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Low-Dose Naltrexone and Pain Relief in Gadolinium Deposition Disease: A Case Series

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Background: Background. Most patients with gadolinium deposition disease (GDD) report early onset of persistent neuropathic pain. No widely available or rapidly acting pain relief method has been reported.

Case Presentations: Five GDD patients without benefit from non-opioid pain relievers and with no history of opioid treatment received a clinical practice trial of open-label, low-dose naltrexone (LDN). Four had received intravenous Ca-DTPA chelation. Before starting LDN, patients rated their pain on a scale of 0 to 10. Patients rated the degree of pain relief weekly using the Global Clinical Impression – Improvement Scale. Pain was very much or much improved for 4 patients, starting during week 2 in one patient and week 4 in 3 patients. Pain relief began at naltrexone dose 3.0 to 4.5 mg per day and reached a maximum after 4 to 8 weeks.

Conclusion: These case results suggest that a well-designed, adequately powered, controlled trial of LDN in GDD patients is merited.

Key words: Case series, gadolinium, naltrexone, pain

BACKGROUND

In 2016, Semelka et al (1) described the symptoms and onset of a rare reaction to exposure to a gadolinium (Gd)-based contrast agent (GBCA)-assisted magnetic resonance imaging (MRI) and termed it gadolinium deposition disease (GDD). The pathophysiology of GDD is not understood, but elevated levels of proinflammatory cytokines in GDD patients compared to normal controls have been reported (2). Subsequent studies demonstrated different, rapid changes in serum cytokine levels in response to Ca-DTPA chelation compared to the changes seen in patients who retained Gd without developing GDD symptoms (3). Most GDD patients report persistent pain and dysesthesia with a neuropathic quality (2,4,5) consistent with small fiber neuropathy. Small fiber neuropathic pain is associated with dysfunction of thinly myelinated Aδ and unmyelinated C fibers. In an animal study, both macrocyclic and linear GBCAs reduced small fiber nerve density and produced terminal axonal swellings, findings which suggest, but do not prove, that Gd exposure can produce small fiber dysfunction resulting in small fiber neuropathy and its symptoms (6).

No treatment other than Ca-DTPA chelation has been reported to relieve this pain in GDD patients. From "mild" (10%-24%) to "substantial" (50% or more) pain relief was reported by a majority of patients after 3 weekly or monthly chelation sessions pairing Ca-DTPA chelation on day one with Zn-DTPA chelation on day 2 (4).

Low-dose naltrexone (LDN) is an opioid antagonist that has analgesic properties and inhibits the proliferation of damaged cells (7,8). Given the neuropathic pain-related suffering of these GDD patients and the literature suggesting that LDN can relieve neuropathic

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pain of differing etiologies (9,10), we prescribed open-label LDN to a small series of GDD patients.

CASES

Patients

Five consecutive study-eligible patients seen in the first author's (IR) private medical clinic in 2020 and 2021 and suffering from GDD-related neuropathic pain with inadequate response to standard pain regimens were offered open-label treatment with LDN (Table 1). The treatment was not offered to GDD patients aged less than 18, pregnant, currently taking opioid medications, having a history of substance abuse, or suffering from hemochromatosis. The risks, side effects, and uncertainty of benefit were described and the patients' questions answered. Each gave informed consent, documented in the medical record, for a trial of LDN.

All patients met the proposed diagnostic criteria for GDD: new onset of ≥ 3 of 8 specified symptoms within 30 days of their GBCA-assisted magnetic resonance imaging (MRI): cognitive disturbance, extremity pain, chest wall pain, arthralgia, skin pain, headache, skin induration, and skin hyperpigmentation; and having an unprovoked 24-hour Gd urine amount exceeding the laboratory norm ≥ 28 days after the symptom-inducing MRI (2). The indications for their MRIs were: new-onset headache, dizziness, visual concerns, weakness, fatigue, or a combination thereof.

