



Universiteit  
Leiden  
The Netherlands

## **Esketamine in the treatment of chronic endometriosis-induced pain: a case report**

Koning, R. de; Zwart, G.; Dahan, A.; Jansen, F.W.; Blikkendaal, M.; Twijnstra, A.

### **Citation**

Koning, R. de, Zwart, G., Dahan, A., Jansen, F. W., Blikkendaal, M., & Twijnstra, A. (2023). Esketamine in the treatment of chronic endometriosis-induced pain: a case report. *Journal Of Endometriosis And Pelvic Pain Disorders*, 15(1), 49-52.  
doi:10.1177/22840265231153518

Version: Publisher's Version

License: [Creative Commons CC BY 4.0 license](https://creativecommons.org/licenses/by/4.0/)

Downloaded from: <https://hdl.handle.net/1887/3754349>

**Note:** To cite this publication please use the final published version (if applicable).

# Esketamine in the treatment of chronic endometriosis-induced pain: a case report

Rozemarijn de Koning<sup>1,2</sup>, Gertjan Zwart<sup>3</sup>, Albert Dahan<sup>4</sup>,  
Frank Willem Jansen<sup>1</sup>, Mathijs Blikkendaal<sup>2</sup> and  
Andries Twijnstra<sup>1</sup>

Journal of Endometriosis and  
Pelvic Pain Disorders  
2023, Vol. 15(1) 49–52  
© The Author(s) 2023



Article reuse guidelines:  
sagepub.com/journals-permissions  
DOI: 10.1177/22840265231153518  
journals.sagepub.com/home/pev



## Abstract

**Introduction:** The pathophysiology of endometriosis-induced pain is complex and current pain management is often inadequate. As a consequence, the quality of life of endometriosis patients is reduced due to persistent and often recurrent severe pain, affecting emotional well-being.

**Case description:** In this case report, we present a 28-year-old patient with deep endometriosis and severe pain resistant to conventional therapy, who experienced, after an 8-h infusion with esketamine, no pain symptoms for 8 weeks.

**Discussion:** Current treatment options to suppress chronic pain symptoms in patients with (deep) endometriosis are often inadequate. Esketamine targets key components of the condition (inflammation, pain, depression), but the use of this drug in the treatment of chronic pain due to endometriosis has not been reported yet. Future trials are necessary to assess the effect of esketamine in the treatment of chronic pain due to endometriosis.

**Conclusion:** This case report highlights the potential of esketamine infusion therapy in the treatment of endometriosis patients with persistent pain despite conventional therapy.

## Keywords

Deep endometriosis, esketamine, pain, quality of life, case report

Date received: 22 December 2022; accepted: 10 January 2023

## Introduction

Endometriosis is a debilitating disease, characterized by extra-uterine endometrium-like tissue and chronic inflammation, affecting approximately 10% of women in their reproductive years.<sup>1</sup> Whilst symptom heterogeneity is high, clinical hallmarks of endometriosis are infertility and severe pain symptoms (e.g. dysmenorrhea, dyschezia, dysuria, dyspareunia, and chronic pelvic pain), resulting in a lower quality of life and reduced emotional well-being.<sup>1,2</sup> Hormonal treatment and laparoscopic resection are both recommended to reduce endometriosis-associated pain.<sup>2</sup> However, treatment efficacy and side effect profiles vary significantly among patients. In addition, chronic pain frequently persists after resection of endometriosis lesions, even in the absence of lesion regeneration, suggesting a complex pain pathophysiology.<sup>3</sup> Frequently prescribed analgesics such as paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs) and opioids, are often insufficient. Moreover the use of opioids comes with various adverse effects including tolerance, addiction and abuse.<sup>4</sup> Therefore, we must seek for alternative long-term pain

treatments. Low-dose esketamine, a non-selective *N*-methyl-D-aspartate receptor (NMDAR) antagonist, has analgesic, anti-depressive, and anti-inflammatory properties and is currently used for a variety of indications including acute and chronic (neuropathic) pain and therapy-resistant depression.<sup>5</sup> To our knowledge, esketamine infusion for the treatment of chronic endometriosis-induced pain has never been described. Here, we report on

