Efectivitat, cost-utilitat i efectes neurobiològics en fibromiàlgia de la natrexona a dosis baixes (**Projecte INNOVA**)

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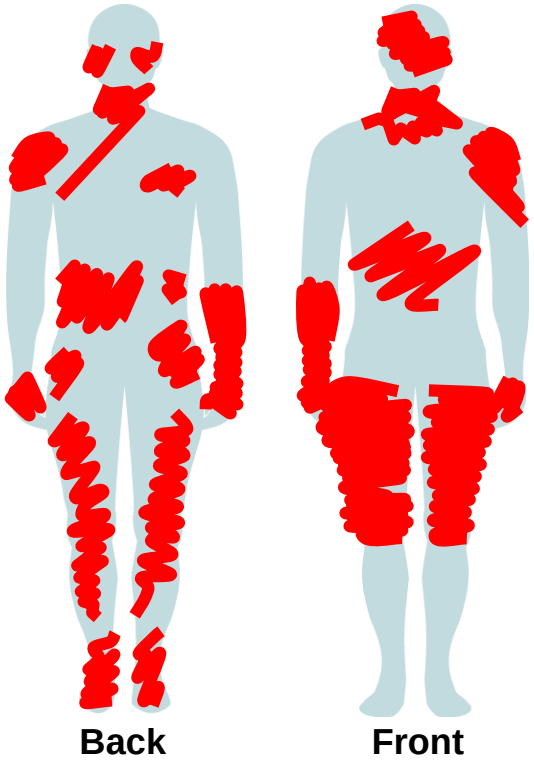
Parc Sanitari Sant Joan de Déu (Sant Boi de Llobregat)

Red de Investigación en Actividades Preventivas y Promoción de la Salud (redIAPP)

Widespread pain in patients with fibromyalgia

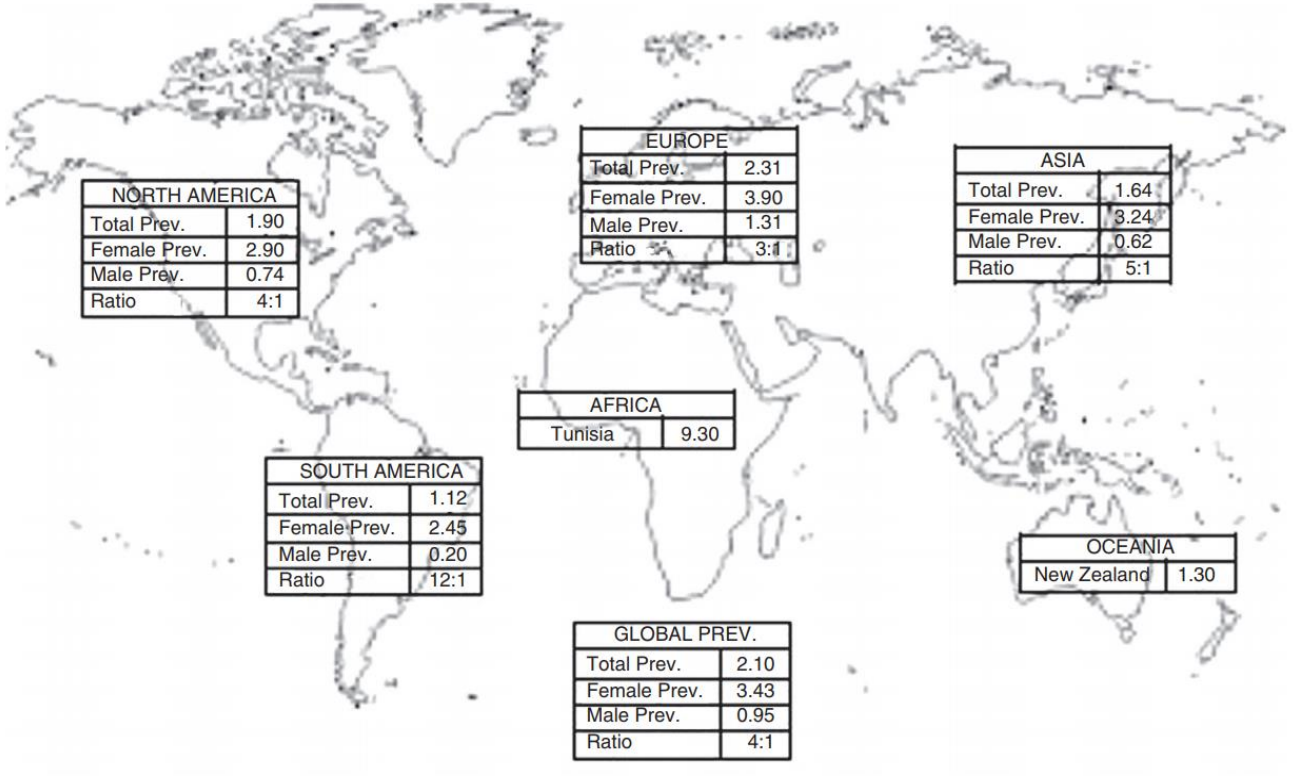
ACR (1990)
(1) A history of widespread musculoskeletal pain for at least 3 months and
(2) Patient report of tenderness in at least 11 of 18 defined tender points when digitally palpated with about 4 kg per unit area of force.