No patient had another condition that might plausibly be the cause of pain, as a full diagnostic workup was done without uncovering an additional etiology for their symptoms. Before starting LDN, one patient had tried aspirin; 5 had tried acetaminophen, nonsteroidal anti-inflammatory drugs, and/or gabapentin; 3 had tried pregabalin; and 4 had tried duloxetine. None had been previously treated with an opioid for the current condition.

Interventions

The pain of patients #1 through #4 had been unresponsive to chelation before they were offered and accepted a trial of LDN. They received no chelation treatment during or after the LDN trial. Because of a history of intolerable adverse reactions to many treatments, patient #5 had not wished to try chelation. Before starting LDN, patients discontinued with appropriate weaning schedules all medications aimed at pain relief. In the attempt to achieve satisfactory pain relief, open-label LDN was begun at a dose of 1.5 mg every night at bedtime and increased by 1.5 mg weekly to a maximum of 4.5 mg per day if needed.

Ca-DTPA Chelation

Ca-DTPA was administered as an intravenous (IV) bolus into a saline drip as described elsewhere (4). In brief, 2.5 mL of Ca-DTPA was injected over a one-minute period. The saline drip was continued and 80 minutes later the remaining 2.5 mg of Ca-DTPA was injected over a one-minute period and the IV continued for another 9 minutes.

Measurements

Before starting LDN, patients rated their pain on a scale of 0 to 10 using the numeric rating scale where mild = 1-3, moderate = 4-6, and severe = 7-10 (11). Patients rated their degree of relief weekly using the categories of the Global Clinical Impression – Improvement Scale (12). The ratings took place in the treating physician's office, with the patient instructed to rate the pain intensity and improvement over the last several days.

Table 1. Patients and Pain Ratings

Patient	Age	Gender	Time Since Symptom Onset	Days Post MRI Symptoms Began	24-Hour Urine Gd Post Chelation	Pain Locations[a]	Pain Quality[b]	Pain Severity[c]
1	51	F	1 yr	21	16 μg	LL, N, B, H	B, E, Z	6
2	74	F	> 1 yr	14	24 μg	LL, B, H, T, UL	E, B	8
3	31	F	6 mos	30	10 μg	LL, UL, H	B	6
4	48	F	18 mos	30	12 μg	LL, UL, T, B, F	B, Z, E	9
5	60	F	3 mos	30	18 μg	LL, UE, F, H, B, T	B, S, Z, E	8

Abbreviations: MRI, magnetic resonance imaging; Gd, gadolinium

[a] Pain Locations: lower limbs (LL), upper limbs (UL), torso (T), back (B), neck (N), head (H), face (F)

[b] Pain Quality: burning (B), stabbing (S), zaps (Z), electrical (E)

[c] Pain Severity: mild = 1-3, moderate = 4-6, severe = 7-10

Urine specimens for quantifying Gd excretion were collected for the 24 hours before and after the first Ca-DTPA chelation to verify that chelation was effectively removing Gd. Clinical management did not require subsequent urine Gd measurements and focused on obtaining symptom relief if possible. Patients did not need to save the first post-chelation urine specimen since it contained urine formed prior to chelation. Urine samples were sent to Doctor's Data, Inc. (DDI; St. Charles, IL), which utilized inductively coupled plasma mass spectrometry to determine the Gd amounts (See: https://doctorsdata.com/licensing). The DDI norm for women is ≤ 0.6 µg per 24 hours, and for men ≤ 1.0 µg per 24 hours, based on unprovoked urine samples from 336 women and 204 men who were asked to refrain from undergoing a GBCA-assisted MRI for ≥ 48 hours before beginning urine collection. The norm limits are the samples' 95th percentiles.

Results

Table 1 displays patient demographics, time since GDD symptom onset, the number of days post MRI that GDD symptoms began, 24-hour urine Gd amounts following Ca-DTPA chelation, and the locations, quality, and severity of the patients' pain.