<sup>1</sup>Department of Gynaecology and Obstetrics, Leiden University Medical Center, Leiden, The Netherlands

<sup>2</sup>Endometriosis in Balance Expertise Center, Haaglanden Medical Center, The Hague, The Netherlands

<sup>3</sup>Department of Anesthesiology, Isala Hospital, Zwolle, The Netherlands

<sup>4</sup>Department of Anesthesiology, Leiden University Medical Center, Leiden, The Netherlands

### Corresponding author:

Rozemarijn de Koning, Leiden University Medical Center, Albinusdreef 2, Leiden 2300 RC, The Netherlands.  
Email: R.de\_koning@lumc.nl

a successful case of chronic pain treatment with esketamine in a patient with deep endometriosis.

## Case description

A 28-year-old nullipara patient (BMI 19.7 kg/m<sup>2</sup>) with deep endometriosis presented at a national referral center for endometriosis. The patient had a history of primary dysmenorrhea, menorrhagia, painful defecation, irregular menstrual cycle, and debilitating abdominal discomfort. The patient used multiple types of hormonal treatment since the age of 14, including oral contraceptives, levonorgestrel intrauterine device and a subcutaneous etonogestrel implant, all without significant effect. Most importantly, these treatments caused recurrent symptoms of depression. Her surgical history included the laparoscopic coagulation of endometriosis lesions in the pouch of Douglas, sacro-uterine ligaments and on the left ovarian fossa, 1 year before presentation in our center. Unfortunately, the alleviation of pain symptoms after surgical treatment lasted no longer than 4 weeks. At the moment of presentation, the patient was on continuous desogestrel therapy, NSAIDs and paracetamol, but was still suffering from severe pain symptoms and reported the following numerical rating scores (NRS): dysmenorrhea NRS 10 (on an 11-point scale with 0=no pain and 10=worst pain imaginable), dysuria NRS 7, dyspareunia NRS 7, dyschezia NRS 10, and chronic pelvic pain NRS 10 (radiating to the lower back and the back of both legs). On pelvic exam, she had an immobile uterus and a painful nodule was palpated on the torus uterinus. A MRI was performed and showed deep endometriosis lesions on the transition of the fornix posterior to the torus uterinus with involvement of both sacro-uterine ligaments. According to the #Enzian classification, endometriosis was classified as A2, B1/1, C0.

For pain management, the patient remained under treatment in a specialized pain center. Because of her reluctance to use opioids and the experience of this center with off-label use of esketamine for chronic pain relief, which is supported by previous randomized controlled trials including patients with complex regional pain syndrome (CRPS), she was planned for intravenous esketamine therapy.<sup>6</sup> Esketamine (Eurocept Pharmaceuticals, Ankeveen, the Netherlands) was administered for 8 consecutive hours on a single day. The initial infusion rate was 2.5 mg/h (0.045 mg/kg/h) and was gradually increased to a maximum of 6.75 mg/h (0.12 mg/kg/h). The patient received a total of 40 mg esketamine during the 8 h of infusion. Apart from symptoms of vertigo, the treatment was well tolerated. After having received the esketamine infusion, she returned home. In the subsequent 2 days, she reported extreme fatigue and some relief from pain symptoms. However, after 1 week, she reported being completely pain-free. Aside from some non-disabling cramps during the

menstruation, the pain-free period continued for 8 weeks, after which the pain symptoms slowly returned to levels experienced before the esketamine infusion. The patient underwent a second esketamine infusion treatment 13 weeks after the first treatment. At the moment, she is experiencing the same treatment effect.

