DRUGS IN CONTEXT
RIGOROUS • RAPID • RESPONSIVE

A continuous publication, open access, peer-reviewed journal

ACCESS ONLINE

CASE REPORT

Experience with nutraceutical supplements in the treatment of pelvic pain in gynaecology: case reports

Francisco Nohales Alfonso

Gynecology Section, Clinical Area of Women´s Diseases, La Fe University Hospital, Valencia, Spain

Abstract

Three women with diverse gynaecological medical histories (one with endometriosis, one having had an episiotomy and obstetric anal sphincter injury during a recent delivery, and one having had a recent cystectomy of the left Bartholin gland) developed acute episodes of gynaecological pelvic pain. In each case, clinical investigations (including objective tools for assessing the source, nature and severity of the pain) were conducted early on, and a multimodal approach to therapy was introduced to control the pain and avoid central sensitization or chronicity. The multimodal approach included hormone therapy, antineuropathic medications, and corticosteroid or botulinum neurotoxin infiltrations in some of the patients according to their medical conditions but consistently included behavioural adjustments, physical interventions and a nutraceutical supplement (alpha-lipoic acid, palmitoylethanolamide and myrrh). In each case, the pelvic pain and associated dyspareunia (Marinoff scale 2 or 3) were largely resolved. These clinical cases support the results of clinical trials showing the benefits of alpha-lipoic acid + palmitoylethanolamide + myrrh for the management of gynaecological pelvic pain, enabling the reduction or withdrawal of other analgesic, anti-inflammatory and antineuropathic medications.

Keywords: alpha-lipoic acid, chronic pain, endometriosis, myrrh, neuropathic pain, nutraceutical supplement, palmitoylethanolamide, pelvic pain.

Citation

Nohales Alfonso F. Experience with nutraceutical supplements in the treatment of pelvic pain in gynaecology: case reports. *Drugs Context*. 2022;11:2021-10-8. https://doi.org/10.7573/dic.2021-10-8

Introduction

Pain can be classified according to the type of injury or trauma and the pathophysiological pathway that leads to the perception of pain.[1,2] Nociceptive pain describes a normal physiological response to tissue damage resulting from trauma, non-healing injury or inflammatory processes. The International Association for the Study of Pain defines nociceptive pain as "*pain that arises from actual or threatened damage to non-neural tissue … due to the activation of nociceptors*".[1] It distinguishes the origin as somatic (through musculoskeletal injury) or visceral (through internal organ injury). Neuropathic pain is defined as pain caused by injury or disease of the somatosensory nervous system due to abnormal neuronal activity. It can affect the central neurons or peripheral nerve fibres.[3] Finally, central sensitization or nociplastic pain is defined as pain arising from impaired nociception despite an absence of clear evidence of actual or threatening tissue damage causing activation of peripheral nociceptors and no evidence of disease or injury within the somatosensory system that causes pain.[1]

Pain can also be described as acute or chronic, depending on how long the patient experiences it. It is acute if it resolves in 3–6 months and is self-limited to the healing or repair of damaged tissue, therefore having a biological purpose. In contrast, chronic pain persists beyond the normal healing time and has no biological purpose. Generally, pain must persist or recur for more than 3 months to be defined as chronic, and such chronic pain may be secondary to an underlying disease or it may be a disease in its own right.[4]

The European Association of Urology defines chronic pelvic pain as "*chronic or persistent pain perceived in the structures related to the pelvis… often associated with negative cognitive, behavioural, sexual and emotional consequences as well as with symptoms suggestive of lower urinary tract, sexual, bowel, pelvic floor or gynaecological dysfunction*".[5] In cases of nociceptive pain that persist over time, it can be continuous or recurrent

and must last for at least 6 months. If the mechanisms of non-acute pain and central sensitization are well documented, it can be considered chronic regardless of duration.[5,6]

The anatomical classification of pain is used to determine which parts of the body are experiencing pain. It is the first clinical assessment of pain. In the field of gynaecology, pelvic pain may be associated, amongst other things, with endometriosis, adenomyosis and fibroids.[7]

It is important to identify the type and origin of pain in order to recommend the best possible treatment, considering that a multimodal and interdisciplinary approach, focused on the patient (including their lifestyle, physical and psychological status, pharmacological factors), will produce the best outcome.[2] This is especially so where, because of the duration of the pain and/or its aetiology, it may become chronic.

