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Low-dose naltrexone as a treatment for vulvodynia: A case series

Renee T. Sullender, R. Gina Silverstein, Diamond M. Goodwin [1], Asha B. McClurg, Erin T. Carey [*]

Division of Minimally Invasive Gynecology Surgery, Department of Obstetrics and Gynecology, University of North Carolina at Chapel Hill, 460 Waterstone Drive, Hillsborough, NC 27278, USA

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ABSTRACT

Vulvodynia is a chronic vulvar pain condition that can be challenging to treat and often requires multi-modal interventions for symptom management. Low-dose naltrexone (LDN) is a reversible competitive antagonist at opioid receptors and may have utility in treating chronic pain conditions. In a specialty gynecology clinic at an academic medical center, patients with poorly controlled vulvodynia who had failed standard treatments were offered LDN as an adjunct pain treatment. This case series describes the experience of three patients with chronic vulvodynia who added LDN to their treatment regimen. All patients reported subjective improvement in their symptoms without side-effects. Additional research is needed on the efficacy of LDN for chronic pelvic pain conditions such as vulvodynia as well as the long-term safety profile of such use.

1. Introduction

Vulvodynia is persistent idiopathic vulvar pain that can occur spontaneously or be provoked by vulvar touch. It may be triggered during attempted vaginal penetration but can also occur with non-sexual stimuli, including tampon insertion, pubic hair removal, wearing tight clothing, physical activity (e.g. bike riding), or stress [1,2]. The prevalence of vulvodynia has been estimated at 10–28 % of women of reproductive age in the United States [3]. Similar to other chronic pain conditions, vulvodynia negatively impacts mental and physical health, interpersonal relationships, and quality of life [4].

Vulvodynia is often challenging to treat, resulting in a frustrating experience for patients and providers alike. Medical therapies include topical anesthetics, oral medications (e.g., antidepressants and anticonvulsants), pelvic floor physical therapy, cognitive behavioral therapy, injections, and excision of a portion or the complete vestibule (vestibulectomy). The efficacy of a single therapy is limited; therefore multimodal therapy is often recommended [5]. Most combination therapies have not been studied, though, clinically, patients frequently use multiple treatments [6]. Given the high prevalence and considerable negative impacts of vulvodynia, the continued investigation of alternative treatment methods is essential.

Low-dose naltrexone (LDN) has been used successfully as a treatment for many types of chronic pain but has not been studied as a treatment for vulvodynia. Naltrexone is a reversible, competitive antagonist at μ, δ, and κ-opioid receptors, approved by the United States Food and Drug Administration (FDA) for opioid and alcohol use disorders in 1984 and 1994, respectively, at doses of 50–150 mg daily [7]. LDN may have utility treating chronic pain conditions via alternate pharmacodynamic pathways reducing pro-inflammatory cytokines. One proposed mechanism of action for analgesia is following a brief period of opioid blockage, there is an adaptive increase in endorphin and enkephalin production [8]. This increase causes an analgesic effect on opioid receptors and results in beneficial modulation of the immune system. These pain benefits are seen only with low doses [9]. An alternative mechanism of action is that LDN blocks toll-like receptor 4 (TLR4) found on macrophages in the central nervous system called microglia. When microglia are activated, they produce inflammatory factors. Opioids activate microglia and this chronic activation may help explain opioid hyperalgesia.

LDN is being studied for use in patients with fibromyalgia, premenstrual syndrome, polycystic ovarian syndrome, Crohn's disease, multiple sclerosis, and endometriosis, with some promising results [9,10]. LDN is typically prescribed in a stepwise fashion, beginning with

* Corresponding author.
E-mail addresses: renee_sullender@med.unc.edu (R.T. Sullender), gina.silverstein@unchealth.unc.edu (R.G. Silverstein), Diamondgoodwin@cshs.org (D.M. Goodwin), asha_mcclurg@med.unc.edu (A.B. McClurg), erin_carey@med.unc.edu (E.T. Carey).
[1] Present address: Minimally Invasive Gynecology Surgery, Department of Obstetrics and Gynecology, Cedars Sinai Medical Center. 8631 W. 3rd St Suite 830E, Los Angeles, CA 90048.

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1.5 mg nightly and slowly increasing to 4.5 mg with additional increases as needed. While there is no standard dose for use of LDN in chronic pain, 4.5 mg is commonly used and is the most researched dose [8,9]. Significantly higher doses have not been associated with analgesic benefit, although there is no defined maximum LDN dose and there are limited studies on doses greater than 4.5 mg daily [9]. While naltrexone is commercially available starting at 50 mg, LDN is available only through specialty pharmacy compounding in a rapid release form.

