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Current Status of the Therapeutic Approach for Dysmenorrhea

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ABSTRACT

Dysmenorrhea is the combination of cramps and pain associated with the menstrual period, and the symptoms affect at least 30% of women worldwide. Tolerance to symptoms depends on each person's pain threshold; however, dysmenorrhea seriously affects daily activities and chronically reduces the quality of life. Some dysmenorrhea cases even require hospitalization due to unbearable symptoms of severe pain. Dysmenorrhea is an underestimated affectation and remains even in different first-world countries as a taboo subject, promoted by the establishment of an apparent policy of gender equality. A person with primary or secondary dysmenorrhea requires medical assistance in choosing the best treatment and an integral approach. This review intends to demonstrate the impact of dysmenorrhea on quality of life. We describe the pathophysiology of this disorder from a molecular point of view and perform a comprehensive compilation and analysis of the most critical findings in the therapeutic management of dysmenorrhea. Likewise, we propose an interdisciplinary approach to the phenomenon of dysmenorrhea at the cellular level in a concise way and the botanical, pharmacological, and medical applications for its management. Since dysmenorrhea symptoms can vary between individuals, medical treatment cannot be generalized and depends on each patient. Therefore, we hypothesized that a suitable strategy could result from the combination of pharmacological therapy aided by a non-pharmacological approach.

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Introduction

Dysmenorrhea is referred to as painful pelvic cramps during menstruation (1). Common clinical manifestations of this condition are sickness, vomiting, diarrhea, abdominal swelling, constipation, and indigestion. Other symptoms include irritability, headache, fatigue, and low back pain (2).

According to global data, dysmenorrhea is the most prevalent gynecological alteration and one of the most common causes of pelvic pain in women of reproductive age worldwide (3). It is clinically divided into primary and secondary dysmenorrhea (4). Primary dysmenorrhea is almost always presented in ovulatory cycles without underlying diseases (4–6). On the other hand, secondary dysmenorrhea is caused by diverse pathologies or structural abnormalities within or outside the uterus (e.g., endometriosis, genital infections, adenomyosis, pelvic inflammatory disease, and interstitial cystitis) (7).

It is noteworthy that the appearance of dysmenorrhea may reduce the quality of life (QoL) significantly in a considerable percentage of affected women (16%-29%) (2,8). Moreover, it has been shown that the degree of discomfort that dysmenorrhea produces may lead to absenteeism from school and work in severe cases (9). Thus, the therapeutic approach to this disorder is essential.

In this regard, first-line treatments for dysmenorrhea include non-steroidal anti-inflammatory drugs (NSAIDs) and oral contraceptive pills (5). Other therapeutical alternatives include intrauterine hormonal devices (IUDs), transcutaneous electric nerve stimulation (TENS), transdermal nitroglycerin patches (TNPs), acupuncture, heating pads, and surgical procedures (in certain underlying pelvic disorders) (10). Likewise, several studies have suggested

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the usefulness of herbal remedies and other complementary and alternative medicine (CAM) options to treat dysmenorrhea (11–16).

In this article, we describe the etiology and prevalence of dysmenorrhea and its negative impact on the quality of life of affected women. Likewise, we provide an updated outlook of the state-of-the-art of pharmacological and non-pharmacological approaches for this alteration. Finally, we discuss future directions for the treatment of dysmenorrhea.

Pathophysiology, etiology, and prevalence

As previously mentioned, there are two defined types of dysmenorrhea, the primary and the secondary, and these types differ in their pathophysiology (Figure 1).

Primary dysmenorrhea is defined as painful spasmodic cramps in the inferior belly earlier or during menstruation; it is presented without detectable pelvic pathology. Primary dysmenorrhea typically starts in adolescence, at or shortly after menarche. Usually, the pain lasts for 8 to 72 h, beginning between 48 and 24 h before the menses, and the most severe symptoms are presented during the first or second day of menstruation (17). The pathophysiological mechanism for this disorder implies an overproduction of uterine prostaglandins (PGs), which is related to the induction of myometrium hypercontractility and arteriolar vasoconstriction (Figure 2). First, a notable decrease in progesterone and estradiol is observed at the beginning of menstruation, which increases the transcription of endometrial collagenases, matrix metalloproteinases (MMPs), and inflammatory cytokines (18). These up-regulated MMPs break down the endometrial tissue, triggering the release of cellular membrane phospholipids. The free phospholipids are converted into arachidonic acid by uterine phospholipases, and then this acid is utilized to synthesize PGs, prostacyclins, and thromboxane-2a via cyclooxygenase (COX)-1 and COX-2 (18,19). Notably, COX-2 expression is highest during menses.

On the other hand, the onset of secondary dysmenorrhea can occur at any time. As mentioned, the pain caused for this disorder can be associated with different pathological conditions, such as endometriosis or adenomyosis (1,20). The most common cause of secondary dysmenorrhea is endometriosis, defined as the presence and growth of uterine glands and stroma outside the uterine cavity. Women with endometriosis exhibit higher PGs concentrations in menstrual blood and present a higher frequency and amplitude of contractions in the uterus than those without this condition (3). Therefore, these abnormal uterine contractions could generate severe dysmenorrhea. In addition, endometriotic wounds may cause deep pelvic pain associated with endometriosis. It has been reported that the aromatase enzyme is undetectable in normal endometrium. In contrast, an increment in the expression of this enzyme is detected in epithelial and stromal cells of endometriotic tissues and peritoneum, triggering an increment in the local biosynthesis of estrogen (1).

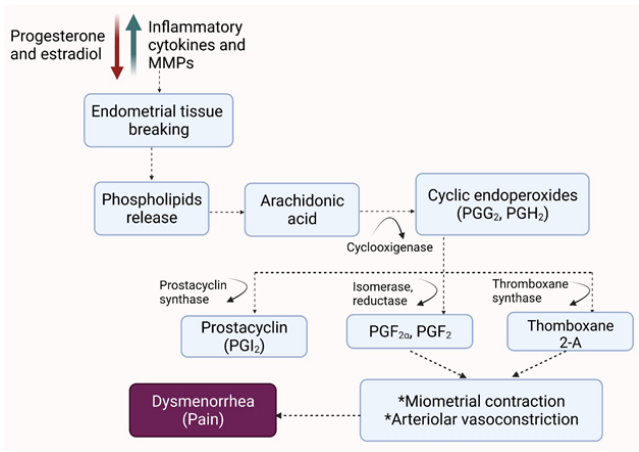


Figure 1. Pathophysiology of dysmenorrhea.

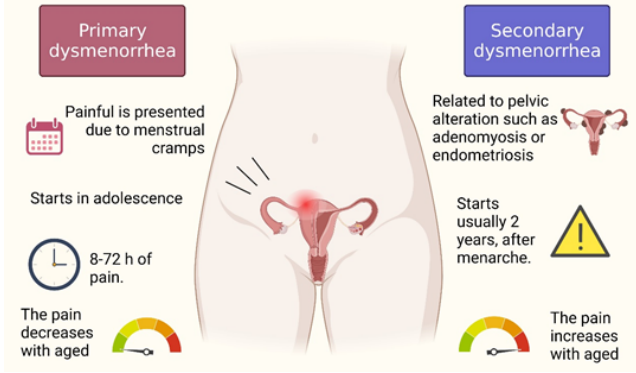


Figure 2. Main differences between primary and secondary dysmenorrhea.

On the other hand, it is reported that the estimated prevalence of dysmenorrhea widely varies from 45 to 93% in women of reproductive age, observing the highest rates in adolescence (17). Different studies have been developed in some countries to study the national incidence. For instance, a survey on primary dysmenorrhea in Iranian undergraduate students was conducted in 2015 (21). The authors reported a prevalence of 89.1%, observing that the higher intensity of dysmenorrhea presented a close relation with younger ages. Likely, Ortiz et al. (22) analyzed the incidence in young Mexican women, and the authors found a prevalence of 48%. Interestingly, 63.4% of these women described limitations in their daily activities triggered by dysmenorrhea pain. Therefore, there is a wide variation in reports of prevalence related to the lack of standard methods for evaluating the severity of the condition.

Impact of dysmenorrhea on QoL

OMS defined the QoL as “an individual’s perception of their position in life in the context of the culture and value systems in which they live and concerning their goals, expectations, standards, and concerns” (23,24). Nowadays, QoL is considered a critical outcome in numerous clinical studies worldwide. In this respect, symptoms of dysmenorrhea may be significantly disabling and decrease QoL considerably in many affected women (Figure 3).

Commonly, the evaluation of how dysmenorrhea affects the QoL of women is through the application of standardized surveys in a representative group of patients. Generally, those surveys try to establish the correlation between the dysmenorrhea symptoms with the influence on day-to-day activities and/or strategies used by the patients to confront the disorder. Therefore, data collected from these studies reveal the magnitude of the symptoms that deteriorate the patient's life.

