Review of Low-Dose Naltrexone in Rheumatologic Disorders

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Introduction

Naltrexone, traditionally prescribed to mitigate withdrawal symptoms in alcohol and opioid use disorder, has recently emerged as a potential therapeutic intervention for chronic pain and specific rheumatologic disorders at low doses, demonstrating its hormetic effects. While often used to treat fibromyalgia, complex regional pain syndrome, and inflammatory bowel syndrome, there is a paucity of literature regarding the efficacy of low-dose naltrexone in arthritic diseases such as osteoarthritis and rheumatoid arthritis. Here we present a case of arthrogryposis–a non-progressive condition characterized by multiple joint contractures, resulting in subsequent osteoarthritis in various joints and requiring treatment with low-dose naltrexone (LDN); while we review the existing literature and level of evidence regarding LDN in arthritic rheumatic diseases.

Patient Presentation

A 59-year-old man with a history of anxiety, depression, and arthrogryposis multiplex congenita complicated by multiple joint osteoarthritis, who had a mechanical fall at work in 2010 presented with chronic lower back pain for the past several years.

Pain Assessment: Located in the lower back (axial) and radiates to the flanks. Described as 8/10, constant aching, throbbing and stabbing. Aggravated by prolonged sitting and alleviated by laying down. Denies fevers, saddle anesthesia, new weakness, or new bowel or bladder issues.

Current Pain Regimen: Flexeril 10 mg BID PRN and Gabapentin 600 mg TID

Prior Pain Therapies: Medications - diclofenac cream, celecoxib, meloxicam, aleve, tapentadol, and other opioids; RFA; multiple orthopedic surgeries involving legs and feet; physical therapy and massage therapy.

Physical exam: 183 lbs and 64 inches in height (BMI of 31.4). Wheelchair bound, wore bilateral lower extremity braces and exhibited multiple deformities to extremities: contractures, muscle atrophy in all extremities, hip externally rotated, and bilateral varus knee.

Imaging: X-Ray of patient's hip & pelvis showed congenital dysplastic hips (see Figure 1). X-Ray of the knees bilaterally showed varus deformity and contour abnormalities (see Figure 2).

Plan: Trial of LDN 4.5mg PO daily. Continued Flexeril 10mg and Gabapentin 600mg.

4 Week follow-up: Patient reported a reduction in his pain score to 6 out of 10 (baseline 8/10).

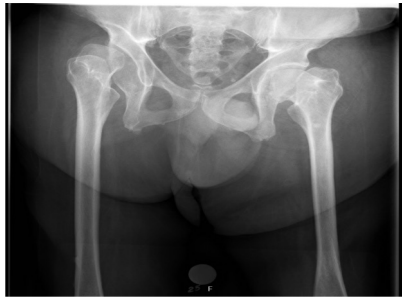

Figure 1: Left and right femoral heads are aspherical, congenital dysplastic. On the right, the acetabulum is shallow and there is superolateral subluxation of the proximal femur.

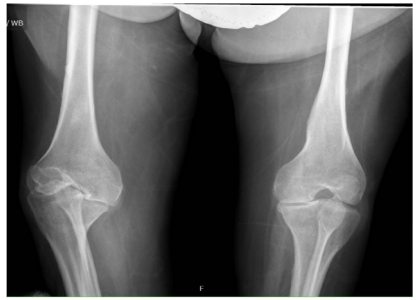

Figure 2: X-ray bilateral knees: varus deformity and contour abnormality of the proximal right tibia (sequela of prior surgery vs developmental). Anterior angulation of the distal femoral diaphysis which may reflect healed fracture.

Literature Review

Study	Study Type (Number of Subjects)	Pathology	Study Characteristics	Findings
Webster et al (2006)	Randomized, double-blind, placebo-controlled, trial (719)	OA	Placebo vs. oxycodone QID vs. Oxytrex BID vs. Oxytrex QID	Oxytrex BID patients attained comparable analgesia and decreased reliance despite significantly lower drug use.
Raknes and Småbrekke (2019)	Controlled before-after study (360)	RA and IA	Patients stratified into three groups based on LDN exposure	Persistent LDN users had reduced dispensing of analgesics, DMARDs, NSAIDs
Beaudette-Zlatanova et al (2023)	Randomized, double-blind, placebo-controlled crossover trial (23)	OA and IA	4.5 mg LDN or placebo for 8 weeks followed by 8 weeks of crossover	No difference in pain interference following LDN treatment (p = 0.90)

Table 1. Summary of LDN's effects on osteoarthritis and rheumatoid arthritis

Limited research has been conducted to explore the efficacy of LDN in the context of osteoarthritis (OA) and inflammatory arthritis (IA). Here we review three research studies.