## Discussion

Endometriosis has a high clinical burden and affects approximately 1 in 10 women (and their partners and families) worldwide.<sup>1</sup> Despite the benign aspect of the disease, endometriosis-associated symptoms, especially pain symptoms, cause a significant reduction in women's quality of life, social participation, sexual intimacy and mental health.<sup>1</sup> Opioids are often prescribed when paracetamol and NSAIDs fail to relieve pain. However, a recent cohort study in the United States shows that endometriosis patients are known to have a four times greater risk of persistent opioid use compared to non-endometriosis patients, resulting in higher opioid tolerance and the potential for abuse and addiction.<sup>4</sup> Therefore, caution is warranted when prescribing these drugs and search for alternatives for long-term pain treatments is urgent.

Relatively little is known about the pathophysiology of endometriotic pain.<sup>3</sup> In general, endometriosis-induced pain is considered nociceptive in nature, triggered by multiple mechanisms as outlined by Maddern et al.<sup>3</sup> Prolonged nociceptive stimulation induces upregulation of the NMDAR, resulting in the amplification of pain signals to the brain.<sup>6</sup> In addition, it is interesting that the incidence of other comorbidities characterized by sensory dysfunction (e.g. irritable bowel syndrome) is higher among women with endometriosis compared to women without endometriosis.<sup>7</sup> Together, evidence suggests that in these patients chronic remodeling of central sensory neural pathways occurs, inducing peripheral and central sensitization and eventually persistent pain.<sup>3</sup> This may explain why disease classification poorly correlates with pain severity and the anatomical location of (deep) endometriosis lesions and why chronic pain frequently returns after surgical removal of endometriosis.<sup>1,3</sup>

Ketamine is a racemic mixture consisting of esketamine and arketamine. Esketamine is the left-handed optical isomer of ketamine and has a three to fourfold greater binding affinity for the NMDAR than arketamine ( $K_i=0.3 \mu\text{M}$  and  $K_i=1.4 \mu\text{M}$ ), allowing the desired effect to be achieved with smaller doses of esketamine compared to ketamine, resulting in fewer side effects.<sup>8</sup> The NMDAR is an excitatory glutamatergic receptor present at spinal and supraspinal sites and is involved in the afferent transmission of nociceptive signals. NMDAR antagonists, such as (es)ketamine, can halt the excessive barrage of nociceptive afferent input to the brain from persistent tissue damage. Although (es)ketamine treatment is considered safe in

controlled clinical settings, multiple side effects have been noted in clinical trials including psychedelic symptoms (memory defects, panic attacks, hallucinations), nausea/vomiting, cardiovascular side effects (tachycardia, systematic and pulmonary hypertension, increased cardiac output and myocardial oxygen consumption) and in some cases reversible hepatotoxicity.<sup>6</sup>

(Es)ketamine's primary indication as rapid acting anesthetic is expanding to other clinical domains, such as treatment for depression or off-label use to alleviate chronic pain.<sup>6</sup> The patient described in this report received low-dose esketamine infusion (40 mg during 8 h). This is significantly lower than the dose to induce anesthesia (0.5–1.0 mg/kg followed by half this dose every 10–15 min to maintain anesthesia) and treatment-resistant depression (56 mg followed by 56 or 84 mg once a week, depending on efficacy and tolerability).<sup>9,10</sup>

We argue that while current endometriosis treatments do not target multiple aspects of the disease (pain, inflammation, depression) simultaneously, (es)ketamine theoretically does. For example, there is evidence from animal and human studies for a ketamine-induced anti-inflammatory effect.<sup>6</sup> And equally important, while the prevalence of depressive symptoms is relatively high in women with endometriosis, (es)ketamine is registered for the treatment of treatment-resistant depression.<sup>6</sup>