For example, Iacovides et al. (25) used a validated short

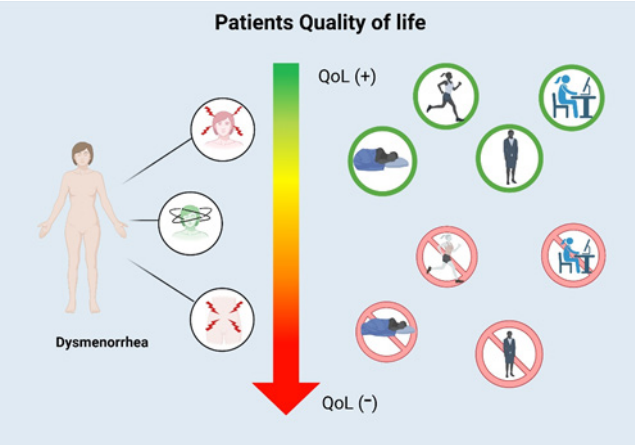


Figure 3. Dysmenorrhea is one of the most common disorders among women of reproductive age, especially adolescents and adults, which can detriment the QoL.

form of the QoL enjoyment and satisfaction questionnaire to determine differences in QoL between women with primary dysmenorrhea and without dysmenorrhea during menstrual pain or painless phase of their menstrual cycles. Scores obtained revealed that women with dysmenorrhea had a significant reduction of QoL (mean ± SD: 54 ± 18% of the maximum score possible) while severe menstrual pain was present, compared with their painless follicular phase (80 ± 14% $p < 0.0001$) and compared with women without dysmenorrhea (81 ± 14% $p < 0.0001$). These data support the theory that the painful menstrual cramps experienced by women with dysmenorrhea significantly reduce their QoL monthly.

Dysmenorrhea is a syndrome with chronic and acute pain features in a specific time-lapse. Intense cyclic pain is associated with restricting physical activity, which can decrease the QoL (18,26). In this regard, women manage their dysmenorrhea with different techniques; thus, their QoL is affected in different magnitudes. A recent study investigated analgesic use, pain acceptance, and pain coping as predictors of QoL among 145 women with primary dysmenorrhea through 4 types of questionnaires (27). The questionnaires explored menstrual symptoms, analgesic use, chronic pain acceptance, coping strategies, and QoL related to physical and mental health. Interestingly, being married or cohabiting with someone correlated with better physical and mental QoL, an effect possibly mediated by pain acceptance. This result suggested that the couples encourage women to continue their everyday activities, nonetheless menstrual pain. Likewise, acceptance of pain mediated the effect of the first painful period of age on mental QoL. According to the author's study, women who have painful periods at a younger age suffer a more significant impact on their mental QoL because these reduce the participation of young people in daily life activities. On the other hand, using analgesics was not a predictor of QoL, although it was negatively correlated with both physical and mental QoL. Possibly, recommended analgesics for mild to moderate pain have little effect, or analgesics use was not accurately measured.

Also, a cross-sectional study explored the possible correlation between psychosocial factors (social support, pain cognitions, and mental health) and the severity of menstrual pain in women with primary dysmenorrhea and endometriosis-related dysmenorrhea (28). The study included anxiety levels, depression, stress, menstrual pain severity, pain catastrophizing, and perceived social support. The survey concluded that women with endometriosis have higher menstrual pain and pain catastrophizing. However, the levels of depression, anxiety, stress, and social support were not different from those with primary dysmenorrhea. Interestingly, another study demonstrated that pain catastrophizing is related to worse QoL (29). Therefore, the importance of monitoring QoL in dysmenorrheic women could be the key to improving clinical treatments for this clinical alteration. In this respect, creating integral strategies where the pharmacological treatment and psychosocial environment work side by side will reduce the pain and helplessness related to dysmenorrhea and support women with this condition.

Pharmacological treatments

The pharmacological treatment of dysmenorrhea depends on the type (primary or secondary) and the severity of each patient's symptoms. First-line treatment aims to provide adequate pain relief, allowing women to perform their usual activities and reducing the loss of productivity associated with dysmenorrhea (30). About the therapeutic management of dysmenorrhea, Osayande et al. (3) proposed an algorithm that consists primarily of identifying a history compatible with primary dysmenorrhea, which includes normal findings in the pelvic examination and negative results in a pregnancy test. If primary dysmenorrhea is diagnosed, treatment with NSAIDs and/or oral contraceptives is suggested. Diagnostic laparoscopy is indicated if dysmenorrheic symptoms persist and chronic pelvic pain is addressed from a multidisciplinary approach to determine endometriosis, adenomyosis, or other conditions causing secondary dysmenorrhea. In those cases, surgical and/or pharmacological treatments are used to treat secondary dysmenorrhea. Table 1 describes the main drugs included in this manuscript and that have been studied as treatments for primary and/or secondary dysmenorrhea.

In addition to NSAIDs and oral contraceptives, other drug treatment options, such as hormonal IUDs and natural or herbal products (Figure 4), can be combined to develop treatment plans that allow better management of both primary and secondary dysmenorrhea.

Oral contraceptives

Oral contraceptives have long been considered the

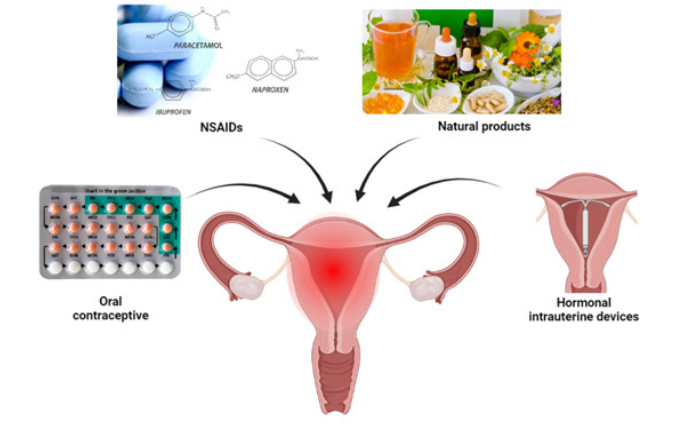
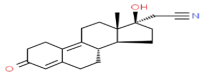
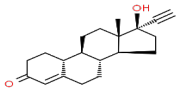
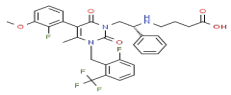
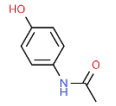
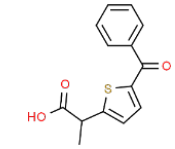
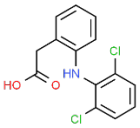
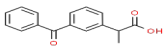
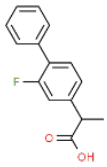
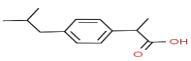
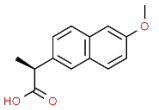


Figure 4. Pharmacological treatments for dysmenorrhea.

Table 1. Drugs employed in the treatment of primary and secondary dysmenorrhea.

Drug name	Molecular structure*	Drug type	Indication**
Dienogest		Progestin	Monotherapy for the treatment of endometriosis
Norethisterone		Progestin	Symptomatic treatment of endometriosis-related pain.
Elagolix		GnRH receptor antagonist	Treatment of moderate to severe pain in endometriosis
Paracetamol		Analgesic	Treatment of mild to moderate pain, including menstrual discomfort
Tiaprofenic acid		NSAID	Treatment mild to moderate pain related to primary dysmenorrhea
Diclofenac		NSAID	First-line therapy for acute and chronic pain and inflammation from diverse causes, including dysmenorrhea
Ketoprofen		NSAID	Symptomatic treatment of primary dysmenorrhea
Flurbiprofen		NSAID	Treatment of pain associated with dysmenorrhea and mild to moderate pain accompanied by inflammation
Ibuprofen		NSAID	Management of mild to moderate pain related to dysmenorrhea
Naproxen		NSAID	First-line treatment for a variety of clinical situations requiring analgesia, including dysmenorrhea