In 2006, *Webster et al* conducted a phase III clinical trial using the combination drug, Oxytrex, consisting of oxycodone and ultra-low-dose naltrexone in patients with moderate to severe pain from OA. The study included four groups: placebo, oxycodone 4x daily, Oxytrex twice daily, and Oxytrex four times daily. Patients in the active treatment groups started at 10 mg/day of oxycodone and the dose rose uniformly while the naltrexone dosage remained constant. Active treatment groups attained comparable analgesia despite significantly lower drug use by oxytrex patients. Oxytrex twice daily yielded significantly superior results in terms of reducing pain intensity and enhancing analgesic quality compared to other modalities. These findings underscore the therapeutic hormesis-based effects of low-dose naltrexone as an opioid receptor antagonist, particularly when juxtaposed with opiates functioning as opioid receptor agonists.

Beaudette-Zlatanova et al conducted a phase 2, double-blind, placebo-controlled crossover trial where participants were given either 4.5 mg LDN or a placebo over 8 weeks, followed by a crossover to the alternative for 8 weeks. 17 patients with OA and 6 with IA completed the study with most characterizing their pain as either nociceptive (n = 9) or mixed (n = 8), as opposed to neuropathic (n = 3). Results showed no change in pain interference after administration of LDN in comparison to placebo (P = 0.90). No significant differences were seen in pain severity, fatigue, depression, or health-related quality of life. Future investigations on LDN should concentrate their efforts on discerning its impact on autoimmune diseases or neuropathic pain. This is particularly crucial given the observed limited effectiveness in ameliorating pain stemming from OA.

Raknes and Småbrekke conducted a controlled before-after study using the Norwegian Prescription Database to investigate the association between LDN exposure and changes in the dispensing of relevant medications (DMARDs, NSAIDs, analgesics, corticosteroids, and TNF-a antagonists) in patients with rheumatoid and seropositive arthritis. Three hundred sixty patients were stratified into three groups: LDN ×1 (one LDN prescription dispensed), LDN ×2–3 (two or three LDN prescriptions dispensed), and LDN ×4+ (four or more LDN prescriptions dispensed). Findings showed that persistent LDN users experienced a 13% relative reduction ($p = 0.003$) in the cumulative defined daily doses (DDD) of all examined medicines one year after starting LDN. There was a 23% reduction in the cumulative DDDs of analgesics ($p < 0.009$) and a reduction in use of NSAIDs, opioids, and DMARDs ($p = 0.028$). The findings from this research indicate that consistent utilization of LDN is associated with a decreased distribution of various medications used in treating rheumatoid and seropositive arthritis.

Conclusions

While evidence on LDN's efficacy in osteoarthritis is conflicting, its potential for pain reduction in rheumatoid arthritis appears promising, with a significant decrease in dispensing of disease-modifying drugs, analgesics, and NSAIDs. A wealth of studies has illuminated its potential efficacy in other conditions such as fibromyalgia, complex regional pain syndrome, and inflammatory bowel disease. However, the body of research exploring the utilization of LDN in rheumatologic disorders remains comparatively limited. The paucity of RCTs specifically addressing its application in rheumatologic contexts underscores the imperative for further investigation.

References

1. Britte Beaudette-Zlatanova et al., Pilot Study of Low-dose Naltrexone for the Treatment of Chronic Pain Due to Arthritis: A Randomized, Double-blind, Placebo-controlled, Crossover Clinical Trial, 2023.
2. Guttorm Raknes and Lars Småbrekke, Low dose Naltrexone: Effects on Medication in Rheumatoid and Seropositive Arthritis. A nationwide Register-based Controlled Quasi-experimental Before-after Study, 2019.
3. Jarred Younger et al., Low-dose naltrexone for the treatment of fibromyalgia: findings of a small, randomized, double-blind, placebo-controlled, counterbalanced, crossover trial assessing daily pain levels, 2013.
4. Michael Bamshad, Ann Van Heest, David Pleasure, Arthrogryposis: A Review and Update, 2009.
5. Webster LR, Butera PG, Moran LV, Wu N, Burns LH, Friedmann N. Oxytrex minimizes physical dependence while providing effective analgesia: a randomized controlled trial in low back pain. J Pain. 2006;7(12):937-946. doi:10.1016/j.jpain.2006.05.005
6. Phillip Kim and Michael Fishman, Low-Dose Naltrexone for Chronic Pain: Update and Systemic Review, 2020.