# Symptomatic Improvement in Irritable Bowel Syndrome With Oral Ketamine

Omar Dyara, MD; Natasha Topoluk, MD, PhD; Harvey J. Woehlck, MD


## ABSTRACT

**Introduction:** Irritable bowel syndrome (IBS) often is treated as a partially diet-responsive functional bowel disorder. Few interventions have been found to be effective in diet-refractory IBS, leading to lifestyle disruptions due to persistent symptoms. The efficacy of low-dose home ketamine therapy suggests others may benefit.

**Case Presentation:** A female patient in her 60s with progressive presumed IBS with diarrhea found diet-based treatments ineffective, resulting in severe lifestyle disruptions. After a hysterectomy, intolerance to opioids for postoperative pain prompted the use of intravenous ketamine. An unexpected and prolonged improvement in IBS symptoms resulted. The patient sought continued treatment with ketamine for IBS symptoms and experienced continued symptomatic relief with 20 mg oral ketamine every 2 weeks at home.

**Discussion:** No other published cases of ketamine for IBS were found.

**Conclusions:** While dietary changes remain the gold standard for IBS, this patient experience highlights ketamine as a potential adjunct therapy.


## INTRODUCTION

Irritable bowel syndrome (IBS) is a common subtype of functional gastrointestinal disorder (FGID). In some patients, symptoms unresponsive to diet currently lack effective therapy. N-methyl-D-aspartate (NMDA) receptor antagonism with ketamine is a common analgesic practice in the treatment of acute and perioperative pain. Ketamine has been shown to successfully alleviate pain in multiple gastrointestinal (GI) syndromes and pathologies.[1-4] However, the successful use of ketamine therapy for functional abdominal pain syndrome has not been described previously. Here we describe a case of FGID with relief of both GI symptoms of diarrhea and abdominal pain with low-dose oral ketamine therapy.

## CASE PRESENTATION

A female patient in her 60s with past medical history significant for IBS and possible celiac disease presented to the pain clinic for evaluation and treatment of chronic diarrhea. She described almost 12 years of fatigue with progressive GI symptoms despite thorough diagnostic testing and multiple intervention modalities, as outlined below. The benefit of ketamine was discovered serendipitously, as the initial prescription was for an unrelated medical issue, namely postoperative surgical pain therapy.

Briefly, 11 years prior, the patient developed lesions consistent with dermatitis herpetiformis, which resolved after initiation of a gluten-free diet. Because of prior episodes of this rash, she was considered to have celiac disease without biopsy confirmation, and she has remained on a gluten-free diet since that time without recurrence of skin lesions. Nine years prior, she began to experience severe fatigue, which she noted started after discontinuing venlafaxine therapy. Eight years prior, she developed 10 palpable nodules concerning for nodular fasciitis that sequentially appeared and resolved but were not all present at the same time. Although literature suggested an association of nodules with Lyme disease, to which the patient may have been exposed, Lyme serologies were negative. The lesions spontaneously resolved prior to biopsy and no definitive diagnosis could be made.

• • •

**Author Affiliations:** Department of Anesthesiology, Medical College of Wisconsin, Milwaukee, Wisconsin (Dyara, Woehlck); Medical College of Wisconsin Affiliated Hospitals, Milwaukee, Wisconsin (Topoluk).

**Corresponding Author:** Harvey Woehlck, MD, Professor of Anesthesiology, Department of Anesthesiology Froedtert Memorial Hospital, 9200 W Wisconsin Ave, Milwaukee, WI 53226; phone 414.805.2715; email hwoehlck@mcw.edu; ORCID ID 0000-0002-1701-392X

For relief of menopausal symptoms – primarily nighttime hot flashes that disturbed sleep and caused additional fatigue – the patient was started on estrogen and progesterone therapy with resolution of the hot flashes but without improvement of the fatigue. She underwent sleep polysomnography to rule out sleep apnea-related causes of fatigue but had a normal sleep study.