GnRH: Gonadotropin-releasing hormone. * Molecular structures made in https://www.chemspider.com/. ** Consulted in https://go.drugbank.com/

first-line treatment for secondary dysmenorrhea associated with endometriosis (3,31,32), which various studies have supported. For example, Harada et al. (33) carried out a randomized controlled trial that demonstrated the effectiveness of the oral estrogen-progestin combination for treating dysmenorrhea associated with endometriosis. Total dysmenorrhea scores assessed by the Verbal Rating Scale decreased significantly at the end of treatment. From the first cycle to the end of treatment, dysmenorrhea in the oral contraceptive group was significantly milder than in the placebo group. Furthermore, endometrioma volume (greater than 3 cm in diameter) decreased considerably in the oral contraceptive group but not in the placebo group. In this way, the authors demonstrated that oral contraceptives could alleviate pain associated with dysmenorrhea. This effect is attributed to the ability of oral contraceptives to limit the growth of the endometrial lining and the decrease in PGs production. This same research group conducted a randomized, double-blind, placebo-controlled trial to evaluate low-dose oral contraceptive pills' efficacy on primary dysmenorrhea. The authors evaluated IKH-01 (0.035 mg ethinylestradiol and 1 mg norethisterone) in 115 patients. The reduction in the total dysmenorrhea score and a Visual Analog Scale (VAS) before and after treatment was significantly greater in the IKH-01 group than in the placebo group, which indicated that low-dose oral contraceptives could be useful for the treatment of primary dysmenorrhea (34). In this regard, Harada and Momoeda (35) evaluated an ultra-low oral contraceptive dose for dysmenorrhea in a placebo-controlled, double-blind, randomized

trial. The authors used NPC-01 (0.02 mg ethinylestradiol and 1 mg norethisterone) in 215 subjects with dysmenorrhea. The results demonstrated significant reductions in total dysmenorrhea and VAS scores after treatment in the NPC-01 group compared to the placebo group. Therefore, this "ultra-low" dosage of oral contraceptives proved to be a novel option for treating dysmenorrhea. With the above, it could be inferred that the anti-dysmenorrheic effect of oral contraceptives is mainly due to the effect of progestin.

Currently, evidence supports progestin-only pills as better treatments for dysmenorrhea than combined estrogen and progestin pills (36). In this respect, a recent survey compared the efficacy of norethisterone acetate (NET-A, 5 mg) versus oral contraceptives (drospirenone 3 mg/ethinylestradiol 20 μg) in the treatment of dysmenorrhea (37). Both drugs were similar in suppressing dysmenorrhea at 3 and 6 months; therefore, NET-A proved to be an equally effective option as oral contraceptive pills and could be preferred as the best therapeutic option because treatment with NET-A is less expensive. Another example of these progestin-only pills is Dienogest, an oral progestin currently used to treat endometriosis or for contraception combined with ethinylestradiol. The efficacy and safety of dienogest (2 mg oral) in the treatment of endometriosis-associated pelvic pain (EAPP) were compared with a placebo in a 12-week study (38). The cohort comprised 198 women of 18 to 45 years with laparoscopically confirmed endometriosis and EAPP scores ≥ 30 on a VAS. Dienogest reduced (p <0.0001) 12.3 mm in VAS score between baseline and week 12. Therefore, dienogest (2 mg daily for 12 weeks) was significantly more effective than a placebo in reducing endometriosis-associated dysmenorrhea.

Hormonal intrauterine devices

IUDs are considered safe and effective contraceptive methods. However, Levonorgestrel-releasing intrauterine devices (LNG-IUDs), designed initially as long-term contraceptives, are also used for non-contraceptive purposes in treating dysmenorrhea (39–41). The LNG-IUD takes advantage of the hormonal load as a conventional treatment that helps to reduce the synthesis of endometrial PGs and, consequently, dysmenorrhea. A study by Lindh and Milsom (41) demonstrated the influence of intrauterine contraception on the severity of dysmenorrhea. The authors evaluated the severity of dysmenorrhea by a multidimensional verbal scoring system (VMS) and VAS. They found that the copper IUD did not influence the severity of dysmenorrhea, whereas LNG- IUD was able to reduce it.

In addition to endometriosis, other types of conditions could be causing secondary dysmenorrhea, such as adenomyosis, a condition characterized by the invasion of the myometrium by the endometrial glands and the stroma. The first-line treatment for these cases may be LNG-IUS, as recently demonstrated in a study on the efficacy of this device in advanced dysmenorrhea (42). Patients suffering from adenomyosis were evaluated at the time of LNG-IUS insertion and six months later, showing a significant decrease in uterine volume and pain relief in all patients (p <0.001). Therefore, the LNG-IUS can be an effective treatment for managing secondary dysmenorrhea caused by adenomyosis.

NSAIDs

NSAIDs are the most popular drugs for treating dysmenorrhea and are often used empirically for pain relief. NSAIDs inhibit COX, preventing the production and release of PGs, prostacyclins, and thromboxanes, which decreases pain (43). A systematic review of 73 randomized controlled trials indicated NSAIDs as the first-line treatment for primary dysmenorrhea (44). That review aimed to assess the effectiveness and safety of NSAIDs used in treating primary dysmenorrhea versus placebo, versus paracetamol, and each other. NSAIDs were significantly more effective at relieving pain than placebo and paracetamol. However, when NSAIDs were compared to each other, there was no evidence of better efficacy of any individual NSAID for pain relief.

Similarly, another study evaluated the relative benefits of different NSAIDs for patients with primary dysmenorrhea through a network meta-analysis (45). In total, 72 randomized controlled trials with 5723 volunteers and 13 NSAIDs were encompassed in the survey. Tiaprofenic acid, piroxicam, naproxen, mefenamic acid, ketoprofen, indomethacin, ibuprofen, flurbiprofen, and diclofenac were more efficacious for pain relief than acetylsalicylic acid. Therefore, the authors reported that flurbiprofen was the best among all the treatments in terms of efficacy. Likewise, tiaprofenic acid and mefenamic acid were the safest drugs. Thus, considering efficacy and safety, flurbiprofen and tiaprofenic acid were optimal treatments for primary dysmenorrhea. Another recent network meta-analysis evaluated five analgesics in 35 trials with 4383 patients (46). Regarding efficacy results, the following four pain relievers were more effective than a placebo in treating dysmenorrhea: naproxen, ibuprofen, diclofenac, and ketoprofen. Likewise, ibuprofen was highlighted as an optimal NSAID for primary dysmenorrhea based on efficacy and safety.

Finally, paracetamol is a pain reliever widely consumed to treat primary dysmenorrhea. Concerning this, a recent meta-analysis on self-care strategies applied by young women with dysmenorrhea reported that paracetamol was the most commonly used analgesic (47). However, it did not always provide sufficient pain relief. Nevertheless, paracetamol has proven to be a safe analgesic of choice for patients with tolerability problems or contraindications of other drugs and/or NSAIDs.

Natural products

Another popular treatment option among patients with dysmenorrhea is herbal or natural products. Numerous herbs have shown some degree of safety and efficacy based on their extended empirical use. These herbs can be used alone or adjunct to other therapies to prevent and treat dysmenorrhea. Some natural products that have been studied for the treatment of dysmenorrhea are *V. opulus* (cramp bark), *V. prunifolium* (black haw), *Foeniculum vulgare* (fennel), *Atropa belladonna* (belladonna), *Zingiber officinale* (ginger), *Trillium spp*. (beetroot), *Rosa spp.* (rose), *Psidium guajava* (guava), *Thymus vulgaris* (thyme), and *Matricaria chamomilla* (chamomile) (16,48–51).

Some researchers have compared the effect of natural products versus NSAIDs on dysmenorrhea pain. In this respect, Salmalian et al. (52) conducted a clinical study comparing *Thymus vulgaris* and ibuprofen's effects in treating primary dysmenorrhea. The study enrolled 84 students randomly assigned to three groups who received *Thymus vulgaris*, ibuprofen, or placebo. There was no

difference in reduction in pain intensity between *Thymus vulgaris* and ibuprofen; however, there was a statistically significant difference for each drug compared to the placebo ($p < 0.001$). Therefore the results suggest that *Thymus vulgaris* and ibuprofen effectively reduce pain intensity in primary dysmenorrhea. Similarly, Shahrahmani et al. (53) recently carried out a meta-analysis that compared the effects of *Foeniculum vulgare* and mefenamic acid on primary dysmenorrhea. The study revealed that the intake of *F. vulgare* significantly decreased the intensity of dysmenorrhea compared to the placebo. Interestingly, the effects of mefenamic acid and *F. vulgare* were not different from each other. Therefore, the authors concluded that *F. vulgare* alleviates dysmenorrhea with a similar potency to the NSAID.

Finally, chamomile is one of the most used plants to treat menstrual cramps, and its effectiveness on dysmenorrhea pain has been explored (54). A clinical study found that after one month of consuming chamomile tea, the study group had a significant decrease in menstrual pain, anxiety, and distress compared to the control group. Therefore, the authors reported that chamomile tea effectively relieves pain caused by primary dysmenorrhea. Likewise, a recent systematic review of clinical trials (2021) determined the effect of chamomile on pain and menstrual bleeding in primary dysmenorrhea. It concluded that chamomile might be an effective treatment for those alterations (55).