Thus, in endometriosis, surgical and hormonal treatments are the mainstay.[8] The appearance of other characteristics of pain, associated with inflammation, may require complementary analgesic treatment. However, hormonal therapy interferes with fertility, and surgical excision/ablation of endometrial lesions tends to provide only temporary relief before the recurrence of lesions.[9]

Neuropathic pain plays an important but poorly recognized role in gynaecology.[10] It is often misdiagnosed and treated inappropriately. Pudendal nerve compression is one possible cause of pudendal neuralgia but careful assessment is required to exclude other possible causes and ensure appropriate medical or surgical intervention.[11]

Certain nutraceuticals have received attention as alternatives for pain management. Alpha-lipoic acid (ALA) is one such nutraceutical. Clinical studies have shown its effectiveness, in combination with palmitoylethanolamide (PEA) and myrrh, in relieving pain in patients with endometriosis and chronic pelvic pain.[12,13] Both PEA[14] and ALA[15] have also been shown, in clinical trials, to relieve pain associated with nerve compression. Moreover, ALA has demonstrated antioxidant activity by neutralizing reactive oxygen species,[16,17] neuroprotective activity by inhibiting the attraction of macrophages to the damaged nerve,[18] and analgesic and anti-inflammatory activity by modifying the calcium current in T-type channels and inhibiting the induction of TNF, VCAM1 and ICAM1.[19,20] Meta-analyses of clinical trials involving the use of PEA for the treatment of chronic pain have shown a progressive reduction in pain intensity, which was significantly greater than in control groups and independent of the type of chronic pain,[21] and consistent analgesic activity.[22] Myrrh has also been shown to possess anti-inflammatory and analgesic properties.[23–25]

The safety of these nutraceuticals in clinical trials has also been reviewed and both PEA and ALA are well tolerated,[14,22,26] the latter proving safe in pregnant mothers and their newborns.[26]

These positive findings encouraged the use of PEA, ALA and myrrh in the cases presented herein.

Methods and consent

All patients presented in the course of routine clinical practice. No information is reported that could enable any patient to be identified; therefore, no patient consent to the reporting of these cases was required. This manuscript, prepared according to CARE guidelines, is a review of case studies and does not involve a research protocol requiring approval by a relevant institutional review board or ethics committee.

Case studies

Case 1 – Multimodal approach, with a nutraceutical supplement, for the management of pelvic pain prior to successful pregnancy

A 32-year-old nulliparous woman with a body mass index (BMI) of 30 had a history of dysmenorrhoea, intercyclic pain and dyspareunia that did not subside with ibuprofen. There were no comorbidities and no medical history of interest.

A diagnostic laparoscopy performed in July 2019 revealed peritoneal endometriosis, confirmed by biopsy. Later, the patient took hormonal contraception with the improvement of dysmenorrhoea and intercyclic pain.

Three months later, in October 2019, the patient presented with stabbing pain, almost daily, in the hypogastrium (visual analogue scale (VAS) score 4) exacerbated (VAS 7) when she sat for a long time or performed physical exertion. She had a tendency towards constipation (<3 bowel movements a week) which caused increased pain (VAS 7). Sexual intercourse was painful (superficial and deep dyspareunia) and was not improved after laparoscopic surgery. The discomfort could interrupt intercourse (Marinoff 2),[27] with later complaints of postcoital vulvar burning. Although her symptoms improved after starting hormonal contraceptives, the patient did not want her fertility compromised. Whilst the patient had difficulty getting to sleep, once asleep the pain did not wake her.

