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Case Reports

Is Fibromyalgia An Endocrine/Endorphin Deficit Disorder? Is Low Dose Naltrexone a New Treatment Option?

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Fibromyalgia is a chronic pain syndrome. Neuman and Buskila[1] noted that fibromyalgia afflicts approximately 5% of women and 1.6% of men. The diagnosis of fibromyalgia is primarily based on chronic widespread pain that has (1) pain on both sides of the body, (2) is above and below the waist, (3) should involve the axial skeleton, and (4) must have been present for more than 3 months. Physical examination must include at least 11 of 18 tender points.[2] In clinical practice, nearly half the population may have fewer tender points. A new proposed fibromyalgia syndrome also includes sleep deficits, daytime fatigue, and altered cognition/mood as a part of the syndrome.[3] Comorbid psychiatric disorders are common in fibromyalgia. Arnold et al.[4] reported that 75% of patients with fibromyalgia have a mood disorder, 60% have an anxiety disorder, and 26% have a substance use disorder.

A clearly defined causative explanation for fibromyalgia has eluded investigators.[5] One of the earliest explanations for fibromyalgia looked at the most obvious source—muscle.[6] However, this theory was disproved quickly, leading to more central explanations. The two most accepted evidence-based theories include: neuropeptide abnormalities (involving entities such as Substance P,[7] serotonin,[8] and endogenous opioids[9]); and neuroendocrine defects (including the hypothalamo-pituitary adrenal [HPA], hypothalamo-pituitary gonadal [HPG], hypothalamo-pituitary-thyroid,[9] and the growth hormone axes[10]).

Endorphins play a significant role in pain perception.[11] Hence, it is not surprising that a number of investigators have looked at perturbations of endorphin function as a possible explanation for fibromyalgia. Vaeroy et al.[12] observed that CSF β-endorphin levels are either normal or lowered in individuals with fibromyalgia. The authors concluded that other endogenous opioids (such as proenkephalin and prodynorphin) may be involved. In a follow-up study, Vaeroy et al.[13] noted that dynorphin and met-enkephalin-Arg-Phe levels (marker unique for pro-enkephalin, which is present on the C-terminus of the precursor protein) were elevated in CSF of individuals with fibromyalgia, suggesting a potential hypersecretory abnormality in the endogenous opioid system. The authors further speculated that this could lead to receptor desensitization, decreased presynaptic inhibition of Substance P in the dorsal horn of the spinal cord, and increased pain.

Naltrexone is an opioid antagonist with a half-life of 4 h. It has an active metabolite 6-β-naltrexol that has a half-life of 13 h.[14] Based on the response of 10 women with fibromyalgia and 10 matched controls to a single dose of naltrexone (50 mg), Younger et al.[15] concluded that there was no evidence for endogenous opioid pathophysiology, particularly the μ-opioid system in fibromyalgia. This was primarily based on the finding that individuals with fibromyalgia and normal controls reported similar changes in pain (threshold, tolerance, and sensitivity) following administration of naltrexone (50 mg).Younger and Mackey[16] also explored the efficacy of low dose naltrexone (LDN) in individuals with fibromyalgia. In a pilot study with 10 subjects, the authors noted a significant 30% reduction in symptoms, particularly pain, fatigue, and stress. They also noted that peak response was reported in 28 days, although

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attenuation of pain was recorded as early as 2 weeks. The response was maintained for approximately 2 weeks after stopping the medication, with an incomplete return to baseline pain. Individuals in this study reported transient insomnia and vivid dreams as side effects of LDN. Significantly, the authors reported that response was directly correlated to erythrocyte sedimentation rates (ESR), suggesting that inflammation in fibromyalgia may contribute to pain and it responds well to LDN. Younger and Mackey[16] concluded that LDN may be more useful in individuals with signs of inflammation. This would be the result of a shift in the balance of immune/inflammatory drivers in peripheral T cells, which are reciprocally inhibited by endorphins.[17]

In this report, we discuss the treatment course of an individual with fibromyalgia (with normal ESR) who demonstrated dramatic improvement in symptoms of fibromyalgia with LDN alone. Contrary to Younger and Mackey's[16] suggestion that LDN is useful in fibromyalgia through an anti-inflammatory pathway, we hypothesized that fibromyalgia reflects a hormonal deficit—low endorphin secretion. The rationale for our use of LDN stems from Brown and Panksepp's discussion[18] that LDN at a dose of 4.5 mg increases μ, δ, and orphanin FQ receptors by creating a transient blockade followed by a surge of endorphin activity. We speculate that LDN improves endogenous endorphin function in fibromyalgia, which leads to attenuation of pain and other symptoms associated with the disease.

