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Primary dysmenorrhea in adolescents

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ABSTRACT

Dysmenorrhea is among the most common gynecological complaints in adolescents. Its diagnosis depends on the exclusion of other underlying pathologies, with the patient's history playing a crucial role. Initial therapy with over-the-counter medications can be initiated solely based on the patient's history. However, factors such as adolescents not seeking care, reliance on family advice, or incomplete evaluations by healthcare providers may contribute to misdiagnosis, leading to delays in both appropriate diagnosis and management. This article presents a narrative review of primary dysmenorrhea in adolescents, addressing its risk factors, pathophysiology, potential underlying conditions, diagnostic approaches, and treatment options. A step-by-step treatment algorithm for primary dysmenorrhea is also proposed, emphasizing that cases unresponsive to initial therapy should prompt reevaluation for secondary causes, such as endometriosis. This review urges healthcare professionals and others working with adolescents to increase awareness of primary dysmenorrhea and its management.

1. Introduction

Dysmenorrhea represents one of the most common yet underestimated and undertreated gynecological conditions and a significant public health problem [1]. It affects school-aged menstruating individuals and is a leading cause of school absenteeism and decreased productivity.

Primary dysmenorrhea specifically refers to painful menstrual bleeding without any identifiable underlying cause. In some families, it is often considered a “normal” or “hereditary” condition, as many members have experienced similar symptoms.

Painful menstrual bleeding may be accompanied by symptoms such as nausea, malaise, vomiting, and low back pain that can radiate into the thighs, as well as severe headaches. Primary dysmenorrhea typically begins 1-2 years after menarche, peaks during adolescence and early adulthood, and gradually decreases around the age of 30. The pain usually begins with the onset of menstruation, intensifies, and lasts no more than 48-72 h. Pain may occur before or simultaneously with the onset of menstruation and gradually decreases in intensity over the subsequent days.

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Secondary dysmenorrhea, unlike primary dysmenorrhea, is associated with an identifiable pathological condition of the reproductive organs. Symptoms vary depending on the underlying cause and may include adenomyosis, endometriosis, endometritis, pelvic inflammatory disease (PID), leiomyomas, and obstructive anomalies of the genital tract. The pain pattern differs in timing, duration, rhythm, and intensity during the menstrual cycle. In some cases, secondary dysmenorrhea presents with abdominal pain that coincides with menstruation but lacks cyclicity.

2. Materials and methods

This article presents a narrative review conducted through a comprehensive search of the available literature. The approach involved analyzing published studies, clinical guidelines, and relevant reports to synthesize current knowledge on primary dysmenorrhea in adolescents. Key topics addressed include risk factors, pathophysiology, underlying conditions, diagnostic approaches, and treatment options. The review also presents a proposed step-by-step treatment algorithm and emphasizes the need to reevaluate cases unresponsive to initial therapy for potential secondary causes, such as endometriosis. The aim is to provide healthcare professionals with practical guidance for managing primary dysmenorrhea and to highlight the need for greater awareness and improved diagnostic evaluation.

3. Prevalence and risk factors for primary dysmenorrhea

The reported prevalence of dysmenorrhea varies widely, influenced by its definition and by cultural factors. Globally, the prevalence has been reported to range between 59% and 89% [2,3], A recent meta-analysis found that the prevalence of primary dysmenorrhea has increased over time, from 58.8% before 2010 to 68.5% after 2010, and 71.5% between 2015 and 2021 [4].

Risk factors are categorized according to the methodology used to group them, although they often interact and are numerous [4]. General risk factors for primary dysmenorrhea include age, race, body-mass index (BMI), lifestyle habits, cigarette smoking, low socio-economic status, alcohol consumption, and nutritional factors [5–9].

Important risk factors from the patient's history include age at menarche, cycle length, menstrual flow intensity, contraceptive use, family history of dysmenorrhea, parity, obstetric history, and sexual activity [6,10–12].

