a recent study.[68]

Our findings using this design in conjunction with those that will be obtained in another ongoing RCT that is being carried out in Denmark (The FINAL study)[69] may facilitate the approval of the first drug indicated for the treatment of FMS in Europe. The FINAL study is an ongoing single-centre, randomised, double-blinded, placebo-controlled trial that is being carried out in Odense (Denmark). A total of 100 women between 18 and 64 years old with FMS will take either LDN or placebo for 3 months. Besides self-report measures, Danish researchers will also examine the levels of pro-inflammatory and anti-inflammatory cytokines. If our respective findings strongly differ in efficacy or safety, we might analyse which factors can account for the divergence and plan a multicountry confirmatory trial with an agreed design and methodology. As pointed out by Kim and Fishman,[70] a common problem with a generic, compounded medication is the lack of commercial support for research. To begin studies such as INNOVA or FINAL, it is crucial to have the synergistic support from public funding bodies, private entities and commercial companies. This has been the case in the present study, with different public and private organisations providing economic and logistic support.

The inclusion of brain and blood immune biomarkers will allow us to determine whether LDN modulates neuroinflammatory processes involving inflammatory cells such as glial cells. These markers will also allow us to explore the 'hormetic' effects of the drug, that is, if a low dose of an antagonist (naltrexone) may paradoxically act as an agonist of the endogenous opiate system. As explained above, it is posited that LDN mainly acts as an immunomodulatory drug via blockade of TLR-4, which provides a therapeutic pathway to reduce activation of the inflammatory cascade and the nociceptive system.[71] In a recent pilot study,[72] patients with opioid induced hyperalgesia and patients with FMS were treated with LDN for 3 months. Via different mechanisms of action, LDN improved pain tolerance (measured with the cold pressor test) in both groups of patients, being the effect even stronger in those participants with opioid induced hyperalgesia. According to the authors, the mechanism of action that would explain the beneficial effects of LDN for FMS may be transient blockade of the opioid growth factor receptor.

Obtaining empirical evidence for cost–utility of treatments or interventions is required by the Ministry of Health in Spain for reimbursement. In Spain, a threshold of €22 000–25 000 per QALY gained is found to be consistent with decisions of adopting new technologies by the

National Health Service.[73] To our knowledge, there is an absence of economic evaluations for LDN; therefore, an important feature of the present study is the cost–utility assessment of the drug.

FMS remains a chronic, debilitating and difficult to manage condition for many individuals around the world. After three decades of intensive research, the clinical benefits of pharmacological treatments remain unclear and limited. This study will evaluate the analgesic efficacy, safety and cost–utility of LDN using a rigorous and powered design. If efficacious and cost-effective, LDN might be the first drug approved for FMS in Europe.

Trial status

This study is currently in the recruitment phase. The first patient will be enrolled in January 2022, and the study is expected to end in August 2024.

Confidentially

Personal data will be stored in accordance with the Spanish regulation guidelines for clinical research. Participants will be allocated a unique identification (ID) number at entry. The master list linking participant personal information and ID number will be maintained in a password-protected hard drive at the Parc Sanitari Sant Joan de Déu (PSSJD; St. Boi de Llobregat, Spain). Data will be stored for 10 years after study completion.

Author affiliations
[1]Teaching, Research & Innovation Unit, Parc Sanitari Sant Joan de Déu, St. Boi de Llobregat, Spain
[2]Department of Basics, Developmental and Educational Psychology, Autonomous University of Barcelona, Cerdanyola del Vallès, Spain
[3]Universidad de Ciencias Médicas de Villa Clara, Santa Clara, Cuba
[4]Department of Basic and Clinical Psychology and Psychobiology, Universitat Jaume I, Castello de la Plana, Spain
[5]Biomedical Research Centre in Physiopathology of Obesity and Nutrition (CIBERobn), Madrid, Spain
[6]Diagnostic Imaging Department, Hospital Sant Joan de Déu, Esplugues de Llobregat, Spain
[7]Personal Social Services Research Unit, London School of Economics and Political Science, London, UK
[8]Department of Psychiatry, Chulalongkorn University, Bangkok, Thailand
[9]University of Alabama at Birmingham, Birmingham, Alabama, USA
[10]Department of Clinical and Health Psychology, Autonomous University of Barcelona, Cerdanyola del Vallès, Spain
[11]Department of Rheumatology, Parc Sanitari Sant Joan de Déu, St. Boi de Llobregat, Spain

Contributors JVL, AR-S and AF-S conceived the study and revised the manuscript. JVL drafted the manuscript. AC-C, JPS-M, HH-N, XB, CS-R, AG-P, JorM, JosM, FD, MM, JWY, AF-S and AR-S provided feedback on the manuscript, and all authors reviewed and approved the final version of the manuscript.

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ORCID iDs
Xavier Borràs http://orcid.org/0000-0003-3972-1385
Juan V Luciano http://orcid.org/0000-0003-0750-1599

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