- While the ACR classification criteria in 1990 focused on 18 points, patients do not usually report tender points
- This is a pain drawing—a patient colors all areas of the body in which they feel pain
- The diagram shows that the pain of FM is widespread



ACR = American College of Rheumatology

Wolfe F, et al. *Arthritis Rheum*. 1990: 33: 160-172.
Silverman SL & Martin SA. In: Wallace DJ, Clauw DJ, eds. *Fibromyalgia & Other Central Pain Syndromes*. Philadelphia, Pa: Lippincott, Williams & Wilkins; 2005:309-319.



Fibromyalgia in Spain would affect an estimated total of **1,117,368 people**

Economic costs: In Spain is has been estimated at more than **13,000 million Euros annually**

EXTENDED REPORT

Comparative efficacy of pharmacological and non-pharmacological interventions in fibromyalgia syndrome: network meta-analysis

Eveline Nüesch,[1,2] Winfried Häuser,[3,4] Kathrin Bernardy,[5,6] Jürgen Barth,[1] Peter Jüni[1]

Pharmacological interventions

SNRIs and pregabalin more effective than placebo on pain and quality of life.

But, questionable clinical relevance!

Non-pharmacological interventions

Multicomponent therapy followed by aerobic exercise and Cognitive Behaviour Therapy (CBT) are the most effective for reducing pain and improving quality of life.

Small-moderate effect-sizes!

EXPERT OPINION ON INVESTIGATIONAL DRUGS, 2016
VOL. 25, NO. 9, 1071–1081
http://dx.doi.org/10.1080/13543784.2016.1197906

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REVIEW

Potential drug therapies for the treatment of fibromyalgia

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WJP World Journal of Pharmacology

Submit a Manuscript: http://www.wjgnet.com/esps/

World J Pharmacol 2017 March 9; 6(1): 1-10

DOI: 10.5497/wjp.v6.i1.1

ISSN 2220-3192 (online)

MINIREVIEWS

Emerging pharmacological strategies for the treatment of fibromyalgia

Kim Lawson

Table 1. Emerging drug therapies with potential efficacy for the treatment of fibromyalgia.