Case Report

Dr. A, a 37-year-old married college professor, presented to the Psychiatric Pain Service with the chief complaint of sharp pain and burning in various "spots" all over the body that had been present for 2 years. He described generalized dull pain throughout his body along with stiffness of his cervical muscles. He had pain on the soles of his feet and unsteadiness while walking. The unsteadiness was described as being episodic with worsening in the evening. He developed dryness and itchiness of eyes and pain in the eye muscles that made it difficult for him to focus his vision. The eye pain became so severe that he could not drive for more than an hour without having to pull his car over to rest his eyes. He reported deterioration in physical endurance with fatigue after minimal activity. He experienced problems with sleep in all three phases: initial, middle, and late insomnia. Dr. A had become unable to work on a sustained basis. He found it difficult to concentrate on his work for more than 3 hours a day. He said that he often found himself being irritable and reported anxiety that was difficult to link to any problem or event. Dr. A's mother, 57, and brother, 35, had identical histories of adult onset chronic pain.

Dr. A had been to numerous physicians before presenting to our service. He had been diagnosed with carpal tunnel syndrome, mild hypoparathyroidism, and more recently, fibromyalgia. Laboratory results had shown normal erythrocyte sedimentation rate (ESR- 5) and C-reactive protein (CRP- 1.2). He had mild osteopenia on dual energy X-ray absorptiometry (DEXA scan) and low vitamin D levels for which he was on vitamin D (50,000 units every 2 weeks). His pain symptoms continued despite appropriate correction of vitamin D levels. He had stopped naproxen (because of GI distress), amitriptyline (because of sedation), and milnacipran (due to dysuria).

Neurological examination was entirely normal. He had pain in all classical tender points: occipital, trapezius, low cervical, supraspinatus, second rib, lateral epicondyle, gluteal, greater trochanter, and medial knee. Psychiatric examination did not reveal a DSM-IV diagnosis. Dr. A was high functioning both personally and professionally.

We diagnosed Dr. A with fibromyalgia; all tender points, trouble concentrating ("fibrofog"), insomnia, and gut symptoms. Two atypical features of his presentation were pain in his extra-ocular muscles and pain on the soles of both feet.

To measure pain tolerance, we used the Cold Pressor Test (CPT). CPT is the most commonly used objective test of pain tolerance.[19] The subject is asked to submerge his/her forearm in a 1°C ice water bath. The amount of time that the subject can hold his/her forearm in the ice water gives an objective measurement of pain tolerance. The 95% confidence interval time for 26 normal controls on our service was >34 seconds. Dr. A's CPT time at initial evaluation of this patient was 7 seconds. He was measurably pain-sensitive.

Dr. A was instructed to take 1 mg of naltrexone for 2 nights, then 2 mg for 2 nights, finally increase it to 4.5 mg. Dr. A misunderstood the directions. He took naltrexone for 2 weeks, and then stopped it for the next 2 weeks. Dr. A restarted LDN at week 4. LDN was continued at 4.5 mg for the next 14 weeks. Within a week of initiation of LDN,

TABLE 1. Response to LDN. This Table Reports CPT and Self-Reported Quality of Life at Different Time Points During the Trial on LDN. Weeks 0, 4, 14, 20, and 27 Indicate Weeks During Which Changes were Made in Dosage of LDN

Week	0	4	8	11	14	16	17	18	20	21	24	27
CPT	7	25	50	57	58	65	83	71	43	58	39	46
Pain (0–10)	7	6	3	3	4	1	1	3	5	5	4	4
Quality of life	2	6	6	8	4	5	5	5	5	5	5	4

LDN = low dose naltrexone; CPT = cold pressor test.