There were no clinical criteria for pelvic sensitization (Aix En Provence, 4 points).[28]

Examination did not find trigger points indicative of pain of musculoskeletal origin but did find selective pain in the vulvar vestibule at multiple points (vestibulodynia localized provoked) without inflammation. There was no accompanying myofascial pain, and no finding of affected pudendal territory.

A pelvic ultrasound revealed ovaries at rest and no images compatible with endometriosis.

A multimodal therapeutic approach was initiated, comprising improvement of intestinal transit (with bowel movements 4–5 times a week), avoiding defecation efforts (with dietary fibre); pelvic stretching and postural re-education exercises (for her work), accompanied by Pilates; maintenance of the

oral contraceptive pill (COCP) to achieve amenorrhoea; topical application of oestrogens and androgens in the vulvar vestibule to desensitize the vestibular mucosa (from COCP use); and the use of a nutraceutical supplement containing ALA (800 mg), PEA (600 mg) and myrrh (200 mg), combining anti-inflammatory, analgesic and antioxidant actions, at a dose of 2 tablets daily.

After 2 months of treatment (December 2019), the patient reported a clear improvement in all symptoms, although a slight deep dyspareunia persisted (Marinoff 1). There was an objective evaluation of improvement (Patient Global Impression of Improvement (PGI-I) score of 2). Examination revealed that fibrosis was maintained in the right uterosacral ligament, which could be the cause of the deep dyspareunia. In the absence of specific ultrasound findings of disease persistence, the patient was keen to become pregnant.

It was recommended that the patient continue the physical/behavioural measures and nutraceutical use; stop the use of topical hormone creams and COCP; and start preconception folic acid (recommended dose 400 µg/day).

After 4 months (April 2020), the patient became pregnant and suspended nutraceutical use to continue with specific pregnancy supplements.

Case 2 – Post-partum neuropathic pelvic pain effectively managed by a multimodal approach including a nutraceutical supplement

A 37-year-old woman, with a BMI of 35, had an instrumental delivery (neonate weighing 4 kg) resulting in right mediolateral episiotomy and an obstetric anal sphincter injury (OASIS category IIIb[29]) that was sutured during delivery. There was no comorbidity and no medical or family history of interest.

After delivery (March 2020), the patient had severe perineal pain that partially subsided with analgesia, but, as she was breastfeeding, she tried to avoid analgesic use. She also had mild stress urinary incontinence (ICQ-SF 8) and gas incontinence (Wexner 5). She was unable to perform pelvic floor physical therapy as initially recommended.

Three months later (June 2020), the patient presented with stabbing, electrical daily pain in the perineum (VAS 6), exacerbated (VAS 9) when she sat for a long time or did some physical activity. The pain was accompanied by a vulvar burning/stinging sensation and was neuropathic in nature (Douleur Neuropathique 4 questionnaire (DN4)[30] score of 4) but did not wake her at night. She avoided defecation because this increased her pain to a severe level as well as sexual intercourse (Marinoff 3). Double incontinence (urinary and anal) persisted, although this was of less concern to the patient than the pain. She had discontinued breastfeeding and was waiting for her menstruation to resume.

There were no clinical criteria for pelvic sensitization (Aix En Provence, 4 points).[28]

Clinical examination found trigger points in the lumbosacral, bilateral sacroiliac and pyramidal muscle (mainly right), with hyperalgesia of the right hemivulva, accompanied by signs of ipsilateral pudendal neuralgia and spontaneous vestibulodynia with low trophism. The anal wink reflex was preserved. There was myofascial pain of the pelvic floor muscle (VAS 7) without hypertonia and with a low Oxford grade (2/5), suggesting global dysfunction and damage of the pelvic floor. The anal sphincter was hypotonic.

A pelvic floor ultrasound showed a wide hiatus and levator ani avulsion and an undamaged anal sphincter. There was no neurophysiological investigation nor other imaging tests of the pudendal nerve.