Drug	Mechanism of action	Domains accessed	Trial sponsor	Status
AGN203818	α2 adrenergic agonist	Pain	Allergan	Terminated 2015, outcome not published
Agomelatine	Melatoninergic receptor agonist and 5-HT2 receptor antagonist	Pain, mood, cognitive function	University of Messina	Phase II, improved pain and mood
Capsaicin	Transient receptor potential vanilloid 1 subunits (TRPV1)	Myalgic, pain, fatigue scores	Rheumatology Service at the Specialist Clinic of Cantabria	Phase II, improved symptoms
Casopitant (GW679769)	Neurokinin1 receptor agonist	FIQ	GlaxoSmithKline	Phase II completed
Dolasetron	5-HT3 receptor antgonist	Pain, fatigue, quality of life	University Hospital of Limoges, France	Phase II, reduced pain only
Dronabinol	Cannabinol	Pain, depression, quality of life	Heidelberg University	Phase II, reduced pain and depression
Droxidopa	Noradrenaline prodrug	Pain, FIQ	Chelsea Therapeutics	Phase II, improved symptoms
DS-5565	α2δ ligand	Pain	Daiichi Sankyo	Phase II planned
EMA401	Angiotensin II receptor antagonist	Pain	Spinifex	Phase II planned
Esreboxetine	Noradrenaline reuptake inhibitor	Pain, FIQ, fatigue, quality of life	Pfizer	Phase II, improved symptoms
Flupirtine	Potassium channel activation	Pain, FIQ	Lupin	Phase II planned
IMC-1	Viral suppression of herpes virus	Pain, fatigue, FIQ	Innovative Med Concepts	Phase II, improved symptoms
Levetiracetam	Synaptic vesicle glycoprotein ligand	Pain	UCB Pharma and University of California	Phase II, inconclusive outcomes
Memantine	NMDA antagonist	Pain, cognitive state, depression	Aragon Institute of Health Sciences	Phase II, improved symptoms
Mirtazapine (Org 3770)	Adrenergic and serotonin receptor antagonist	Pain, FIQ	Meiji Seika Pharma Co., Ltd.	Pilot, reduced pain, and FIQ scores
Nabilone	Cannabinoid receptor agonist	Pain, sleep, quality of life	Winnipeg Regional Health Authority	Phase II, improved symptoms
Naltrexone	Opioid receptor antagonist	Pain, fatigue, mood, sleep	Stanford University	Phase II, improved pain and mood
Neurotropin	Neuromodulator	Pain	*Yukioka Hospital, Osaka*	Phase II, reduced pain
Paroxetine	Serotonin reuptake inhibitor	Pain, mood, sleep, functionality	Duke University Medical Center, USA and GlaxoSmithKline	Phase II, improved symptoms
Pramipexole	Dopamine agonist	FIQ	Boehringer Ingelheim	Phase II, improved symptoms
Quetiapine	Antipsychotic	FIQ	East Tennessee State Uni and Astra Zeneca	Phase II benefits limited to patient subgroup
TD-9855	Noradrenaline serotonin reuptake inhibitor	Pain, fatigue, FIQ	*Theravance Biopharm*	Phase II, improved symptoms
TNX102SL cyclobenzaprine	Noradrenaline, serotonin reuptake inhibition	Pain, sleep	Tonix Pharmaceuticals	Phase II improved symptoms
Trazodone	5-HT receptor antagonist and serotonin reuptake inhibitor	FIQ	Universidad de Granada EP Calandre	Phase II, improved symptoms
Yokukansan	Herbal medication	Insomnia	St. Marianna University School of Medicine	Phase II planned
ZYN001	Cannabinoid	Pain, quality of life	*Zynerba*	Phase II planned

LDN for Fibromyalgia

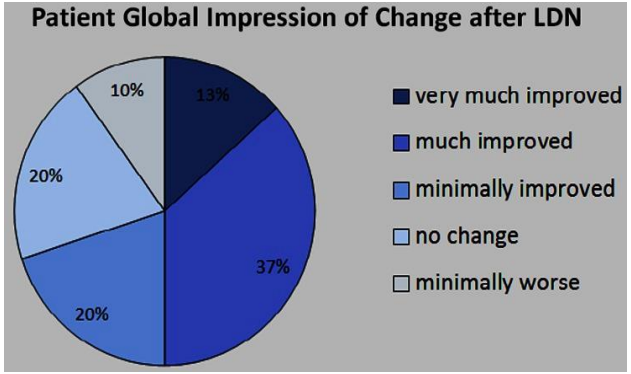
ARTHRITIS & RHEUMATISM
Vol. 65, No. 2, February 2013, pp 529–538
DOI 10.1002/art.37734

Low-Dose Naltrexone for the Treatment of Fibromyalgia

Findings of a Small, Randomized, Double-Blind, Placebo-Controlled, Counterbalanced, Crossover Trial Assessing Daily Pain Levels

Jarred Younger, Noorulain Noor, Rebecca McCue, and Sean Mackey

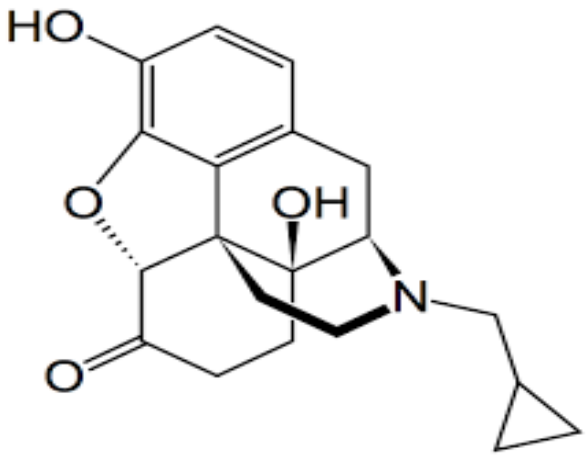
- Randomized double blind placebo-controlled, counterbalanced, **crossover** trial **31 women** (4.5 mg of naltrexone, 12wks).