The presented case stresses the importance to explore alternative treatments in order to improve the quality of life of endometriosis patients. Although 1 day of esketamine infusion had a remarkable effect on our patient, prolonged infusion with esketamine may result in an even longer symptom-free period. For example, in the study of Sigtermans et al. patients with CRPS type 1 were treated with 4 days infusion of esketamine, which resulted in long-term pain relief lasting up to 3 months.<sup>6</sup> Similar observations were made in CRPS patients receiving a daily 4-h infusion of ketamine for 10 days.<sup>6</sup> Currently, one randomized controlled trial (RCT) is investigating the potential of a single ketamine shot (0.6 mg/kg) to reduce postoperative pain after laparoscopic endometriosis resection in women with chronic pelvic pain (the UPKEEEP study).<sup>11</sup> Future research and RCTs should also focus on analyzing the efficacy and safety of (es)ketamine infusion therapy and assessing the clinical utility of (es)ketamine as an additional treatment option to bridge the time to surgery or even as maintenance therapy for chronic pelvic pain caused by endometriosis when conventional therapy fails.<sup>5</sup>

## Conclusion

Esketamine is a versatile drug that possesses analgesic, anti-inflammatory and anti-depressive properties. This

makes esketamine a promising treatment option for patients with chronic endometriosis-induced pain.

## Acknowledgements

None.

## Author contributions

RdK wrote the case report under the supervision of MB, FWJ and AT. MB and AT are both gynecologists and endometriosis experts. In this case, MB is the treating physician regarding endometriosis and GZ is the treating physician regarding pain management. AD is an (es)ketamine expert and he supervised the information provided in this report on esketamine. All authors contributed to the final manuscript.

## Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

## Ethical approval

The local IRB (METC Isala Zwolle) has been contacted and they confirmed that no medical ethical approval concerning Medical Research Involving Human Subjects Act (WMO) is necessary because the patient gave permission to write and publish this case report. Furthermore, esketamine infusion for chronic pain is part of standardized healthcare in the Netherlands.

## Informed consent to participate

Written informed consent was obtained from the patient described in this case report and is available upon request at any time.

## Informed consent to publish

Written informed consent was obtained from the patient described in this case report and is available upon request at any time.

## Trial registration

Not applicable.

## ORCID iDs

Rozemarijn de Koning  <https://orcid.org/0000-0001-9955-5150>

Mathijs Blikkendaal  <https://orcid.org/0000-0002-3939-9448>

## References

1. Zondervan KT, Becker CM and Missmer SA. Endometriosis. *N Engl J Med* 2020; 382: 1244–1256.

2. Becker CM, Bokor A, Heikinheimo O, et al. ESHRE guideline: endometriosis. *Hum Reprod Open* 2022; 2022: hoac009.
3. Maddern J, Grundy L, Castro J, et al. Pain in endometriosis. *Front Cell Neurosci* 2020; 14: 590823.
4. Chiuve SE, Kilpatrick RD, Hornstein MD, et al. Chronic opioid use and complication risks in women with endometriosis: a cohort study in US administrative claims. *Pharmacoepidemiol Drug Saf* 2021; 30: 787–796.
5. Zanos P, Moaddel R, Morris PJ, et al. Ketamine and Ketamine metabolite pharmacology: insights into therapeutic mechanisms. *Pharmacol Rev* 2018; 70: 621–660.
6. Niesters M, Martini C and Dahan A. Ketamine for chronic pain: risks and benefits. *Br J Clin Pharmacol* 2014; 77: 357–367.
7. Surrey ES, Soliman AM, Johnson SJ, et al. Risk of developing comorbidities among women with endometriosis: a retrospective matched Cohort Study. *J Womens Health* 2018; 27: 1114–1123.
8. Ebert B, Mikkelsen S, Thorkildsen C, et al. Norketamine, the main metabolite of ketamine, is a non-competitive NMDA receptor antagonist in the rat cortex and spinal cord. *Eur J Pharmacol* 1997; 333: 99–104.
9. Jalloh M. Esketamine (Spravato) for treatment-resistant depression. *Am Fam Physician* 2020; 101: 339–340.
10. Eurocept International BV. Summary of product characteristics: Esketiv. 2018.
11. Huang K and Zaslavsky J. The Using Postoperative Ketamine and Exploring the Effect on Endometriosis Pain (UPKEEEP) Study. ClinicalTrials.gov identifier: NCT05229653. 2022.