The following multimodal approach to therapy was instigated: improvement of intestinal transit (with bowel movements 5–6 times a week), avoiding defecation efforts (with dietary fibre); pelvic stretching exercises, pelvic floor physiotherapy and avoidance of sexual activity; use of a nutraceutical supplement containing ALA (800 mg), PEA (600 mg) and myrrh (200 mg), combining anti-inflammatory, analgesic and antioxidant actions, at a dose of 2 tablets daily; pregabalin 75 mg every 12 hours; and amitriptyline 1 tablet (10 mg) at night (the dose doubled every 15 days in the absence of improvement).

After 3 months of treatment (September 2020), the patient reported clear improvement in all domains (absence of incontinence and pain; PGI-I 2). She had not had sexual intercourse and presented a hypermenorrhoea, accompanied by severe dysmenorrhoea. The onset of defecation was reported as painful. She had not needed to increase the antineuropathic dosage.

Clinical examination showed a lower vestibular sensitivity, higher pelvic floor muscle tone (Oxford grade 3/5) with slightly increased sensitivity (VAS <4), normal anal sphincter tone (but very painful on examination) and recovered vulvovaginal trophism.

Gynaecological ultrasound was consistent with a hypertrophic uterus with signs of adenomyosis. There was normal follicular activity of the ovaries.

It was recommended that the patient continue the behavioural/physical measures and nutraceutical use; gradually abandon antineuropathic therapy (first pregabalin and then amitriptyline); introduce COCP; introduce perineal massages with rosehip oil; receive infiltration with corticosteroids (up to three injections in decreasing doses from 1 mL to 0.5 mL, to 0.25 mL separated at intervals of 7–15 days) on the anal sphincter and perineum.

At a subsequent follow-up, the patient was assessed as being able to recommence sexual intercourse (Marinoff 1) and sex counselling was recommended.

Case 3 – Post-surgical Bartholin gland and pelvic pain managed by a multimodal approach including nutraceutical supplement

A 25-year-old patient with a BMI of 18 had primary dysmenorrhoea and a history of migraine. She underwent a cystectomy of the left Bartholin gland for repeated episodes of acute Bartholinitis in May 2020.

At baseline (June 2020), the patient presented with burning pain and electric shocks in the vulvar scar area (DN4 score: 6), accompanied by dysuria after urination. She could not wear tight clothes and sit for long periods and reported that sexual intercourse was impossible. Her pain increased during menstruation. She did not report incontinence. She took conventional anti-inflammatory/analgesic medication but her baseline pain did not improve (VAS 7).

Examination revealed hyperaesthesia of the left hemivulva with signs of pudendal neuralgia (perineal branch) and accompanying myofascial pain in the left superficial (transverse) planes (VAS >4). The vulvar scar was very painful to superficial friction, without signs of inflammation or objective dermatological lesions. There was no inguinal adenopathy, her anal wink reflex was preserved and the levator ani muscle was tender.

There were criteria for pelvic sensitization (Aix en Provence criteria category 5).

The following combination was recommended for managing this patient's condition: general measures: avoid tight clothing, vulvar washings with anti-inflammatory solutions, assess thermal response to cold, avoid sitting without perineal protection; use of a nutraceutical supplement containing ALA (800 mg), PEA (600 mg) and myrrh (200 mg), 2 tablets per day; pregabalin 75 mg every 12 hours; amitriptyline 1 tablet (10 mg) at night, with instructions to double the dose every 15 days in the absence of improvement; and introduction of COCP.

After a week, the patient contacted the clinic by phone due to severe intolerance to the antineuropathic drugs (including, amongst other symptoms, dizziness and confusion). Those medications were discontinued despite some improvement in the patient's condition. The nutraceutical supplement and hormonal contraception were maintained.

In June 2020, when the patient had a baseline VAS of 7, botulinum neurotoxin type A (BoNT) 100 IU infiltrations were started, distributed in the vulvar scar and along the left superficial transverse muscle, up to the exit of the perineal branch of the pudendal nerve.

By September 2020, the patient was much better (PGI-I score of 2), with only mild discomfort (VAS <4) and superficial dyspareunia (Marinoff 1). Given the characteristics of centralized pain, introduction of cognitive behavioural therapy was proposed.