- *Low adverse effects!*

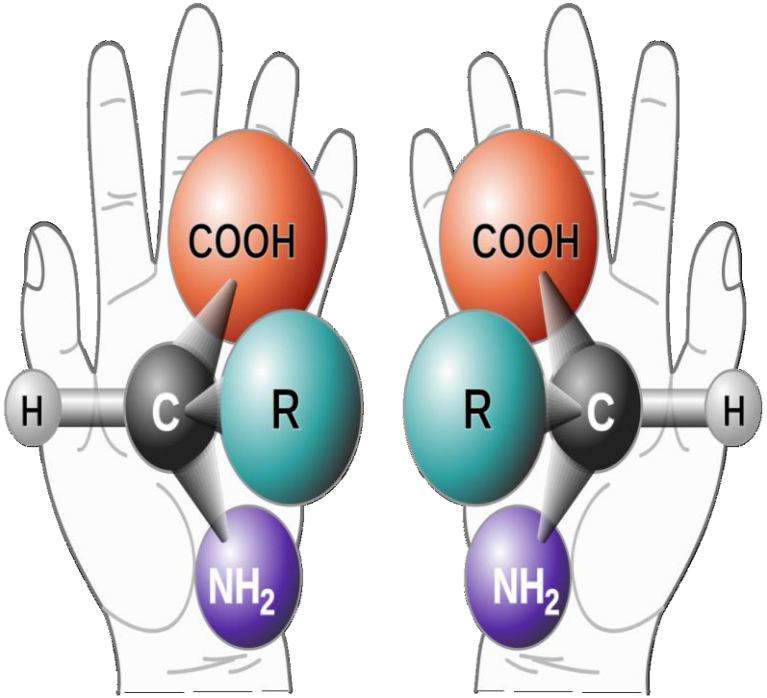
Naltrexone

- Approved by FDA in 1984 as **opiate antagonist**.
- Indicated **to treat Opiate and Alcohol addiction**.
- Usual Dose: between **50-300mg/day**.



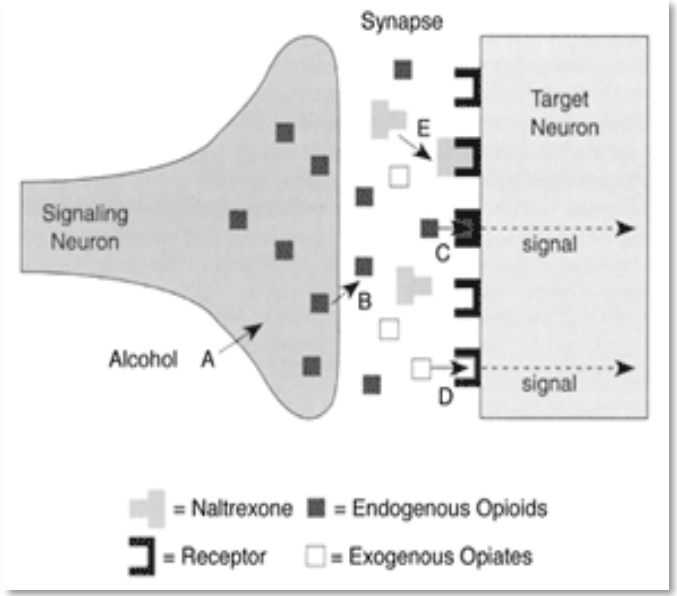
Naltrexone-Mechanisms of Action

- Naltrexone HCl is a 50:50 mixture of both *D (dextro) & L (levo)* Isomers
- Each isomer has a very different and distinct biologic activities