In a single-specialty gynecology clinic at a tertiary academic center, patients with poorly controlled vulvodynia were offered LDN as an adjunct pain treatment after counseling that LDN is experimental and that its use for chronic vulvar pain is off-label. Patients were seen for follow-up in clinic where they rated their pain 0–10 on a numeric rating scale (NRS) and also subjectively described their experience with the medication. This retrospective study was approved by the University of North Carolina at Chapel Hill Institutional Review Board (#22–0695). The participants described in this paper consented to publication.

2. Case Presentations

2.1. Case 1

A 72-year-old woman had a 3-year history of vulvodynia when she trialed LDN. Her bilateral vulvar pain started as intermittent, only during and after intercourse, but evolved to constant, daily pain. Co-morbid pain disorders included fibromyalgia and myofascial pelvic pain. Her average pain level prior to starting LDN was 7/10 on the NRS. Her pain was worsened by intercourse, urinating, defecating, driving, standing, sitting, and contact with clothing. On exam, there was no allodynia noted of the vestibule or vulva with gentle touch of a cotton swab (cotton swab test [11]). Pelvic floor muscle tone was high with tenderness of the levator ani muscles. She did not have vaginal atrophy noted.

The patient had previously tried pelvic floor physical therapy (PFPT), oral gabapentin, oral prednisone, topical estrogen/lidocaine, vaginal estrogen, cannabidiol (CBD) suppositories, and oral lorazepam. When LDN was added, she was using multiple topical compounded creams, including estradiol 0.02 %/lidocaine 5 %/testosterone 0.01 %, topical baclofen, topical naltrexone 1 % in hydrophilic petrolatum, oral palmitoylethanolamide, and pre-coital vaginal valium suppositories. She was particularly interested in trialing oral LDN given she reported improvement with her pain with the topical naltrexone compound. She continued these medications and added a LDN dose of 1.5 mg/day. She reported "significant" improvement with 10.5 mg/day at 4-month follow-up, when her score on the NRS was 4/10 in intensity at its worst, 1/10 in intensity at its least, and average pain level 1/10 (prior average pain 7/10 on the NRS).

2.2. Case 2

A 75-year-old woman with a 6-year history of vulvodynia at initiation of LDN, as well as a medical history notable for poorly controlled bladder pain syndrome (BPS), rated her pre-LDN average vulvodynia pain as 6/10 on the NRS, reporting bilateral, constant, burning pain of the vulva. She was not sexually active and denied pain triggers. On exam, the cotton swab test of the vestibule and vulva were negative. No myofascial tenderness or increased tone was noted on the pelvic floor muscle exam. She was noted to have moderate vaginal atrophy.

Prior treatments for her vulvodynia and BPS included PFPT, vaginal valium, topical estradiol 0.5 mg/g/lidocaine 5 %, oral clonazepam, oral citalopram, oral duloxetine, oral gabapentin, and topical ketamine. When she started LDN, she was also using oral nortriptyline, vaginal estradiol twice weekly, and topical aloe vera. Two years after initially being prescribed LDN, she continued at 4.5 mg daily, reporting "significant improvement" in her vulvodynia, with her last average pain reported on the NRS as 3/10 (prior average pain 6/10 on NRS).

2.3. Case 3

A 54-year-old woman had an 11-year history of vulvodynia when she initiated LDN. Her co-morbid conditions included post-traumatic stress disorder, stable lichen sclerosis, and myofascial pelvic pain. She reported her worst pain as 7/10 on the NRS and average pain 5/10. Prolonged sitting and intercourse worsened the pain. Physical exam revealed a negative cotton swab test of the vestibule, but allodynia of the left labia majora. She also had tenderness of her pelvic floor. She did not have vaginal atrophy noted on exam.

She had previously tried PFPT, acupuncture, oral gabapentin, oral pregabalin, oral duloxetine, oral nortriptyline, oral tapentadol, pudendal nerve blocks, and pudendal nerve ablation. When LDN was added, she discontinued oral tapentadol, but continued oral amitriptyline, oral trazodone, oral methocarbamol, and oral clonazepam. She returned eight months after initiating LDN and reported a desire to continue the LDN 4.5 mg daily, reporting "significant improvement" in her vulvodynia symptoms and no desire to resume opioid medications. Despite the reported significant improvement, there was no change in her NRS score, with her worst pain reported as 7/10 and average pain 5/10.