Several efforts have been made to quantify symptom severity using pain scales and scoring systems, which have demonstrated good accuracy [13]. Some studies have reported a high prevalence of moderate to severe dysmenorrhea, reaching 52%. Fortunately, most reported cases of dysmenorrhea present with mild to moderate symptoms. Approximately 10% of women describe the pain as “unbearable” [14]. Dysmenorrhea is a major cause of work absenteeism and the leading cause of school absenteeism among adolescents [15]. Although dysmenorrhea is not life-threatening, it is a disabling and psychologically distressing condition [4,16]. Many women and girls choose to self-treat and do not seek medical assistance. This behavior may stem from familial perceptions of painful periods as “normal,” although some evidence suggests a genetic link to dysmenorrhea [17].

3.1. Pathophysiology of dysmenorrhea

The pain is caused by ischemia of endometrium, resulting from frequent and prolonged uterine contractions. This leads to the disruption of cell membranes and the release of phospholipids, which can follow either the cyclooxygenase (COX) or lipoxygenase pathway. The COX pathway involves the conversion of phospholipids into arachidonic acid and subsequently into cyclic endoperoxides by the enzyme cyclooxygenase. The products of this pathway include prostaglandin F2 alpha ($PGF_2\alpha$), prostaglandin E2 (PGE_2), and thromboxane A2 (TXA_2). These mediators induce uterine contractions, vasoconstriction of uterine vessels, and hypersensitization of pain-sensitive nerve fibers. The lipoxygenase pathway converts phospholipids into hydroperoxyeicosatetraenoic acid-producing leukotriene A, B, and C, which also induce uterine contractions. Some studies have shown elevated urinary levels of leukotrienes in adolescents with dysmenorrhea [18].

Other contributing factors may include decreased levels of nitric oxide [19], elevated levels of vasopressin [20], and increased expression of CB1 receptors in the myometrium [21].

Normal uterine peristalsis is characterized by a basal tone of less than 10 mm Hg, with three to four rhythmic and synchronized contractions at 10-min intervals. The active pressure does not exceed 120 mm Hg.

In primary dysmenorrhea, the basal tone exceeds 10 mm Hg. The contractions are neither coordinated nor rhythmic, and their frequency exceeds 5 in 10-min intervals. The active pressure ranges from more than 120 to 180 mm Hg, and, in some cases, reaches up to 400 mm Hg. These conditions result in poor uterine perfusion; ischemia worsens, and the levels of metabolites that stimulate small type-C neurons increase. This sequence of events leads to pain. Moreover, $PGF_2\alpha$ and PGE_2 can stimulate the bronchi and bowel and contract vascular smooth muscles, leading to bronchoconstriction, nausea, vomiting, diarrhea, and hypertension.

Doppler studies have shown reduced vascularity in the uterine vessels due to increased resistance in adolescents and young adults with dysmenorrhea [22,23].

Additionally, studies on the pathophysiology of primary dysmenorrhea have explored the role of inflammatory cytokines [24] presenting the condition as a pro-inflammatory state. There is substantial evidence of central nervous system sensitization and maladaptive pain modulation [25,26].

3.2. Symptomatology

Symptoms of primary dysmenorrhea can vary widely. The leading symptom is cramping pain in the lower abdomen that accompanies menstruation. Radiating pain in the thighs and lower back, along with nausea, vomiting, diarrhea, sweating, headaches, palpitations, fatigue, malaise, and dizziness, may also be present. Importantly, symptoms begin immediately before or at the onset of menstrual bleeding and last for 8 to 72 h.

Neuroscientific research provides new insights into the condition. The repetitive nature of the condition can lead to emotional distress and mental health issues. Some studies have reported depression and sleep disturbances in girls with dysmenorrhea [27]. Studies have shown that the pain threshold for experimentally induced pain in women with dysmenorrhea is lower than that of women with normal menstruation [28]. This hypersensitivity is evident not only during menstruation but also throughout the entire menstrual cycle. One study even found an association between primary dysmenorrhea and attention-deficit/hyperactivity disorder in adolescents [29].