Other pharmacological approaches

Despite the availability of different medications for dysmenorrhea, new alternatives are currently being explored. In this regard, Elagolix (an oral gonadotropin-releasing hormone (GnRH) antagonist) is a novel and widely studied treatment for endometriosis-associated dysmenorrhea. It prevents the action of endogenous GnRH, suppressing both luteinizing and follicle-stimulating hormones (56–62). In 2018, the Food and Drug Administration (FDA) authorized the use of this non-peptide molecule, and available presentations are 150 mg and 200 mg tablets. The recommended dose is 150 mg/24 h for up to two years, and if there is dyspareunia, 200 mg every 12 hours for a maximum of 6 months. A recent study evaluated the efficacy of elagolix and health-related quality of life (HRQOL) in women with endometriosis, including data from two 6-month placebo-controlled phase 3 studies evaluating two doses of elagolix (150 mg once a day and 200 mg twice a day). The pain reduction reported by women at month 3 was significant in all subgroups taking elagolix 200 mg twice daily and in most subgroups taking elagolix 150 mg once daily. Therefore, elagolix was effective in reducing dysmenorrhea and improving HRQOL in patients.

Non-pharmacological approaches

Different non-pharmacological approaches have been proposed to manage dysmenorrhea, including TENS, TNPs, surgical interventions, acupuncture, acupressure, heating pads, aromatherapy, and increased intake of some nutrients (Figure 5 and Table 2).

Transcutaneous electric nerve stimulation

TENS is a non-pharmacological strategy that has gained popularity over time for alleviating nociceptive, neuropathic, and musculoskeletal pain (15). TENS is based on the application of self-adhering conducting pads (electrodes) on the skin that transmit an electric current generated by a portable pulse generator (63). Depending on the physiological intention and the clinical technique used (e.g., low or high intensity), it can be classified as conventional, acupuncture-like, or intense TENS (64). It presents some advantages like self-administration, dosage as required, no potential toxicity, no effect on uterine activity, and can be purchased without a medical prescription. However, some contraindications to using the TENS are inflamed, infected or anesthetic skin, cardiac pacemaker or internal defibrillation device, stimulation over the anterior neck (which may cause laryngospasm or hypotension), and some patients are unable to understand the technique (65).

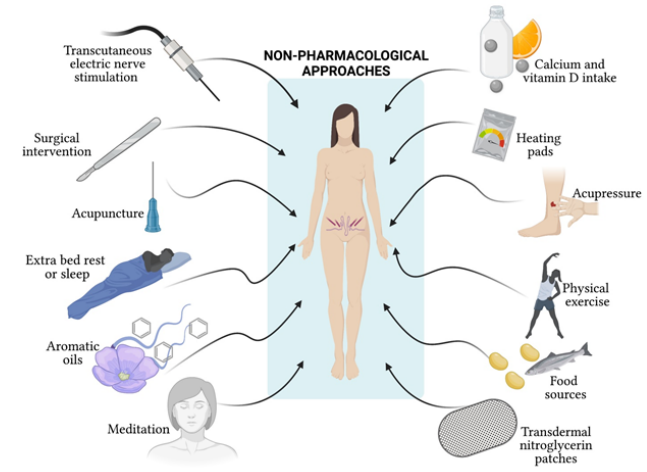


Figure 5. Non-pharmacological approaches for pain relief during dysmenorrhea.

A systematic review of randomized controlled trials with no treatment or medical treatment for primary dysmenorrhea found that high-frequency TENS (pulse rate 70-100 Hz, pulse width 40-200 μs) was more effective for pain relief than placebo (66). Interestingly, low-frequency TENS (pulse rate 1-5 Hz, pulse width 40-250 μs) was no more effective in reducing pain than placebo. On the other hand, Wong et al. (67) found that a multimodal therapy (as an adjunct to oral contraceptives) combining TENS (applied in a quadripolar arrangement at high-frequency 100 Hz, 0.2 ms, for 20 min), spinal manipulation, and topical heat appeared to provide short-term improvements in primary dysmenorrhea pain.

Transdermal nitroglycerin patches

The physicochemical properties of nitroglycerin, such as partition characteristics, solubility, low melting point, and small size, make it an ideal substance to deliver transdermally through TNPs (68). The nitroglycerin contained in TNPs dilates the peripheral blood vessels, and its effect begins within 30 minutes (69,70). TNPs are longer-acting since the first-pass metabolism is avoided, and there is sufficient evidence to suggest that their action lasts between 20 and 26 hours (71). However, some side effects associated with the use of TNPs include tolerance to chronic therapy, attenuation of the response to nitroglycerin, and reduction in the duration of action and efficacy (71).

According to various reports, transdermal nitroglycerin administration on the first day of menstruation is sufficient

Table 2. Action mechanisms and materials of some non-pharmacological approaches for dysmenorrhea.

Approaches	By using…	Mechanism of action
Transcutaneous electric nerve stimulation	Electrodes	An electric current activates underlying nerves that block the transmission of pain signals.
Transdermal nitroglycerin	Patches	Dilatation of the peripheral blood vessels.
Surgical interventions	Laparoscope	Ablation of the uterosacral nerve, presacral neurectomy, or hysterectomy.
Acupuncture	Needles	Restoration and balance in the flow of energy and harmony.
Acupressure	Hands	Restoration and balance in the flow of energy and harmony.
Heat	Pads, water bags, towels, or bottles	Reduction of muscle tension, relaxation of the abdominal muscles, and increment of pelvic blood circulation.
Increased supplements intake	Calcium and vitamin D	Calcium regulates the ability of muscle cells to respond to nerve stimulation, and vitamin D regulates prostaglandin levels.

to reduce reported menstrual pain for menses (72). For example, Moya et al. (73) determined transdermal glyceryl trinitrate's effects on pain associated with primary dysmenorrhea. This study analyzed patients who received TNP or placebo patches during three menstrual cycles. In all cases, pain intensity scores statistically improved for the TNP. Therefore, the authors concluded that transdermal nitroglycerin helps to modulate uterine contractility and may be used to treat primary dysmenorrhea.

On the other hand, the Transdermal Nitroglycerine/dysmenorrhoea Study Group performed a multinational study that included 65 women with histories of moderate-to-severe pain associated with menses (74). The women were treated with TNP that delivered 0.2 or 0.1 mg/h. Remarkably, 90% of the patients obtained pain relief with the first dose on the first day, and they reported pain relief from satisfactory to excellent. Headache was the most frequent side effect for both studies, with 26% and 20% of the patients.

Surgical interventions

Surgical interventions are indicated only in rare cases of patients who present a severe state of dysmenorrhea. The surgical strategies used are laparoscopic uterosacral nerve ablation (LUNA), presacral neurectomy, and hysterectomy (10). A disadvantage of these surgical approaches is that they are inappropriate for adolescents (75). Additionally, repeated use of these procedures can induce stress and develop other possible pain syndromes, such as neuropathic pain and adhesions (5).

Lichten and Bombard (76) evaluated the LUNA technique in patients with primary dysmenorrhea. Approximately 81% of the patients reported significant relief from menstrual pain after the surgery, and half the treated women reported continued relief of menstrual pain at 12 months. On the other side, Luna-Rojas et al. (77) evaluated two groups of women with severe dysmenorrhea associated with some degree of endometriosis. One group received LUNA, and the other one presacral neurectomy. Ninety-six % of the group that underwent the intervention for presacral neurectomy exhibited pain relief for one year compared to the group that underwent LUNA, within which only 42% presented it. According to the authors, LUNA achieves certain pain relief during the first year, but pain reappears and increases in more than one-half of the patients after 11 months. In this context, other reports have indicated that women with dysmenorrhea without endometriosis improved significantly more with LUNA compared with control patients (5).

Acupuncture

Acupuncture is one of the traditional Chinese medicine treatment methods. This method is widely used for supportive and palliative care and pain relief (78). This method is based on the theory that diseases result from an energy flow imbalance, and the early clinical trials began in Japan in the 1960s (79). Thus, fine needles are inserted in specific body points (acupoints) to correct this lack of balance and restore harmony (80). Prospective studies about the safety of acupuncture indicated that the most common adverse events were needle pain from treatments, bleeding, and tiredness (81). However, 86% of patients reported feelings of relaxation. In another clinical trial, a group of women with primary dysmenorrhea received acupuncture for 20 minutes/day, for 15 days/month, and for 90 days (82). This study presented a significant reduction in all the studied variables, such as the VAS score for pain, headache, menstrual cramps, diarrhea, dizziness, fainting, tiredness, mood changes, nausea, and vomiting, compared with those who did not receive the treatment. On the other hand, Kiran et al. (83) compared acupuncture and NSAIDs as therapy in primary dysmenorrhea. They found that acupuncture was as effective as NSAID therapy after one month's treatment with decreases in the mean pain score of 52.2% and 69.5% in the NSAID and acupuncture groups, respectively.