Discussion

The three cases presented here represent a different circumstance in which female pelvic pain, of complex aetiology, required effective medical intervention. In all cases, a positive outcome was achieved with a multimodal approach involving behavioural adjustments, physical interventions, hormone therapy, nutraceutical supplements and antineuropathic medications.

Case 1 had a recent history of endometriosis managed initially with hormone contraceptive therapy, but exacerbation of the pelvic pain and her desire to become pregnant required an alternative approach to therapy. In Case 2, the neuropathic pelvic pain developed post-partum, some months after a complicated instrumental delivery. In Case 3, the pelvic pain arose soon after a cystectomy for recurring Bartholinitis. In all three cases, the pain was exacerbated by sitting for long periods, and all had dyspareunia.

An understanding of the different types of pain is an essential starting point for establishing effective treatment programmes for gynaecological pain but identifying this can be complicated. For example, when does acute pain become chronic where the pain (or its severity) is cyclical? Is the pain of primary origin or secondary to another disease process, or does it involve a combination of the two? To what extent does the pain, particularly if chronic, involve central sensitization or nociplastic pain? Chronic primary pain, which persists or recurs for more than 3 months, is often associated with significant emotional distress and/or functional disability (interfering with activities of daily living).[4] Thus, a primary target of pain therapy is early management to reduce the risk of central sensitization. With endometriosis, there is now evidence that there is chronic remodelling of the nervous system in shared sensory neural pathways, inducing a state of protracted peripheral and central sensitization.[9]

The development of objective tools/scales, allowing assessment of the severity of symptoms (e.g. VAS, Marinoff), the degree of pelvic sensitization (e.g. Levesque) and the evolution of the condition (e.g. degree of improvement on the PGI-I scale) are important for the diagnosis and management of patients with pelvic pain. These tools need to be routinely incorporated into general clinical practice.

Common elements of the multimodal therapy used in the three cases reported here were behavioural adjustments, physical strategies, and the use of a nutraceutical supplement containing ALA, PEA and myrrh. ALA has demonstrated a range of clinical benefits, including antioxidant activity, neuroprotective activity, and analgesic and anti-inflammatory activity,[16–20] and myrrh has also been shown to possess anti-inflammatory and analgesic properties.[23–25] The beneficial results also confirm earlier clinical trials demonstrating the effectiveness of PEA, in combination with other treatment modalities, for pain management in women with pelvic pain. In women with suspected endometriosis and severe

pelvic pain, 2 tablets daily of a combination of PEA (400 mg) and polydatin (40 mg) for 90 days statistically significantly improved pelvic pain, dysmenorrhoea and dyspareunia, with accompanying improvement in quality of life and a statistically significant reduction in the consumption of non-steroidal anti-inflammatory drugs (NSAIDs).[31] In another study, a similar formulation (combination of PEA 400 mg + transpolydatin 40 mg, 1 tablet a day for 10 days) improved pelvic pain in 98.2% of young women with primary dysmenorrhoea compared with only 56.4% of placebo recipients ($p<0.001$).[32]

The combination of ALA with PEA (300 mg + 300 mg, respectively, twice daily) significantly improved pain and all categories of quality of life after 6 and 9 months ($p<0.001$ *versus* baseline) in a clinical trial in 56 women with endometriosis-associated pelvic pain.[13]

In a clinical trial in patients with endometriosis and chronic pelvic pain, 2 tablets of a nutraceutical supplement of ALA, PEA and myrrh, daily for 6 months, significantly reduced pelvic pain and dyspareunia.[12] In that study, the authors suggested that, subject to further investigation of the short-term benefits of this nutraceutical formulation, it may be beneficial for replacing short-term NSAID use in these patients. In Cases 2 and 3 of the present report, this nutraceutical combination, together with hormonal contraception and corticosteroid or botulinum neurotoxin type A infiltrations, enabled the withdrawal of pregabalin and amitriptyline therapy.