Naltrexone HCL (*L*-isomer) Mechanisms of Action

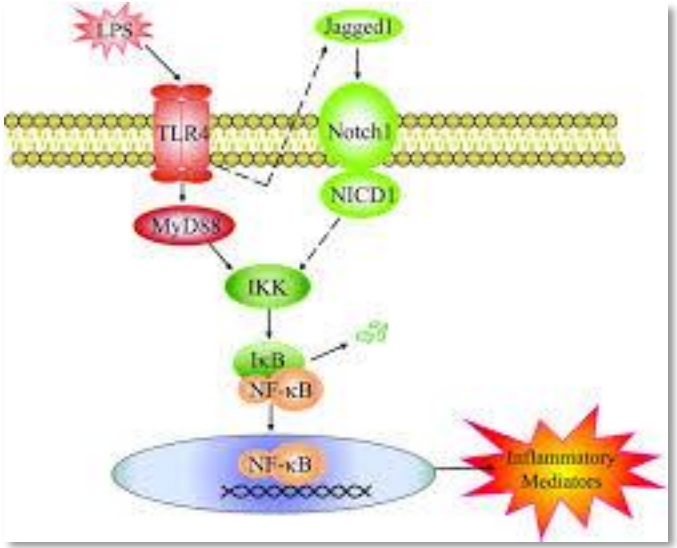
- Is a **reversible pure opioid antagonist**.
- *Low Dose Naltrexone* blocks the opioid receptor transiently and **triggers a rebound stimulation of endorphins the following day** (x3 β-endorphin levels / x12 enkephalin levels).



Naltrexone HCL (*D*-isomer) Mechanisms of Action

- Is an antagonist of **Toll Like Receptors** (i.e. TLR4)
- TLR4 is found on **microglia**. Microglia are central nervous system immune cells.
- *Activation TLR4 → activation microglia → production of **inflammatory** & excitatory factors such as **glutamate**.*

NOTE: This immunomodulatory effect is **NOT seen in doses of 50-300mg**



Wang X.et al. Pharmacological characterization of the opioid inactive isomers (+)-naltrexone and (+)-naloxone as antagonists of toll-like receptor 4. *British Journal of Pharmacology* 2016, 173: 856–869.

Neuroinflammation in Fibromyalgia

- Evidence of of both **systemic inflammation** (plasma) and **neuroinflammation** (CSF) in fibromyalgia patients (Bäckryd et al., 2017)
- **Microglial hyper-activation** (Albercht et al., 2019)
- **Heightened levels of glutamate** in pain-related processing areas (Fayed et al., Murga et al., 2017)

LDN for Fibromyalgia

biomedicines
http://www.mdpi.com/journal/biomedicines
MDPI

Article

Reduced Pro-Inflammatory Cytokines after Eight Weeks of Low-Dose Naltrexone for Fibromyalgia

Luke Parkitny and Jarred Younger *

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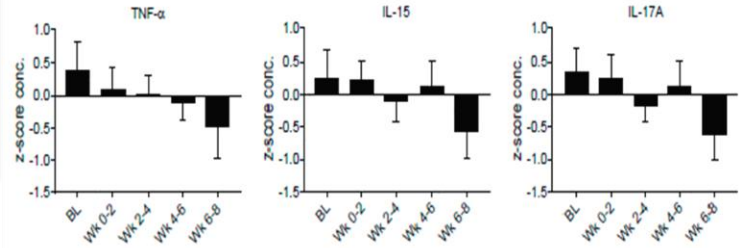
Academic Editors: Kim Lawson and Shaker Mousa
Received: 13 February 2017; Accepted: 12 April 2017; Published: 18 April 2017

- **10-week, single-blind, crossover trial with 8 women.**
- Blood samples were collected twice weekly.
- **Significant reduction of FM-associated pain (15%), overall symptoms (18%) and inflammatory markers.**



Low-Dose Naltrexone in patients with fibromyalgia (INNOVA Project)

Researchers: A Rozadilla, JV Luciano, A Feliu-Soler, X Borràs, A Pérez-Aranda, L Andrés-Rodríguez (AGORA), N Fayed, P Herrera (ZGZ), J Muchart, J Sánchez (HSJD), C Suso (UJI), E Calandre, J Hidalgo, C Molina (Granada), M Slim (Canada), J Younger (US), M Maes (Thailand), F D'Amico (LSE)

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THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