Acupressure

Acupressure is mentioned in the literature as a non-invasive technique that targets the same energy meridian as acupuncture (84). This technique applies pressure on the body surface, making it safer than the comparatively invasive use of needles in acupuncture. The efficacy results of acupressure depend on the acupoints targeted (Figure 6), techniques utilized, and session frequency. Likewise, the application by trained personnel appears to be critical, as suggested by a recent systematic review (13). According to that study, acupressure application in dysmenorrhea patients considerably diminished pain closely after the intervention. Interestingly, the effects were only noticed when trained personnel applied the technique, while interventions administered by patients needed multiple monthly cycles to exert therapeutic action on pain.

Based on Chinese medical theory, dysmenorrhea can present in excess and deficiency syndromes associated with acupoints that can be treated with acupressure. For example, the acupoints used in excess syndrome are LIV3, LI4, SP10, SP8, and B23, and of these, LIV3 and LI4 can be treated with acupressure. On the other hand, the

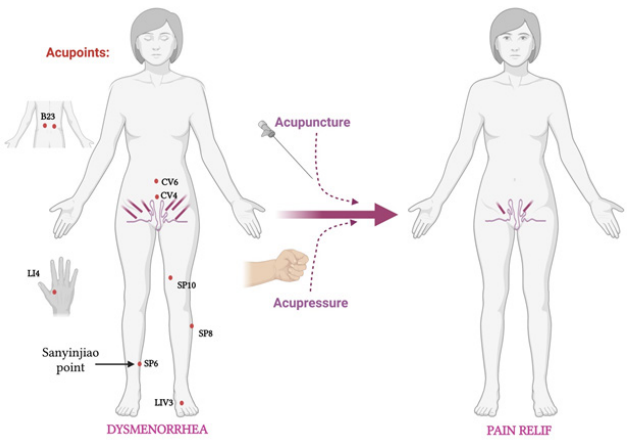


Figure 6. Common acupoints used in acupuncture and acupressure to relieve pain during dysmenorrhea.

acupoints B20, B23, and SP6 are used in deficiency syndrome. Studies have reported that primary dysmenorrhea is alleviated by applying pressure on the acupoints CV6, CV4, SP6, SP10, and LIV3. It has even been seen that acupressure at LIV3 acupoint compared to placebo point could reduce the severity of dysmenorrhea and improve the quality of life (85).

Similarly, Kashef et al. (86) analyzed a group of women with dysmenorrhea who received acupressure at SP6 point and a control group that received sham acupressure. The severity of dysmenorrhea diminished after intervention in both groups during their first menstrual cycle; however, the symptoms reduced more in the group that received acupressure at SP6 at 30 min, 1, 2, and 3 h after intervention. Therefore, the authors claimed that acupressure at SP6 can be an effective and inexpensive therapy for treating primary dysmenorrhea.

Heating pads for cramps

Heat therapy is another technique that shows potential as an adjunct remedy in treating primary dysmenorrhea (14). The external application of heat in women with dysmenorrhea can reduce muscle tension, relax the abdominal muscles, and increase pelvic blood circulation, which reduces pain. Surface heat can be administered to the application site by hot water bags, electric pads, towels, or bottles, and the temperature is between 40–45 °C (87). A study evaluated the effects of a low-dose heat patch on pain symptoms in dysmenorrhea compared with analgesics and no treatments. Significant differences were found between the groups in pain severity after 8 hours of application based on a VAS, concluding that the heat pad is an effective method for reducing dysmenorrhea and that the heat pads would be more effective if they were used in combination with analgesics (88). Although heat application is one of the oldest treatment methods for dysmenorrhea, it has been abandoned due to the increased possibility of acute inflammation (88). Another disadvantage is the lack of accessibility to a heating pad when women are at work or school.

Intake of micronutrients and macronutrients

Several nutritional habits have shown positive effects in the relief of menstrual cramps. For example, decreasing food intake with a high content of arachidonic acid precursors (e.g., coconut and soybean oils, butter, chicken, and eggs) may reduce dysmenorrhea pain (11,89). Likewise, it is also preferred to avoid saturated fats (potent vasoconstrictor of the uterine muscle), salt (fluid retention and swelling), sugar (reduces the absorption of vitamin B and minerals, causing the uterine muscle to contract), and alcohol (depletes the amount of magnesium, which causes an increase in spasms).

On the other hand, increasing food consumption like beans, seeds, fruit, and vegetables decreases the production of arachidonic acid. This food contains different types of macronutrients (protein, fat, carbohydrates, fiber) and micronutrients (vitamins A, B_1, B_2, B_3, C, D, calcium, magnesium, phosphorous, zinc) that may reduce dysmenorrhea severity (11,89). For instance, fiber consumption may decrease the pain in the menstrual cycle because it alters estrogen status. Nagata et al. (90) reported that a soy and fiber diet inversely correlated with menstrual pain in Japanese women (19–24 years). Similarly, polyunsaturated fatty acids reduce pain and have anti-inflammatory effects in primary dysmenorrhea by reducing pro-inflammatory PGs (91). Interestingly, the combination with vitamin B_{12} has a more significant impact in reducing pain. Likewise, zinc reduces PGs synthesis and has antioxidant and anti-inflammatory effects. A study conducted by Kashefi et al. (92) found that zinc sulfate significantly lowered pain in women with dysmenorrhea (15 to 18 years of age) compared to the placebo group.

On the other hand, it has been suggested that calcium and vitamin D deficiency are related to dysmenorrhea; thus, consuming these substances might relieve its symptoms. This assumption is supported by a survey by Osman Karacin et al. (93), who studied 184 women with primary dysmenorrhea. The dysmenorrhea group had significantly lower serum calcium, lower serum vitamin D, and higher serum parathyroid hormone than the control group. Furthermore, depression, irritability, mood swings, fatigue, headache, and breast tenderness were significantly more frequent in the vitamin D deficiency group. Likewise, serum calcium levels rise during different menstrual cycle stages and are higher during the follicular phase than during the luteal phase (94). The above process can produce or aggravate the symptoms associated with dysmenorrhea by causing restlessness, depression, or hallucinations. Calcium regulates the ability of muscle cells to respond to nerve stimulation, and low calcium levels can lead to muscle spasms and contractions. On the other hand, vitamin D plays a prominent role in regulating PGs levels, contributing to dysmenorrhea symptoms (95). A study found that calcium intake effectively reduced menstrual pain intensity (96). However, the combination of 1,000 mg of calcium with 5,000 units of vitamin D daily did not generate a significant difference compared to the placebo group. On the other hand, another study reported that the consumption of calcium and magnesium had significantly better outcomes than the group that only received calcium regarding pain relief and rest length (97). Finally, a meta-analysis conducted by Saei Ghare Naz et al. (98) indicated that zinc sulfate, magnesium, calcium, and vitamins (K, D, B1, and E) have beneficial effects on pain severity in primary dysmenorrhea.

Physical exercise and meditation

Numerous studies have examined the effects of yoga, meditation, or physical activity on pain perception. A

study in adolescent girls with primary dysmenorrhea revealed that when girls did a physical activity, the perception of pain was reduced from severe (25%) and moderate (60–75%) to moderate (80%) and mild (20%) (99). Physical exercise increases the comforting sense by producing endorphins that act as natural sedatives. Likewise, when girls carried out meditation, their pain perception changed from moderate (55%) and severe (45%) pain to mild (50%), moderate (45%), and severe pain (5%). Meditation is a technique that produces physiological effects such as a decrease in pulse, pressure, and muscle tone, activities that help reduce pain (100).

Aromatic oils

Aromatherapy is a widely practiced CAM, and essential oils used for pain during dysmenorrhea (massage, spraying, or oral form) can be extracted from different plants, as shown in Figure 7. However, the therapeutic effects of these oils are not well-supported by clinical studies; only the volatile chemicals in essential oils are known to induce relaxation, improving pain and mental health (12,101).

Essential oils, as a treatment for menstrual pain, can be administered by inhalation, orally, and absorption through the skin. Many articles on this type of alternative therapy have been published in the last few years. Lee et al. (12) summarized evidence on the efficacy of aromatherapy in a study carried out on 19 previously selected publications that used essential oils from rose, lavender, zataria, thymus, peppermint, fennel, and a mixture of essential oils. The study revealed moderately superior effects of aromatherapy for pain reduction compared to a placebo.

Recently Samadipour et al. (102) evaluated black seed oil of *Nigella sativa* (topical - massage administration) as a prophylactic agent against dysmenorrhea in 124 young women (three days before the start of menstruation). The study revealed a pain decrease in the *N. sativa* group compared with the control group ($p = 0.046$). The analgesic effect may be due to different lipid molecules, which may contribute to the pharmacological mechanism for pain. Those molecules include thymoquinone (anti-inflammatory effect), thymohydroquinone, dihydro-thymoquinone (inhibitory activity of COX-2 enzyme), tocopherols, thymol, cymene, trans-anethole, 4-terpineol (decrease oxidative stress). Those molecules may also have some antioxytocic activity.