Anti-inflammatory and antineuropathic medications have a place in the management of patients with chronic pelvic pain where there is underlying relevant pathophysiology. For example, the cyclo-oxygenase 2–prostaglandin E_2 (COX2–PGE_2) pathway is involved in various inflammatory processes, including in disease-associated pain in women with endometriosis,[33,34] making NSAIDs (as COX2 inhibitors) appropriate therapeutic tools, providing that care is taken to monitor their potential for gastrointestinal toxicity.[35] Equally, where there is chronic pelvic pain associated with pudendal nerve damage, antineuropathic medications (including gabapentin, pregabalin and amitriptyline) may have a therapeutic place.[36] However, as observed in Case 3, antineuropathic medications can be poorly tolerated.

Conclusions

Women presenting with pelvic pain should be assessed early to establish any factors indicating that the pain could become chronic, and a multimodal management strategy should be introduced to try to prevent central sensitization and the development of pain memory.

The nutraceutical ALA + PEA + myrrh enables a reduction or withdrawal of the use of antineuropathic drugs, which have tolerability and adherence complications. Thus, as an adjuvant treatment, it contributes to the effective management of pelvic pain in women.

Contributions: The author meets the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, takes responsibility for the integrity of the work as a whole, and has given approval for this version to be published.

Disclosure and potential conflicts of interest: The author declares that they have no conflicts of interest relevant to this manuscript. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors is available for download at: https://www.drugsincontext.com/wp-content/uploads/2021/11/dic.2021-10-8-COI.pdf

Acknowledgements: Medical writing assistance was provided by Content Ed Net (Madrid, Spain), with funding from Uriach.

Funding declaration: There was no funding associated with this article other than for medical writing assistance.

Article URL: https://www.drugsincontext.com/experience-with-nutraceutical-supplements-in-the-treatment-of-pelvic-pain-in-gynaecology-case-reports

Correspondence: Francisco Nohales Alfonso, Gynecology Section, Clinical Area of Women´s Diseases, La Fe University Hospital, Valencia, Spain. Email: fnohalesa@gmail.com

Provenance: Submitted; externally peer reviewed.

Submitted: 29 October 2021; **Accepted:** 26 November 2021; **Publication date:** 12 January 2022.

Drugs in Context is published by BioExcel Publishing Ltd. Registered office: Plaza Building, Lee High Road, London, England, SE13 5PT.

BioExcel Publishing Limited is registered in England Number 10038393. VAT GB 252 7720 07.

For all manuscript and submissions enquiries, contact the Editorial office editorial@drugsincontext.com

For all permissions, rights and reprints, contact David Hughes david.hughes@bioexcelpublishing.com