Seven years prior, the patient underwent upper and lower GI endoscopy for increasing diarrhea, flatulence, and bloating associated with worsening fatigue. The endoscopy showed colonic diverticulosis but normal gastric and small bowel mucosa without villous atrophy or inflammatory pathology. Over the next year, she continued to experience increased frequency and worsening severity of diarrhea, despite multiple antibiotic courses for presumed intestinal dysbiosis. Eosinophils were noted to be elevated as part of an investigation into fatigue, but no eosinophilic inflammation had been detected in intestinal biopsies.

The patient experienced her first episode of severe abdominal pain requiring urgent evaluation 5 years prior. No indications for surgical exploration were identified via abdominal imaging or white blood cell counts, and she was given ketorolac with resolution of abdominal pain. For the next 6 months, her bloating remained constant with 3 to 4 days per week of diarrhea. Transition to a low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diet provided partial relief of diarrhea, although this intervention increased the severity of abdominal pain. At this time, eosinophils were noted to have increased to 16% (absolute count 1000). Out of concern for possible human intestinal spirochetosis, she completed a course of metronidazole therapy without improvement in symptoms. Two months later, she was in constant severe abdominal pain and experienced a period of rapid weight loss (8 lbs in 3 weeks to 107 pounds, body mass index [BMI] 16.8) resulting in further evaluation at urgent care centers and emergency departments. Abdominal computed tomography and magnetic resonance imaging scans showed no identifiable pathology. She was started on dexamethasone therapy with improvement of pain to allow participation in activities of daily living.

Four days after initiation of steroid therapy, the patient had return of normal appetite and was without diarrhea. Within 1 month of starting steroid therapy, she was referred to an endocrinologist and underwent corticotrophin stimulation testing significant for low-normal morning cortisol and adrenocorticotropic hormone levels. She was instructed to stop steroid therapy. Two days after stopping steroid therapy, she experienced another episode of severe abdominal pain. She underwent repeat endoscopy showing no significant pathology. At this time, eosinophil count and tryptase were within normal range. Genetic testing was significant for neither DQ-2 nor DQ-8 markers of celiac disease. A functional bowel disorder consistent with IBS with nonceliac gluten intolerance was considered given historically elevated eosinophils and IgE levels. However, a subsequent trial of oral cromolyn therapy did not result in improvement of symptoms.

Two years prior, the patient started a 6-month course of tetracycline and folic acid therapy for treatment of possible tropical sprue, without improvement in symptoms. Symptoms persisted despite another trial of dexamethasone therapy 2 years prior.

Two years later, or about 1 year before present, the patient underwent hysterectomy. She described nausea and vomiting with perioperative opioids and was given ketamine to avoid further opioid administration. She subsequently experienced significant alleviation of her IBS symptoms for the first 5 to 6 postoperative weeks. Diarrhea began to recur thereafter, and a trial of very low-dose oral ketamine, 5 mg to 10 mg weekly, was initiated, with improvement in diarrhea and abdominal pain. Further adjustment of the dose revealed that 20 mg of oral ketamine once every 2 weeks was adequate to control symptoms of abdominal pain and diarrhea.

The patient kept a detailed symptom and diet diary for 60 days prior to hysterectomy, leading up to oral ketamine prescription and for 156 days after initiation of oral ketamine therapy. The diary indicated 9 out of 60 days with >6 bowel movements per day prior to initiation of oral ketamine therapy and only 5 out of 156 days after ketamine initiation ($P<0.05$ by chi-square analysis). Similarly, the diary indicated 7 out of 60 days with symptoms preventing activities of daily living prior to initiation of oral ketamine therapy and only 4 out of 156 days after ketamine initiation ($P<0.05$ by chi-square analysis). As long as she adhered to the low-FODMAP diet, she had the same low incidence of diarrhea and abdominal symptoms. She has been able to reintroduce many foods that previously caused symptoms and has gained back 11 pounds (118 pounds, BMI 18.5).

In follow-up for a year after initiation of ketamine, the dose requirement had not increased and efficacy remained constant. The patient described how after a 20 mg of oral ketamine administered in a sublingual lozenge, she will typically have to lie down for about 2 hours but remains conscious and does not experience side effects like hallucinations. She can read or get up to go to the bathroom but avoids any tasks requiring coordination, like cooking, driving, or outdoor activities.