Future perspectives

Different treatments have effectively reduced the symptoms of primary and secondary dysmenorrhea. However, the degree of relief from pharmacological and non-pharmacological treatments can also vary because the pain threshold varies from person to person. However, in any case, an adequate diagnosis is essential to make the best decisions on the therapeutic approach. In the absence of efficacy with NSAIDs treatment, preparations with natural products and non-pharmacological strategies can adequately contribute to alleviating the discomfort. There is a vast field of research and multiple proposals with natural products to regulate inflammatory and analgesic processes.

Conclusions

Dysmenorrhea is a public health problem worldwide.

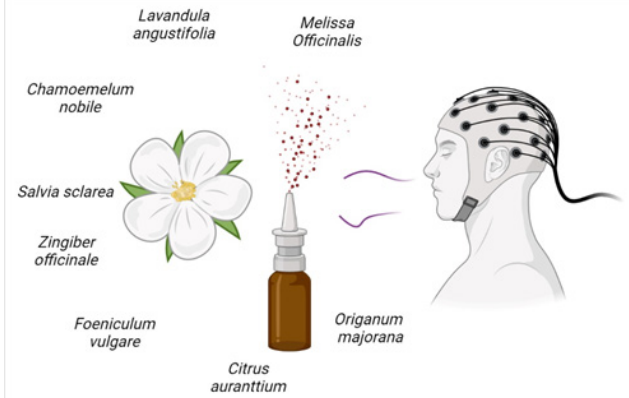


Figure 7. Some essential oils are used for dysmenorrhea pain.

Dysmenorrhea is expressed as a set of cramps and pain but is associated with other symptoms that can vary between individuals. Therefore, medical treatment cannot be generalized and depends on each patient. The pharmacological treatment of the first choice corresponds to NSAIDs, followed by contraceptives. Secondary dysmenorrhea usually requires a surgical approach for cases of endometriosis. Non-pharmacological treatments offer a greater degree of variation in response to dysmenorrhea symptoms. In addition, the mental state helps the patient cope with the affectation of dysmenorrhea; however, it is not a solution that can be globally used because it depends on the degree of resilience of each individual. Therefore, a suitable strategy may result from the combination of pharmacological treatment aided by a non-pharmacological approach.

Competing interests

All authors declare that they have no conflict of interest.

Author contributions

All co-authors contributed to the design and execution of the research and the writing of the manuscript. Each of the co-authors has approved the final version of the manuscript.

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References

1. Harel Z. Dysmenorrhea in Adolescents and Young Adults: Etiology and Management. J Pediatr Adolesc Gynecol. 2006;19(6):363–71.
2. Alsaleem MA. Dysmenorrhea, associated symptoms, and management among students at King Khalid University, Saudi Arabia: An exploratory study. J Fam Med Prim care. 2018;7(4):769–74.
3. Osayande A, Mehulix S. Diagnosis and Initial Management of Dysmenorrhea. Am Fam Physician. 2014;89(5):341–6.
4. De Sanctis V, Soliman A, Bernasconi S, Bianchin L, Bona G, Bozzola M, et al. Primary Dysmenorrhea in Adolescents: Prevalence, Impact and Recent Knowledge. Pediatr Endocrinol Rev. 2015 Dec;13(2):512–20.
5. Burnett M, Lemyre M. No. 345-Primary Dysmenorrhea Consen-

sus Guideline. J Obstet Gynaecol Canada. 2017 Jul;39(7):585–95.
6. Harlow SD, Park M. A longitudinal study of risk factors for the occurrence, duration and severity of menstrual cramps in a cohort of college women. Br J Obstet Gynaecol. 1996 Nov;103(11):1134–42.
7. Wildemeersch D, Schacht E, Wildemeersch P. Treatment of primary and secondary dysmenorrhea with a novel "frameless" intrauterine levonorgestrel-releasing drug delivery system: A pilot study. Eur J Contracept Reprod Heal Care. 2001;6(4):192–8.
8. Ju H, Jones M, Mishra G. The prevalence and risk factors of dysmenorrhea. Epidemiol Rev. 2014;36:104–13.
9. Zannoni L, Giorgi M, Spagnolo E, Montanari G, Villa G, Seracchioli R. Dysmenorrhea, absenteeism from school, and symptoms suspicious for endometriosis in adolescents. J Pediatr Adolesc Gynecol. 2014 Oct;27(5):258–65.
10. Guimarães I, Póvoa AM. Primary Dysmenorrhea: Assessment and Treatment. Rev Bras Ginecol Obstet. 2020 Aug;42(8):501–7.
11. Hudson T. Using Nutrition to Relieve Primary Dysmenorrhea. Altern Complement Ther. 2007;13(3):125–8.
12. Uysal M, Doğru HY, Sapmaz E, Tas U, Çakmak B, Ozsoy AZ, et al. Investigating the effect of rose essential oil in patients with primary dysmenorrhea. Complement Ther Clin Pract. 2016;24:45–9.
13. Abaraogu UO, Igwe SE, Tabansi-Ochiogu CS. Effectiveness of SP6 (Sanyinjiao) acupressure for relief of primary dysmenorrhea symptoms: A systematic review with meta- and sensitivity analyses. Complement Ther Clin Pract. 2016 Nov;25:92–105.
14. Igwea SE, Tabansi-Ochuogu CS, Abaraogu UO. TENS and heat therapy for pain relief and quality of life improvement in individuals with primary dysmenorrhea: A systematic review. Complement Ther Clin Pract. 2016 Aug;24:86–91.
15. Walsh DM. Transcutaneous electrical nerve stimulation and acupuncture points. Complement Ther Med. 1996 Apr;4(2):133–7.
16. Yarnell E. Herbal Medicine for Dysmenorrhea. Altern Complement Ther. 2015 Oct;21(5):224–8.
17. Sultan C, Gaspari L, Paris F. Adolescent dysmenorrhea. Endocr Dev. 2012;22:171–80.
18. Iacovides S, Avidon I, Baker FC. What we know about primary dysmenorrhea today: A critical review. Hum Reprod Update. 2015;21(6):762–78.
19. Harel Z. Dysmenorrhea in adolescents. Ann N Y Acad Sci. 2008;1135:185–95.
20. Harel Z. Dysmenorrhea in adolescents and young adults: From pathophysiology to pharmacological treatments and management strategies. Expert Opin Pharmacother. 2008;9(15):2661–72.
21. Habibi N, Huang MSL, Gan WY, Zulida R, Safavi SM. Prevalence of Primary Dysmenorrhea and Factors Associated with Its Intensity Among Undergraduate Students: A Cross-Sectional Study. Pain Manag Nurs. 2015;16(6):855–61.
22. Ortiz MI, Rangel-Flores E, Carrillo-Alarcón LC, Veras-Godoy HA. Prevalence and impact of primary dysmenorrhea among Mexican high school students. Int J Gynecol Obstet. 2009;107(3):240–3.
23. THE WHOQOL GROUP. Development of the World Health Organization WHOQOL-BREF Quality of Life Assessment. Psychol Med. 1998 May;28(3):551–8.
24. Quick F, Mohammad-Alizadeh-Charandabi S, Mirghafourvand M. Primary dysmenorrhea with and without premenstrual syndrome: variation in quality of life over menstrual phases. Qual Life Res. 2019;28(1):99–107.
25. Iacovides S, Avidon I, Bentley A, Baker FC. Reduced quality of life when experiencing menstrual pain in women with primary dysmenorrhea. Acta Obstet Gynecol Scand. 2014;93(2):213–7.
26. Baker FC, Driver HS, Rogers GG, Paiker J, Mitchell D. High nocturnal body temperatures and disturbed sleep in women with primary dysmenorrhea. Am J Physiol - Endocrinol Metab. 1999;277(6):1013–21.
27. Kapadi R, Elander J. Pain coping, pain acceptance and analgesic use as predictors of health-related quality of life among women with primary dysmenorrhea. Eur J Obstet Gynecol Reprod Biol. 2020;246:40–4.
28. Evans S, Dowding C, Olive L, Payne LA, Druitt M, Seidman LC, et al. Pain catastrophizing, but not mental health or social support, is associated with menstrual pain severity in women with dysmenorrhea: A cross-sectional survey. Psychol Health Med. 2021;1–11.
29. McPeak AE, Allaire C, Williams C, Albert A, Lisonkova S, Yong PJ. Pain Catastrophizing and Pain Health-Related Quality-of-Life in Endometriosis. Clin J Pain. 2018;34(4):349–56.
30. Schoep ME, Adang EMM, Maas JWM, De Bie B, Aarts JW, Nieboer T. Productivity loss due to menstruation-related symptoms: a nationwide cross-sectional survey among 32 748 women. BMJ Open. 2019 Jun;9(6):1–10.
31. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 110: noncontraceptive uses of hormonal contraceptives. Obstet Gynecol. 2010 Jan;115(1):206–18.
32. King J. Noncontraceptive uses of hormonal contraception. J Midwifery Womens Health. 2011 Nov;56(6):628–35.
33. Harada T, Momoeda M, Taketani Y, Hoshiai H, Terakawa N. Low-dose oral contraceptive pill for dysmenorrhea associated with endometriosis: a placebo-controlled, double-blind, randomized trial. Fertil Steril. 2008 Nov;90(5):1583–8.
34. Harada T, Momoeda M, Terakawa N, Taketani Y, Hoshiai H. Evaluation of a low-dose oral contraceptive pill for primary dysmenorrhea: a placebo-controlled, double-blind, randomized trial. Fertil Steril. 2011 May;95(6):1928–31.
35. Harada T, Momoeda M. Evaluation of an ultra-low-dose oral contraceptive for dysmenorrhea: a placebo-controlled, double-blind, randomized trial. Fertil Steril. 2016 Dec;106(7):1807–14.
36. Casper RF. Progestin-only pills may be a better first-line treatment for endometriosis than combined estrogen-progestin contraceptive pills. Fertil Steril. 2017 Mar;107(3):533–6.
37. Al-Jefout M, Nawaiseh N. Continuous Norethisterone Acetate versus Cyclical Drospirenone 3 mg/Ethinyl Estradiol 20 µg for the Management of Primary Dysmenorrhea in Young Adult Women. J Pediatr Adolesc Gynecol. 2016 Apr;29(2):143–7.
38. Strowitzki T, Faustmann T, Gerlinger C, Seitz C. Dienogest in the treatment of endometriosis-associated pelvic pain: a 12-week, randomized, double-blind, placebo-controlled study. Eur J Obstet Gynecol Reprod Biol. 2010;151(2):193–8.
39. Ramazanzadeh F, Tavakolianfar T, Shariat M, Firuzabadi SJP, Hagholahi F. Levonorgestrel-releasing IUD versus copper IUD in control of dysmenorrhea, satisfaction and quality of life in women using IUD. Iran J Reprod Med. 2012 Jan;10(1):41–6.
40. Adeyemi-Fowode OA, Bercaw-Pratt JL. Intrauterine Devices: Effective Contraception with Noncontraceptive Benefits for Adolescents. J Pediatr Adolesc Gynecol. 2019 Sep;32(5):2–6.
41. Lindh I, Milsom I. The influence of intrauterine contraception on the prevalence and severity of dysmenorrhea: a longitudinal population study. Hum Reprod. 2013 Jul;28(7):1953–60.
42. Costanzi F, De Marco MP, Colombrino C, Ciancia M, Torcia F, Ruscito I, et al. The treatment with Levonorgestrel Releasing Intrauterine System (LNG-IUS) in patients affected by menometrorrhagia, dysmenorrhea and adenomimyois: clinical and ultrasonographic reports. Eur Rev Med Pharmacol Sci. 2021;25(9):3432–9.
43. Xu Y, Zhao W, Li T, Bu H, Zhao Z, Zhao Y, et al. Effects of acupoint-stimulation for the treatment of primary dysmenorrhoea compared with NSAIDs: a systematic review and meta-analysis of 19 RCTs. BMC Complement Altern Med. 2017 Aug;17(1):1–12.
44. Marjoribanks J, Ayeleke RO, Farquhar C, Proctor M. Nonsteroi-