References

1. International Association for the Study of Pain. *IASP Terminology*. https://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1698. Accessed September 21, 2021.
2. Freynhagen R, Parada HA, Calderon-Ospina CA, et al. Current understanding of the mixed pain concept: a brief narrative review. *Curr Med Res Opin*. 2019;35(6):1011–1018. https://doi.org/10.1080/03007995.2018.1552042
3. Colloca L, Ludman T, Bouhassira D, et al. Neuropathic pain. *Nat Rev Dis Primers*. 2017;3:17002. https://doi.org/10.1038/nrdp.2017.2
4. Treede RD, Rief W, Barke A, et al. Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). *Pain*. 2019;160(1):19–27. https://doi.org/10.1097/j.pain.0000000000001384
5. European Association of Urology. *Chronic Pelvic Pain – Full Text Guidelines*. ISBN 978-94-92671-13-4. https://uroweb.org/guideline/chronic-pelvic-pain/. Accessed September 21, 2021.
6. Scholz J, Finnerup NB, Attal N, et al. The IASP classification of chronic pain for ICD-11: chronic neuropathic pain. *Pain*. 2019;160(1):53–59. https://doi.org/10.1097/j.pain.0000000000001365
7. Eid S, Loukas M, Tubbs RS. Clinical anatomy of pelvic pain in women: a gynecological perspective. *Clin Anat*. 2019;32(1):151–155. https://doi.org/10.1002/ca.23270
8. Falcone T, Flyckt R. Clinical management of endometriosis. *Obstet Gynecol*. 2018;131(3):557–571. https://doi.org/10.1097/AOG.0000000000002469
9. Maddern J, Grundy L, Castro J, Brierley SM. Pain in endometriosis. *Front Cell Neurosci*. 2020;14:590823. https://doi.org/10.3389/fncel.2020.590823
10. Tu FF, Hellman KM, Backonja MM. Gynecologic management of neuropathic pain. *Am J Obstet Gynecol*. 2011;205(5):435–443. https://doi.org/10.1016/j.ajog.2011.05.011
11. Ploteau S, Cardaillac C, Perrouin-Verbe MA, Riant T, Labat JJ. Pudendal neuralgia due to pudendal nerve entrapment: warning signs observed in two cases and review of the literature. *Pain Physician*. 2016;19(3):E449–E454.
12. De Leo V, Cagnacci A, Cappelli V, Biasioli A, Leonardi D, Seracchioli R. Role of a natural integrator based on lipoic acid, palmitoiletanolamide and myrrh in the treatment of chronic pelvic pain and endometriosis. *Minerva Ginecol*. 2019;71(3):191–195. https://doi.org/10.23736/S0026-4784.19.04384-3
13. Caruso S, Iraci M, Cianci S, Fava V, Casella E, Cianci A. Comparative, open-label prospective study on the quality of life and sexual function of women affected by endometriosis-associated pelvic pain on 2 mg dienogest/30 µg ethinyl estradiol continuous or 21/7 regimen oral contraceptive. *J Endocrinol Invest*. 2016;39(8):923–931. https://doi.org/10.1007/s40618-016-0460-6
14. Keppel Hesselink JM, Kopsky DJ. Palmitoylethanolamide, a neutraceutical, in nerve compression syndromes: efficacy and safety in sciatic pain and carpal tunnel syndrome. *J Pain Res*. 2015;8:729–734. https://doi.org/10.2147/JPR.S93106
15. Boriani F, Granchi D, Roatti G, Merlini L, Sabattini T, Baldini N. Alpha-lipoic acid after median nerve decompression at the carpal tunnel: a randomized controlled trial. *J Hand Surg Am*. 2017;42(4):236–242. https://doi.org/10.1016/j.jhsa.2017.01.011
16. Nguyen H, Gupta V. Alpha-lipoic acid. In: *StatPearls*. StatPearls Publishing; 2021. https://www.ncbi.nlm.nih.gov/books/NBK564301/?
17. Moura FA, de Andrade KQ, dos Santos JC, Goulart MO. Lipoic acid: its antioxidant and anti-inflammatory role and clinical applications. *Curr Top Med Chem*. 2015;15(5):458–483. https://doi.org/10.2174/1568026615666150114161358
18. Tóth F, Cseh EK, Vécsei L. Natural molecules and neuroprotection: kynurenic acid, pantethine and α-lipoic acid. *Int J Mol Sci*. 2021;22(1):403. https://doi.org/10.3390/ijms22010403
19. Lee WY, Orestes P, Latham J, et al. Molecular mechanisms of lipoic acid modulation of T-type calcium channels in pain pathway. *J Neurosci*. 2009;29(30):9500–9509. https://doi.org/10.1523/JNEUROSCI.5803-08.2009
20. Di Nicuolo F, Castellani R, De Cicco Nardone A, et al. Alpha-lipoic acid plays a role in endometriosis: new evidence on inflammasome-mediated interleukin production, cellular adhesion and invasion. *Molecules*. 2021;26(2):288. https://doi.org/10.3390/molecules26020288
21. Paladini A, Fusco M, Cenacchi T, Schievano C, Piroli A, Varrassi G. Palmitoylethanolamide, a special food for medical purposes, in the treatment of chronic pain: a pooled data meta-analysis. *Pain Physician*. 2016;19(2):11–24.
22. Gabrielsson L, Mattsson S, Fowler CJ. Palmitoylethanolamide for the treatment of pain: pharmacokinetics, safety and efficacy. *Br J Clin Pharmacol*. 2016;82(4):932–942. https://doi.org/10.1111/bcp.13020
23. Su S, Wang T, Duan JA, et al. Anti-inflammatory and analgesic activity of different extracts of Commiphora myrrha. *J Ethnopharmacol*. 2011;134(2):251–258. https://doi.org/10.1016/j.jep.2010.12.003
24. Su S, Hua Y, Wang Y, et al. Evaluation of the anti-inflammatory and analgesic properties of individual and combined extracts from *Commiphora myrrha*, and *Boswellia carterii*. *J Ethnopharmacol*. 2012;139(2):649–656. https://doi.org/10.1016/j.jep.2011.12.013
25. Dolara P, Luceri C, Ghelardini C, et al. Analgesic effects of myrrh. *Nature*. 1996;379(6560):29. https://doi.org/10.1038/379029a0
26. Parente E, Colannino G, Picconi O, Monastra G. Safety of oral alpha-lipoic acid treatment in pregnant women: a retrospective observational study. *Eur Rev Med Pharmacol Sci*. 2017;21(18):4219–4227.
27. Marinoff SC, Turner ML. Vulvar vestibulitis syndrome. *Dermatol Clin*. 1992;10(2):435–444.