## DISCUSSION

The patient was diagnosed with IBS with diarrhea due to the constellation of GI symptoms and abdominal pain without confirmed underlying pathology despite extensive diagnostic testing, which was consistent with FGID. While debate continues in published medical opinions, dysbiosis, dysmotility, and visceral hypersensitivity all have been implicated as contributors to FGID symptomatology. Disruption of the innate microbiota – dysbiosis – can cause and worsen GI symptoms. Studies also have shown dysmotility promotes dysbiosis, sometimes manifested as small intestinal bacterial overgrowth syndrome (SIBO).[5] Therapies com-

monly employed to treat the symptoms of functional abdominal pain syndrome, including loperamide, may reduce gut motility, potentially worsening SIBO and furthering a cycle of seemingly intractable GI symptoms. While not completely elucidated, both peripheral and central sensitization have been implicated in visceral pain perception.[6]

We present 2 possible mechanisms for symptom alleviation: NMDA mediation of central sensitization and toll-like receptor (TLR) pathway mediation of dysbiosis. Ketamine is an NMDA antagonist commonly administered for its analgesic properties, including chronic pain involving the GI tract. Central sensitization results from increased responsiveness of dorsal horn neurons and heterosynaptic potentiation of these neurons, creating the perception of an increased and more widespread pain than the original area of neuronal excitation.[6-7] This phenomenon of central sensitization has been linked to the NMDA receptor via multiple mechanisms, for which ketamine as an NMDA antagonist is beneficial.[6-8]

Ketamine has been used in both acute and acute on chronic pancreatitis with reported successful analgesia in both intravenous (IV) and oral formulations.[1-2] Though the exact mechanism has not been elucidated, ketamine has successfully alleviated symptoms in other GI pathologies, including cyclic vomiting syndrome and Crohn's disease.[3-4] A small, randomized, double-blinded, crossover study evaluated IV ketamine's ability to mitigate induced visceral hypersensitivity caused by esophageal acid infusion.[7] The study reported both reduction and prevention of esophageal pain thresholds with IV ketamine bolus. However, ketamine therapy alleviating pain and GI distress in this type of functional bowel disorder, as seen in this case, has not been reported previously in the literature.

A second possible mechanism accounting for both improvements in GI function as well as perceived abdominal pain involves ketamine action on TLR pathways. In vivo studies in mice have linked dysbiosis with up-regulation of TLR pathways, including TLR 4.[9] Ketamine has been shown to suppress TLR 4 signaling pathways in the lungs and intestines of rats.[10,11] Thus, ketamine could improve symptoms of GI distress and abdominal pain through TLR-mediated regulation of dysbiosis. Additionally, while anatomic factors and antidiarrheal drugs that slow small bowel and colonic transit are associated with dysbiosis,[5] ketamine does not appear to have adverse effects on gut motility,[12] potentially limiting the cyclic contribution of dysmotility and dysbiosis to overall symptomatology.

Non-IV ketamine therapy is a novel concept, with older literature indicating administration in a health care setting[13] and more contemporary reports indicating a transition to home ketamine therapy for intractable pain and treatment-resistant depression.[14,15] The low dose required by this patient has resulted in successful home therapy, avoiding the cost and inconvenience of in-clinic administration. The lack of tolerance or escalation in dose requirement suggests that the treatment may have long-term benefit in some patients.