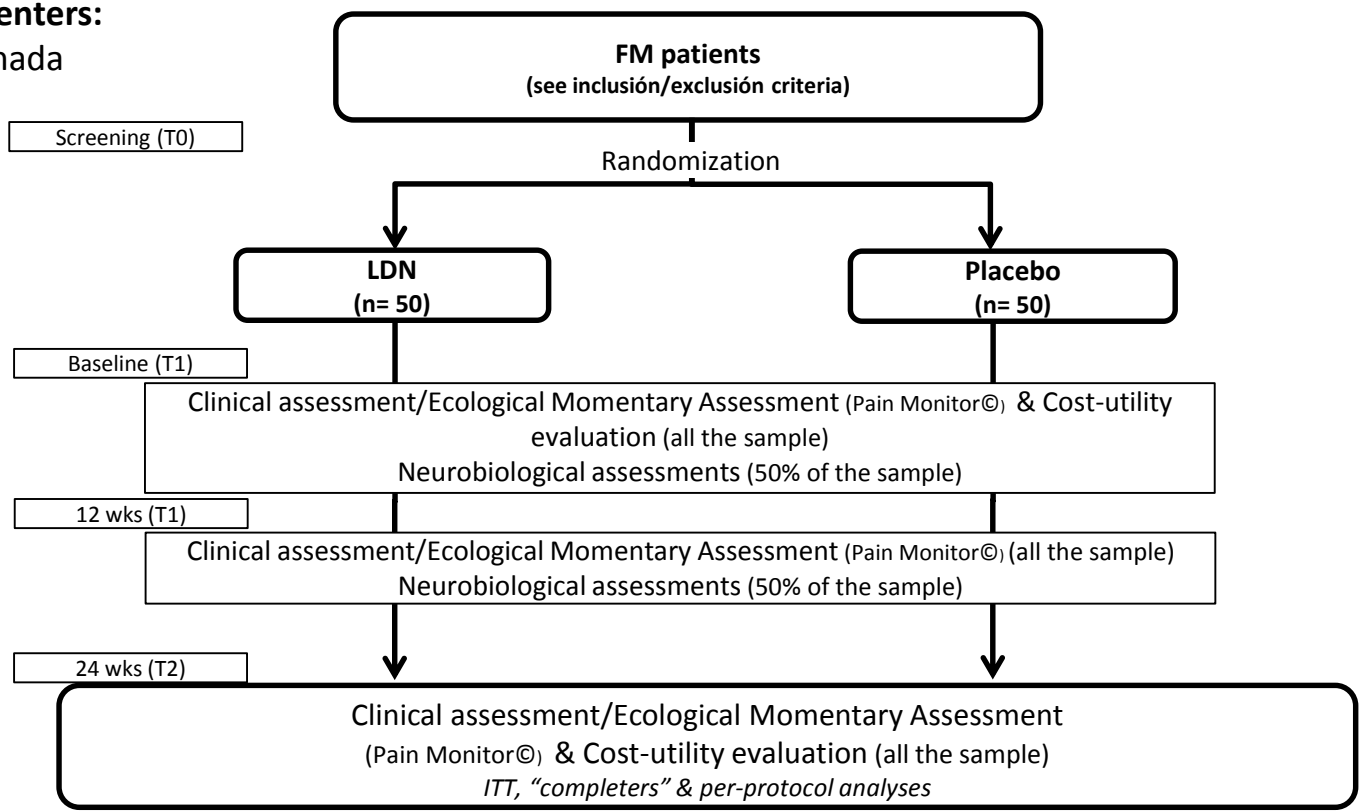
Chulalongkorn University

SickKids

LSE THE LONDON SCHOOL OF ECONOMICS AND POLITICAL SCIENCE

CONSORT Flow Diagram of the INNOVA Project

2 recruiting centers:
PSSJD/Granada



Objectives:

- **O1.** To assess the **clinical efficacy and safety** of LDN treatment at 12 and 24 weeks of treatment (vs. Placebo) in improving self-reported pain (primary outcome), clinical FM symptoms and quality of life.
- **O2.** To evaluate the **cost-utility** of LDN treatment (vs. Placebo) from the government and healthcare perspective (24-weeks time horizon).
- **O3.** To evaluate the changes (baseline-12 weeks) in the **levels of glutamate** in areas linked to the processing of pain and that show evidence of alterations in FM (i.e. posterior insula, posterior cingulate cortex, anterior cingulate cortex, left ventolateral prefrontal cortex) associated with LDN treatment (vs. Placebo).
- **O4.** To compare the changes associated with LDN vs. Placebo (baseline-12 weeks) on the levels of **blood immune-inflammatory markers**.