dal anti-inflammatory drugs for dysmenorrhoea. Cochrane database Syst Rev. 2015 Jan;2015(7):1–125.
45. Feng X, Wang X. Comparison of the efficacy and safety of nonsteroidal anti-inflammatory drugs for patients with primary dysmenorrhea: A network meta-analysis. Mol Pain. 2018 Apr;14:1–14.
46. Nie W, Xu P, Hao C, Chen Y, Yin Y, Wang L. Efficacy and safety of over-the-counter analgesics for primary dysmenorrhea: A network meta-analysis. Medicine (Baltimore). 2020;99(19):1–11.
47. Armour M, Parry K, Al-Dabbas MA, Curry C, Holmes K, MacMillan F, et al. Self-care strategies and sources of knowledge on menstruation in 12,526 young women with dysmenorrhea: A systematic review and meta-analysis. PLoS One. 2019 Jul;14(7):1–18.
48. Saltan G, Süntar I, Ozbilgin S, Ilhan M, Demirel MA, Oz BE, et al. Viburnum opulus L.: A remedy for the treatment of endometriosis demonstrated by rat model of surgically-induced endometriosis. J Ethnopharmacol. 2016 Dec;193:450–5.
49. Khalesi ZB, Beiranvand SP, Bokaie M. Efficacy of Chamomile in the Treatment of Premenstrual Syndrome: A Systematic Review. J Pharmacopuncture. 2019;22(4):204–9.
50. Karimian Z, Sadat Z, Bahrami N, Kafaie M. Comparison of chamomile and mefenamic acid capsules in hemorrhage of menstruation. Iran J Obstet Gynecol Infertil. 2015;18(157):11–7.
51. Bokaie M, Farajkhoda T, Enjezab B, Khoshbin A, Mojgan KZ. Oral fennel (Foeniculum vulgare) drop effect on primary dysmenorrhea: Effectiveness of herbal drug. Iran J Nurs Midwifery Res. 2013 Mar;18(2):128–32.
52. Salmalian H, Saghebi R, Moghadamnia AA, Bijani A, Faramarzi M, Amiri FN, et al. Comparative effect of thymus vulgaris and ibuprofen on primary dysmenorrhea: A triple-blind clinical study. Casp J Intern Med. 2014;5(2):82–8.
53. Shahrahmani H, Ghazanfarpour M, Shahrahmani N, Abdi F, Sewell R DE, Rafieian-Kopaei M. Effect of fennel on primary dysmenorrhea: a systematic review and meta-analysis. J Complement Integr Med. 2021 Jun;18(2):261–9.
54. Jenabi E, Ebrahimzadeh S. Chamomile tea for relief of primary dysmenorrhea. Iran J Obstet Gynecol Infertil. 2010 Jan;13(1):39–42.
55. Niazi A, Moradi M. The Effect of Chamomile on Pain and Menstrual Bleeding in Primary Dysmenorrhea: A Systematic Review. Int J Community Based Nurs Midwifery. 2021 Jun;9(3):174–86.
56. Surrey E, Taylor HS, Giudice L, Lessey BA, Abrao MS, Archer DF, et al. Long-Term Outcomes of Elagolix in Women With Endometriosis: Results From Two Extension Studies. Obstet Gynecol. 2018;132(1):147–60.
57. Surrey ES, Soliman AM, Agarwal SK, Snabes MC, Diamond MP. Impact of elagolix treatment on fatigue experienced by women with moderate to severe pain associated with endometriosis. Fertil Steril. 2019 Aug;112(2):298–304.
58. Suleiman AA, Nader A, Winzenborg I, Beck D, Polepally AR, Ng J, et al. Exposure-Safety Analyses Identify Predictors of Change in Bone Mineral Density and Support Elagolix Labeling for Endometriosis-Associated Pain. CPT pharmacometrics Syst Pharmacol. 2020 Nov;9(11):639–48.
59. Taylor HS, Giudice LC, Lessey BA, Abrao MS, Kotarski J, Archer DF, et al. Treatment of Endometriosis-Associated Pain with Elagolix, an Oral GnRH Antagonist. N Engl J Med. 2017 Jul;377(1):28–40.
60. Pokrzywinski RM, Soliman AM, Chen J, Snabes M, Diamond MP, Surrey E, et al. Impact of elagolix on work loss due to endometriosis-associated pain: estimates based on the results of two phase III clinical trials. Fertil Steril. 2019 Sep;112(3):545–51.
61. Taylor HS, Soliman AM, Johns B, Pokrzywinski RM, Snabes M, Coyne KS. Health-Related Quality of Life Improvements in Patients With Endometriosis Treated With Elagolix. Obstet Gynecol. 2020 Sep;136(3):501–9.
62. Agarwal SK, Singh SS, Archer DF, Mai Y, Chwalisz K, Gordon K, et al. Endometriosis-Related Pain Reduction During Bleeding and Nonbleeding Days in Women Treated with Elagolix. J Pain Res. 2021;14:263–71.
63. Hingne PM, Sluka KA. Differences in Waveform Characteristics Have No Effect on the Anti-Hyperalgesia Produced by Transcutaneous Electrical Nerve Stimulation (TENS) in Rats With Joint Inflammation. J Pain. 2007 Mar;8(3):251–5.
64. Jones I, Johnson MI. Transcutaneous electrical nerve stimulation. Contin Educ Anaesth Crit Care Pain. 2009 Aug;9(4):130–5.
65. Lynch L, Simpson KH. Transcutaneous electrical nerve stimulation and acute pain. BJA CEPD Rev. 2002 Apr;2(2):49–52.
66. Proctor M, Farquhar C, Stones W, He L, Zhu X, Brown J. Transcutaneous electrical nerve stimulation for primary dysmenorrhoea. Cochrane Database Syst Rev. 2002 Jan;2002(1):1–113.
67. Wong JJ, Laframboise M, Mior S. Multimodal Therapy Combining Spinal Manipulation, Transcutaneous Electrical Nerve Stimulation, and Heat for Primary Dysmenorrhea: A Prospective Case Study. J Chiropr Med. 2018 Sep;17(3):190–7.
68. Hadgraft J. Pharmaceutical aspects of transdermal nitroglycerin. Int J Pharm. 1996 Jun;135(1–2):1–11.
69. Todd B. Transdermal nitroglycerin ointment and patches. Geriatr Nurs (Minneap). 1986 May;7(3):152–4.
70. Shah VP, Tymes NW, Yamamoto LA, Skelly JP. In vitro dissolution profile of transdermal nitroglycerin patches using paddle method. Int J Pharm. 1986 Oct;32(2–3):243–50.
71. Atkins JM. Some issues concerning transdermal nitroglycerin patches. Am Heart J. 1986 Jul;112(1):229–32.
72. Oladosu FA, Tu FF, Hellman KM. Nonsteroidal antiinflammatory drug resistance in dysmenorrhea: epidemiology, causes, and treatment. Am J Obstet Gynecol. 2018;218(4):390–400.
73. Moya RA, Moisa CF, Morales F, Wynter H, Ali A, Narancio E. Transdermal glyceryl trinitrate in the management of primary dysmenorrhea. Int J Gynecol Obstet. 2000 May;69(2):113–8.
74. Ré O and TTNSG. Transdermal nitroglycerine in the management of pain associated with primary dysmenorrhoea: a multinational pilot study. The Transdermal Nitroglycerine/Dysmenorrhoea Study Group. J Int Med Res. 1997;25(1):41–4.
75. Nackenson MJ. Dysmenorrhea in the Adolescent. In: Reference Module in Biomedical Sciences. Elsevier; 2021. p. 1–8.
76. Lichten EM, Bombard J. Surgical treatment of primary dysmenorrhea with laparoscopic uterine nerve ablation. J Reprod Med. 1987 Jan;32(1):37–41.
77. Luna-Rojas M, Iga-Canavati G, Gonzalez-Guajardo E, Treviño-Alanis R. Surgical treatment of dysmenorrhea in patients with endometriosis. Obstet Gynecol. 2003 Apr;101(4):S58.
78. Wu X, Chung VC, Hui EP, Ziea ET, Ng BF, Ho RS, et al. Effectiveness of acupuncture and related therapies for palliative care of cancer: overview of systematic reviews. Sci Rep. 2015 Dec;5(1):1–15.
79. Birch S, Lee MS, Kim T-H, Alraek T. Historical perspectives on using sham acupuncture in acupuncture clinical trials. Integr Med Res. 2021 Apr;11(1):1–6.
80. Yuan Q, Wang P, Liu L, Sun F, Cai Y, Wu W, et al. Acupuncture for musculoskeletal pain: A meta-analysis and meta-regression of sham-controlled randomized clinical trials. Sci Rep. 2016 Nov;6(1):1–24.
81. Ernst E, White AR. Prospective studies of the safety of acupuncture: a systematic review. Am J Med. 2001 Apr;110(6):481–5.
82. Shetty GB, Shetty B, Mooventhan A. Efficacy of Acupuncture in the Management of Primary Dysmenorrhea: A Randomized Con-