3. Discussion

This case series presents three patients with refractory vulvar pain who demonstrated subjective improvement in their symptoms with adjunct LDN. No side-effects were reported. Two patients found adequate relief on 4.5 mg/day and one self-titrated to 10.5 mg/day for desired effect. With the significant number of therapies the patients had previously tried, their continuation of LDN suggests meaningful improvement in their pain.

LDN for chronic pain conditions remains experimental and we are conducting additional research to evaluate its impact on chronic pelvic pain in general and vulvodynia specifically. There are efforts ongoing to evaluate the impact of LDN on other chronic pain conditions including endometriosis and fibromyalgia [10,12]. Many patients who have chronic pain have overlapping pain conditions and it remains to be seen if these patients are more or less likely to report improvement with LDN, given the possibility of LDN to treat a variety of pain conditions [13].

Naltrexone has been found to be safe and well tolerated, although there is limited information on the long-term safely of use in low doses. Forty percent of patients report having vivid dreams, which generally decrease over time [9]. Other side-effects include headaches, anxiety, tachycardia, nausea, and dry mouth. Uniquely, there do not appear to be withdrawal symptoms when LDN is stopped, despite prolonged use. There is no known abuse potential to LDN. As an opioid antagonist, LDN can cause severe adverse reactions when taken with opioids and should be discontinued two days prior to surgery or planned opioid use. Although LDN is suspected to modulate the immune system, there have been no reports of an increased risk of infection or cancer as a result and there may even be an immune system boost in some studies [8]. Given LDN requires specialty compounding, it can be expensive, and off-label drug use such as for vulvodynia may not be covered by insurance companies.

A limitation of this case series is the post-menopausal status of all three patients. There was no evidence on history or exam suggesting genitourinary symptoms of menopause (GSM) was the primary cause of their symptoms, although vulvodynia is often overlapping with other causes of pelvic pain, including GSM, myofascial pelvic pain, painful bladder syndrome, and others which may present as confounders. In post-menopausal patients in particular, physical exam should include evaluation for vaginal atrophy and vaginal estrogen should be prescribed if identified and found to be a contributing component of the physical complaints.

While the incidence of vulvodynia is higher in younger women (most commonly ages 20–40), vulvodynia can affect women of all ages. In women aged 60, the annual incidence of vulvodynia has been estimated

at 3.3 % compared with 7.6 % of women aged 20 [14]. One United States (U.S.) population-based study identified the prevalence of vulvodynia at 9.4 % among women aged 18–70, with a decrease to 2.4 % in those over 70, though in sexually active women over 70 vulvodynia symptoms were prevalent at the younger rate [15]. Another population-based study of US women aged 57–85 revealed that 17 % reported symptoms of postmenopausal vulvodynia [16]. These epidemiological findings indicate that vulvodynia is a common gynecological pain condition affecting women of all ages, including postmenopausal women. In this case series, the three patients who responded to LDN had symptoms of vulvodynia starting after age 40. Future studies in postmenopausal women with vulvodynia will be needed to explore if age-related vulvodynia requires alternative treatments compared to onset during at an earlier age.

This case series demonstrates the potential utility of LDN as an adjunct therapy for vulvodynia by highlighting the subjective improvement in pain experienced by three patients with refractory vulvodynia. This is especially noteworthy given the limited effective treatment options for vulvodynia [17]. As LDN has shown promise in treating other pain conditions, additional high-quality research is needed on the utility of the safe and well tolerated LDN as an adjunct option for patients with vulvodynia.

Contributors

Renee T. Sullender contributed to conception of the case series, acquiring and interpreting the data and drafting the manuscript, undertaking the literature review, and revising the article critically for important intellectual content.

R. Gina Silverstein contributed to conception of the case series, acquiring and interpreting the data, drafting the manuscript, undertaking the literature review and revising the article critically for important intellectual content.

Diamond M. Goodwin contributed to conception of the case series, acquiring and interpreting the data, drafting the manuscript, undertaking the literature review and revising the article critically for important intellectual content.

Asha B. McClurg contributed to conception of the case series, acquiring and interpreting the data, drafting the manuscript, undertaking the literature review and revising the article critically for important intellectual content.

Erin T. Carey contributed to patient care, conception of the case series, acquiring and interpreting the data, drafting the manuscript, undertaking the literature review and revising the article critically for important intellectual content.

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Patient consent

Obtained.

Ethical approval

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Conflict of interest statement

The authors declare that they have no direct conflict of interest. ETC provides expert witness testimony and is an inventor on a patent application related to vulvodynia filed by the University of North Carolina, Office of Technology Commercialization (UNC OTC) (PCT International Application PCT/US20/55816).

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