Inclusion/exclusion criteria

Efficacy & cost-utility study (entire sample)

- Inclusion criteria :
  - **FMS diagnosis** (ACR 1990 criteria)
  - Women 18-75 years
  - Moderate-severe Musculoeskeletal pain (> 4/10)
  - Able to understand the Spanish language.
  - Having a smatphone (for EMA)
  - Provide informed consent to participate.
- Exclusion criteria:
  - **Receiving opiod medication** in the last 3 months;
  - Comorbidity with **severe mental or medical disorders** which interfere with treatment (severe medical illness, psychotic symptoms, substance abuse).
  - Known allergy to naltrexone or naloxone.
  - Having any hematologic disorder.
  - Abnormal hepatic function.
  - Taking anticoagulation medication.
  - Alcohol consumption during the study period.
  - Participation in other RCTs.
  - Pregnancy or planning to get pregnant during the study period.
  - Breastfeeding.
  - Involved in ongoing litigation relating to FMS.

Neurobiological sub-study (PSSJD sample)

- Inclusion criteria:
  - Be right-handed
- Specific exclusion criteria:
  - Infection/cold symptoms on the day of blood extraction.
  - Needle phobia.
  - BMI > 36 kg/m^2 or weight > 110Kg.
  - Other rheumatologic diseases (e.g. rheumatoid arthritis, lupus)
  - Use of oral or local corticosteroids or anticytokine therapy.
  - Fever (>38ºC) or infection in the last 2 weeks.
  - Vaccination in the last 4 weeks.
  - Consuming more than 8 caffeine units per day.
  - Smoking >5 cigarettes per day.
  - Impossibility to be evaluated by means of MRI (due to claustrophobia, metal implants, pace-makers, etc.).
  - Acute pain not -related to FMS on the day of the study (e.g. headache, lumbar pain).
  - Taking anti-inflammatory drugs in the previous 72h to blood extracion/MRI.

→ **Patients will be allowed to continue with their stable medical treatment**. Changes in pharmacological/non-pharmacological treatment will be monitored throughout the study and may be a cause of drop-out from the final analyses.

Clinical and cost-utility variables

Primary outcome:

- **Pain Monitor©** app [7] will be used to evaluate changes in perception of pain intensity (in a -Numerical Rating Scale-NRS- from 0-10) in an EMA design.

Secondary outcomes:

- - *Revised Fibromyalgia Impact Questionnaire* (**FIQR**; [11]). 21-item questionnaire on physical function, overall impact and severity of the symptoms associated with FM. Additionally, six items from the symptom-subscale of the FIQR (i.e. fatigue, stiffness, depression, anxiety, memory/attentional problems, quality of sleep) -rated from 0 to 10- will be also included as part of the Pain Monitor© protocol.
- - *Hospital Anxiety and Depression Scale* (**HADS**; [12]). Brief scale to evaluate anxious and depressive symptomatology.
- - *Multidimensional Inventory of Subjective Cognitive Impairment* (**MISCI**; [13]). 10-item inventory for evaluating fibrofog (perceived dyscognition) in patients with FM.
- - *EuroQoL-5D* (**EQ-5D-5L**; [14]). Instrument for evaluating health-related quality of life. It is composed of two parts: 1) reduced mobility, self-care-related problems, pain/discomfort and anxiety/depression; and 2) current health status (from 0-100).
- - *Client Service Receipt Inventory* (**CSRI**; [15]). Retrospective case report form on the use of healthcare and social services during the last 6 months.
- - *Patient Global and Specific Impression of Change* (**PGIC/PSIC**; [16]). Indicator of meaningful overall change and change in specific domains (physical and social functioning, work-related activities, mood, and pain).
- - ***Adverse events*** *linked to the treatments*. Ad hoc measure to evaluate safety during the study.

Neurobiological measures

MRI Spectroscopy:

- Protocol: MRI 3T Phillips Ingenia.
- Main outcome: **Glutamate and Glutamate+Glutamine levels**
- Other metabolites also evaluated: Myo-inositol, N-acetilaspartate, coline & creatine (and related ratios)
- Locations: **posterior insula, posterior cingulate cortex, ventrolateral prefrontal cortex**

Blood inflammatory markers:

- Pro-inflammatory: IL-1β, IL-6, sIL6r, sgp130, IL-8, TNF-α, High-sensitive C-Reactive Protein
- Anti-inflammatory: IL1-ra, IL-10

Next steps...

- Get funding (ISCIII 2019, pharma-industry…)
- Do the RCT (2020-2022)

Moltes gràcies per la vostra atenció!