trolled Trial. J Acupunct Meridian Stud. 2018 Aug;11(4):153–8.
83. Kiran G, Gumusalan Y, Ekerbicer HC, Kiran H, Coskun A, Arikan DC. A randomized pilot study of acupuncture treatment for primary dysmenorrhea. Eur J Obstet Gynecol Reprod Biol. 2013 Jul;169(2):292–5.
84. Mirbagher-Ajorpaz N, Adib-Hajbaghery M, Mosaebi F. The effects of acupressure on primary dysmenorrhea: A randomized controlled trial. Complement Ther Clin Pract. 2011 Feb;17(1):33–6.
85. Bazarganipour F, Taghavi S-A, Allan H, Hosseini N, Khosravi A, Asadi R, et al. A randomized controlled clinical trial evaluating quality of life when using a simple acupressure protocol in women with primary dysmenorrhea. Complement Ther Med. 2017 Oct;34:10–5.
86. Kashefi F, Ziyadlou S, Khajehei M, Ashraf AR, Reza Fadaee A, Jafari P. Effect of acupressure at the Sanyinjiao point on primary dysmenorrhea: A randomized controlled trial. Complement Ther Clin Pract. 2010 Nov;16(4):198–202.
87. Jo J, Lee SH. Heat therapy for primary dysmenorrhea: A systematic review and meta-analysis of its effects on pain relief and quality of life. Sci Rep. 2018 Dec;8(1):1–8.
88. Potur DC, Kömürcü N. The Effects of Local Low-Dose Heat Application on Dysmenorrhea. J Pediatr Adolesc Gynecol. 2014 Aug;27(4):216–21.
89. Fatima A, Khalid S, Aslam M, Waseem H. Assessment of dietary patterns among females suffering from dysmenorrhea. Asian J Allied Heal Sci. 2020 Dec;5(1):12–8.
90. Nagata C, Hirokawa K, Shimizu N, Shimizu H. Associations of menstrual pain with intakes of soy, fat and dietary fiber in Japanese women. Eur J Clin Nutr. 2005 Jan;59(1):88–92.
91. Hansen SO, Knudsen UB. Endometriosis, dysmenorrhoea and diet. Eur J Obstet Gynecol Reprod Biol. 2013 Jul;169(2):162–71.
92. Kashefi F, Khajehei M, Tabatabaeichehr M, Alavinia M, Asili J. Comparison of the effect of ginger and zinc sulfate on primary dysmenorrhea: a placebo-controlled randomized trial. Pain Manag Nurs Off J Am Soc Pain Manag Nurses. 2014 Dec;15(4):826–33.
93. Karacin O, Mutlu I, Kose M, Celik F, Kanat-Pektas M, Yilmazer M. Serum vitamin D concentrations in young Turkish women with primary dysmenorrhea: A randomized controlled study. Taiwan J Obstet Gynecol. 2018 Feb;57(1):58–63.
94. Abdi F, Ozgoli G, Rahnemaie FS. A systematic review of the role of vitamin D and calcium in premenstrual syndrome. Obstet Gynecol Sci. 2019;62(2):73–86.
95. Abdi F, Amjadi MA, Zaheri F, Rahnemaei FA. Role of vitamin D and calcium in the relief of primary dysmenorrhea: a systematic review. Obstet Gynecol Sci. 2021 Jan;64(1):13–26.
96. Zarei S, Mohammad-Alizadeh-Charandabi S, Mirghafourvand M, Javadzadeh Y, Effati-Daryani F. Effects of Calcium-Vitamin D and Calcium-Alone on Pain Intensity and Menstrual Blood Loss in Women with Primary Dysmenorrhea: A Randomized Controlled Trial. Pain Med. 2017 Jan;18(1):3–13.
97. Mohammad-Alizadeh Charandabi S, Mirghafourvand M, Nezamivand-Chegini S, Javadzadeh Y. Calcium With and Without Magnesium for Primary Dysmenorrhea: A Double-Blind Randomized PlaceboControlled Trial. Int J Women's Heal Reprod Sci. 2017 Apr;5(4):332–8.
98. Saei Ghare Naz M, Kiani Z, Rashidi Fakari F, Ghasemi V, Abed M, Ozgoli G. The Effect of Micronutrients on Pain Management of Primary Dysmenorrhea: a Systematic Review and Meta-Analysis. J Caring Sci. 2020 Mar;9(1):47–56.
99. Widyanata KAJ, Putra IGY, Daryaswanti PI, Febianingsih NPE. Physical Activity And Meditation To Reduce Primary Dysmenorrhea In Adolescent. Adv Heal Sci Res. 2017;3:18–20.
100. Nag U and MK. Medıtatıon And Yoga As Alternatıve Therapy For Prımary Dysmenorrhea. Int J Med Pharm Sci. 2013;3:39–44.
101. Hutapea LMN. Massage and Inhalation Aromatherapy as Alternative Medicine in Pain Management of Primary Dysmenorrhea. J Int Sch Conf - ALLIED Heal. 2016;1(5):100–10.
102. Samadipour E, Rakhshani MH, Kooshki A, Amin B. Local Usage of Nigella sativa Oil as an Innovative Method to Attenuate Primary Dysmenorrhea: A Randomized Double-blind Clinical Trial. Oman Med J. 2020 Sep;35(5):1–6.