The patients, all women, ranged in age from 31 to 74, and ranged in time since symptom onset from 3 to 18 months. All had constant pain in multiple locations, with neuropathic pain qualities including burning, stinging, and electric-shock sensations. Pain was rated at the top of the moderate range by 2 patients and in the severe range by 3.

After starting LDN treatment, patient #5 developed insomnia at 1.5 mg per day and discontinued the treatment. With continued LDN treatment, patients #2, #3, and #4 experienced clear and sustained pain relief beginning at 3.0 mg per day; patient #1 did not. Patient #2 was satisfied with this degree of relief. Patients #1, #3 and #4 requested a trial of a dose higher than 3.0 mg per day. All 3 patients experienced further meaningful, sustained, and satisfying pain relief at a LDN dose of 4.5 mg per day (Table 2). At the time of writing, relief has persisted for 6 to 8 months on continued LDN without a need to increase the dose.

DISCUSSION

This small case series suggests that LDN may be a useful medication in the management of GDD neuropathic pain. No clear predictors of treatment success or necessary dose were evident, although the maximum dose required for 3 patients was 4.5 mg per day. Although LDN-induced insomnia prevented patient #5 from continuing the treatment trial at the starting dose of 1.5 mg per day, LDN is usually very well tolerated. LDN side effects include insomnia, vivid dreams, headache, nausea, and less often, nightmares, although these side effects rarely cause LDN discontinuation (13).

How LDN brings about pain relief in GDD is not yet clear. LDN induces increased production of endogenous opioids (7). It also has a neuroprotective effect via inhibiting microglial activation and decreases cellular signaling that stimulates the production of proinflammatory cytokines (9). Interestingly, plasma levels of 3 of the proinflammatory cytokines down-regulated by LDN in an 8-week study (14) – IL-2, TNF-α, and TGF-α – were reported to be statistically significantly elevated in GDD patients compared to normal controls (2). Whether LDN-induced reduction in plasma levels of these cytokines occurs earlier is unknown.

This report is limited by the small number of pa-

Table 2. Patients' Treatment Response

Patient	LDN Dose When Clear, Sustained Relief Began	Rx Week When Clear, Sustained Relief Began	LDN Dose When Relief Maximum	Rx Week When Relief Maximum	Degree Of Pain Relief [a]
1	4.5	4	4.5	7	1
2	3.0	2	3.0	4	2
3	3.0	4	4.5	6	1
4	3.0	4	4.5	8	2
5	Never. Did not tolerate LDN	Never	Never. Did not tolerate LDN	Never	6

Abbreviations: LDN, low-dose naltrexone; Rx, treatment.
[a] 1 = Very much improved; 2 = Much improved; 3 = Minimally improved; 4 = No change; 5 = Minimally worse; 6 = Moderately worse; 7 = Very much worse

tients, absence of blinded rater pain ratings, and lack of blinded random assignment of patients to active treatment or placebo. Ratings of potential changes in functional disability in work/school, social, and family life would have been desirable.

CONCLUSION

The therapeutic result experienced by 4 of the 5 GDD patients treated with LDN suggests that further research is warranted, as do the very limited availability and expense of Ca-DTPA chelation. To increase their value, future studies should utilize designs incorporating blinded LDN vs placebo or blinded LDN vs. a pain medicine, random patient assignment, blinded independent rater ratings of pain, and other GDD symptoms in addition to patient ratings, and should be powered to detect moderate effect sizes. Ratings of potential changes in functional disability in work/school, social, and family life would be desirable. Preliminary studies (2,3) suggest that measuring changes in proinflammatory cytokines might help reveal mechanisms by which LDN helps relieve GDD pain, if in fact this proves to be the case.

Author Contributions

LK made substantial contributions to conception of the treatment plan, data analysis and interpretation, as well as drafting the article and conducting the literature search and summaries of previous related work and preparing the article's final draft.

IR treated the patients and made substantial contributions to conception of the treatment plan and design, acquisition of data, and data analysis and interpretation. IR also contributed to revising the article critically and approved the final version. Both authors contributed to revising the article in response to the reviewers' comments.

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