**Financial Disclosures:** None declared.

**Funding/Support:** None declared.

**Acknowledgement:** The patient gave written authorization for publication of this case report.

## REFERENCES

**1.** Mulder DJ, Sherlock ME, Lysecki DL. NMDA-receptor antagonism in pediatric pancreatitis: use of ketamine and methadone in a teenager with refractory pain. *J Pediatr Gastroenterol Nutr.* 2018;66(5):e134-e136. doi:10.1097/MPG.0000000000001907

**2.** Bouwense SA, de Vries M, Schreuder LT, et al. Systematic mechanism-orientated approach to chronic pancreatitis pain. *World J Gastroenterol*. 2015;21(1):47-59. doi:10.3748/wjg.v21.i1.47

**3.** Cheung F, Doherty SM, Tatara AW. Ketamine in refractory cyclic vomiting syndrome: a case report and review of literature. *J Pharm Pract*. 2022;35(5):805-810. doi:10.1177/08971900211000684

**4.** Bredlau AL, McDermott MP, Adams HR, et al. Oral ketamine for children with chronic pain: a pilot phase 1 study. *J Pediatr.* 2013;163(1):194-200.e1. doi:10.1016/j.jpeds.2012.12.077

**5.** Bures J, Cyrany J, Kohoutova D, et al. Small intestinal bacterial overgrowth syndrome. *World J Gastroenterol*. 2010;16(24):2978-2990. doi:10.3748/wjg.v16.i24.2978

**6.** Matthews PJ, Aziz Q. Functional abdominal pain. *Postgrad Med J.* 2005;81(957):448-455. doi:10.1136/pgmj.2004.030577

**7.** Willert RP, Woolf CJ, Hobson AR, Delaney C, Thompson DG, Aziz Q. The development and maintenance of human visceral pain hypersensitivity is dependent on the N-methyl-D-aspartate receptor. *Gastroenterology*. 2004;126(3):683-692. doi:10.1053/j.gastro.2003.11.047

**8.** Doan LV, Wang J. An update on the basic and clinical science of ketamine analgesia. *Clin J Pain.* 2018;34(11):1077-1088. doi:10.1097/AJP.0000000000000635

**9.** Aguilera M, Cerdà-Cuéllar M, Martínez V. Antibiotic-induced dysbiosis alters host-bacterial interactions and leads to colonic sensory and motor changes in mice. *Gut Microbes*. 2015;6(1):10-23. doi:10.4161/19490976.2014.990790

**10.** Xu D, Sun X, Zhang Y, Cao L. Ketamine alleviates HMGB1-induced acute lung injury through TLR4 signaling pathway. *Adv Clin Exp Med*. 2020;29(7):813-817. doi:10.17219/acem/121936

**11.** Yu M, Shao D, Yang J, Feng S, Xu J. Ketamine suppresses intestinal TLR4 expression and NF-kappaB activity in lipopolysaccharide-treated rats. *Croat Med J.* 2006;47(6):825-831.

**12.** Shafton AD, Bogeski G, Kitchener PD, Sanger GJ, Furness JB, Shimizu Y. Effects of NMDA receptor antagonists on visceromotor reflexes and on intestinal motility, in vivo. *Neurogastroenterol Motil*. 2007;19(7):617-624. doi:10.1111/j.1365-2982.2007.00942.x

**13.** Blonk MI, Koder BG, van den Bemt PM, Huygen FJ. Use of oral ketamine in chronic pain management: a review. *Eur J Pain*. 2010;14(5):466-472. doi:10.1016/j.ejpain.2009.09.005

**14.** Marchetti F, Coutaux A, Bellanger A, Magneux C, Bourgeois P, Mion G. Efficacy and safety of oral ketamine for the relief of intractable chronic pain: a retrospective 5-year study of 51 patients. *Eur J Pain*. 2015;19(7):984-993. doi:10.1002/ejp.624

**15.** Hull TD, Malgaroli M, Gazzaley A, et al. At-home, sublingual ketamine telehealth is a safe and effective treatment for moderate to severe anxiety and depression: findings from a large, prospective, open-label effectiveness trial. *J Affect Disord*. 2022;314:59-67. doi:10.1016/j.jad.2022.07.004

advancing the art & science of medicine in the midwest

WMJ

*WMJ* (ISSN 1098-1861) is published through a collaboration between The Medical College of Wisconsin and The University of Wisconsin School of Medicine and Public Health. The mission of *WMJ* is to provide an opportunity to publish original research, case reports, review articles, and essays about current medical and public health issues.



**Visit www.wmjonline.org to learn more.**