Dr. A reported significant reduction in "spot" pain. Over 1 month, the dull pain in his back and neck improved along with reduction in gait unsteadiness. Subjective pain measured on a scale of 1 to 10 (1 being the least and 10 being the worst) was 6/10 at week 4. By week 8 it had decreased to 4/10. At subsequent visits, Dr. A described pain in the 1–4/10 range. There was an improvement in his cold pressor times from 7 seconds to 50 seconds by Week 8, indicating a dramatic increase in objectively measured pain tolerance. He also reported significant improvements in fatigue, sleep, and work capacity; from an average of 2–3 hours to 6 hours. Further, he reported improvement in mood and quality of life. These improvements were maintained for a period of 2 months (Table 1).

At the initiation of LDN, he reported increase in dull generalized body ache, with increased yawning and diarrhea. These symptoms subsided within 2–3 days. After a period of 2 months, Dr. A reported dry mouth and increased thirst. There also seemed to be a plateau in the improvement of pain. Towards the latter half of the third month, he reported an increase in fatigue with a gradual decrease in his quality of life. He had a trial off LDN (week 14). When LDN was stopped, he reported that the symptoms of dry mouth and increased thirst resolved in 3 days.

Dr. A felt subjectively best at week 17, and then reported recurrence of symptoms of fibromyalgia (pain scale of 5/10). He was started back on LDN 4.5 mg at week 20. However, he continued to complain of significant pain. It was decided to change the dose of LDN. The dose was reduced to 3.0 mg at week 23, and further reduced to 2 mg at week 27.

Dr. A continued on 2 mg of LDN for a short period (1 month) with increase in pain (subjective pain approximately 5–6 on 10). Unfortunately, due to his active engagement in his work, he was unable to keep his regular appointments for CPT. He did stay in touch with the treatment team and continued to report his subjective symptoms. He was switched back to 3 mg after 1 month and has been on this dose for the last 6 months. He reports minimal improvement in pain symptoms (subjective pain approximately 4–5 on 10), but adds that his overall quality of life and socio-occupational functioning is good. Thus, the treatment has reduced the severity of symptoms and allowed Dr. A to work, but it has not eliminated the disease.

Discussion

This case illustrates the efficacy of LDN in one individual with fibromyalgia. Dr. A met the diagnostic criteria for fibromyalgia in terms of history and physical examination. There is a family history of fibromyalgia symptoms in two first-degree relatives, which is typical of the illness. Although he reported symptoms of anxiety and insomnia, these did not warrant a diagnosis of a comorbid psychiatric disorder. Dr. A had unsuccessfully attempted typical approved/off-label treatments. Treatment with LDN significantly decreased his pain and improved his quality of life.

Dr. A's initial complaints of dry mouth and increased generalized pain are reminiscent of an opioid withdrawal symptom, suggesting that LDN affects the endogenous opioid system. The course of the treatment showed a lag period of 2 weeks to improvement in pain, suggesting that it may take 2 weeks for the endorphin system to reconstitute itself. This latency of onset of action would be typical of the time required to shift a hormonal system. It appears that there may be a plateau to improvement and that symptoms recur with withdrawal of the medication.

The concept of treatment of fibromyalgia with LDN is analogous to treatment of infertility by administration of clomiphene. Clomiphene blocks estrogen negative feedback at the hypothalamic level and provokes increased secretion of follicle stimulating hormone and luteinizing hormone. LDN causes transient blockade of

opioid receptors centrally resulting in a rebound of endorphin function.[18] This may be the mechanism by which LDN attenuates the pain of the fibromyalgia, by increasing the patient's own pain-fighting ability.

Limitations

The only objective measure of pain tolerance in this report was CPT. Measurement of changes in endorphin levels would have been the most ideal way of testing the hypothesis. Endorphin levels were not measured pretreatment or during treatment. Although CPT is an objective measure, testing was not carried out in a blinded manner. The treating physician was also the person who administered the CPT. Further, rating measures were primarily self-report to the treating physician. This could have introduced a measurement bias.

Conclusion

The most common medications given for newly diagnosed individuals with fibromyalgia are opioids – 56%, antiepileptics – 29%, and tricyclic antidepressants – 21%.[20] If the presented hypothesis that fibromyalgia is an endocrine disorder holds true, using opioids for pain control would be the exact opposite of effective treatment, as exogenous opioids would suppress the endorphin system, eventually worsening symptoms. This case clearly identifies definitive response of symptoms of fibromyalgia to LDN in one individual. LDN may be a useful, cheap, and relatively safe medication for the management of fibromyalgia.

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