28. Levesque A, Riant T, Ploteau S, Rigaud J, Labat JJ; Convergences PP Network. Clinical criteria of central sensitization in chronic pelvic and perineal pain (Convergences PP Criteria): elaboration of a clinical evaluation tool based on formal expert consensus. *Pain Med*. 2018;19(10):2009–2015. https://doi.org/10.1093/pm/pny030
29. Harvey MA, Pierce M, Alter JE, et al. Obstetrical Anal Sphincter Injuries (OASIS): prevention, recognition, and repair. *J Obstet Gynaecol Can*. 2015;37(12):1131–1148. https://doi.org/10.1016/s1701-2163(16)30081-0
30. Bouhassira D, Attal N, Alchaar H, et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). *Pain*. 2005;114(1–2):29–36. https://doi.org/10.1016/j.pain.2004.12.010
31. Lo Monte G, Soave I, Marci R. Utilizzo della palmitoiletanolamide micronizzata (PEA)- transpolidatina nel trattamento del dolore pelvico cronico in donne affette da endometriosi: risultati preliminari [Administration of micronized palmitoylethanolamide (PEA)-transpolydatin in the treatment of chronic pelvic pain in women affected by endometriosis: preliminary results]. *Minerva Ginecol*. 2013;65(4):453–463.
32. Tartaglia E, Armentano M, Giugliano B, et al. Effectiveness of the association N-palmitoylethanolamine and transpolydatin in the treatment of primary dysmenorrhea. *J Pediatr Adolesc Gynecol*. 2015;28(6):447–450. https://doi.org/10.1016/j.jpag.2014.12.011
33. Wu MH, Shoji Y, Chuang PC, Tsai SJ. Endometriosis: disease pathophysiology and the role of prostaglandins. *Expert Rev Mol Med*. 2007;9(2):1–20. https://doi.org/10.1017/S146239940700021X
34. Ray K, Fahrmann J, Mitchell B, et al. Oxidation-sensitive nociception involved in endometriosis-associated pain. *Pain*. 2015;156(3):528–539. https://doi.org/10.1097/01.j.pain.0000460321.72396.88
35. Lai ZZ, Yang HL, Ha SY, et al. Cyclooxygenase-2 in endometriosis. *Int J Biol Sci*. 2019;15(13):2783–2797. https://doi.org/10.7150/ijbs.35128
36. Soon-Sutton TL, Feloney MP, Antolak S. Pudendal neuralgia. In: *StatPearls*. StatPearls Publishing; 2020. https://www.ncbi.nlm.nih.gov/books/NBK562246/