Neuroimaging studies [30] have shown alterations in CNS structure and function. Structural changes, such as enlargement of gray matter areas in regions including the orbitofrontal cortex, insula, primary and secondary sensory cortices, precuneus, and posterior cingulate cortex, have been observed. Simultaneously, significant volume reductions in subcortical regions such as the caudate nucleus, thalamus, and amygdala have been observed in patients with primary dysmenorrhea. These regions are known to be responsible for the processing and modulation of pain information [31].

The processes of endogenous inhibition and pain modulation are strongly correlated with sex hormone levels [32,33], resulting in variations in pain perception across different menstrual phases. A possible explanation involves the interaction between serotonergic and noradrenergic neurons in the nucleus raphe magnus and locus coeruleus, which are rich in estrogen and progesterone receptors. This interaction activates endogenous pain-inhibitory pathways and promotes the release of endogenous opioids, such as enkephalins, in the medulla spinalis. Results indicate that pain modulation is stronger during ovulation and weaker during the early follicular or menstrual phases [34].

Alterations are also present in white matter microstructure. Diffusion MRI studies have demonstrated modifications in the default mode network within pain-related connectomes, particularly in the cingulum, leading to increased pain perception [35].

Functional alterations in patients with primary dysmenorrhea are primarily related to changes in functional connectivity [31,36]

Primary dysmenorrhea represents a model of chronic, cyclic, and repetitive pain characterized by alternating periods of pain and pain-free intervals. Repeated stress may alter autonomic balance by increasing sympathetic activity or decreasing parasympathetic activity. Consequently, dysmenorrhea may predispose individuals to chronic pain conditions such as fibromyalgia, chronic headaches, chronic low back pain, irritable bowel syndrome (IBS), and painful bladder syndrome [24,31]

4. Diagnosis of primary dysmenorrhea

4.1. The diagnosis of primary dysmenorrhea is primarily based on the patient's medical history

A detailed general and gynecological history, including the age at menarche, menstrual cycle characteristics, onset, duration, and type of pain, as well as its quantification, is essential for the diagnosis of primary dysmenorrhea.

Although not mandatory when the history is suggestive of primary dysmenorrhea, physical examination can help exclude potential causes of secondary dysmenorrhea.

If a patient presents with dysmenorrhea soon after menarche or later with worsening symptoms, abnormal uterine bleeding, dyspareunia, or vaginal discharge, secondary dysmenorrhea should be suspected. The occurrence of cramping pain before menarche in girls with developed secondary sexual characteristics should suggest an obstructive Mullerian anomaly.

Pelvic ultrasonography is the initial diagnostic tool for identifying pelvic pathology.

Imaging modalities such as MRI and CT scans can help exclude organic pathology in the pelvis. Diagnostic laparoscopy or hysteroscopy should be reserved for cases where suspicion of secondary dysmenorrhea is high and surgical intervention is required.

Sexually transmitted infections (STIs) should be screened for and excluded in sexually active individuals.

Quantifying pain and grading dysmenorrhea based on pain intensity and its impact on daily activities are essential for treatment planning. Numeric scales (1-5) and verbal scales (mild, moderate, severe) are used to describe pain intensity but are often subjective. The Visual Analogue Scale (VAS) is more sensitive but limited by its one-dimensional focus on pain, disregarding associated symptoms. Multidimensional scales have been developed, but also criticized [37,38].

5. Treatment

5.1. Treatment aims to both alleviate symptoms and address the underlying causes that trigger the primary signs of dysmenorrhea

5.1.1. NSAID

The mechanism of action of this drug class involves inhibition of prostaglandin synthesis at multiple levels. They represent the first-line treatment option and are available as over the counter (OTC) medications. Although widely used, these drugs may cause serious side effects such as peptic ulcers, gastrointestinal bleeding, and perforation. There is insufficient data on which of the NSAIDs is most efficient and safest [39]. Specific COX-2 inhibitors were shown not to cause gastric damage, but they are not approved in adolescents under 18 years of age. Some agents have demonstrated potential cardiovascular and dermatologic adverse effects and have been

withdrawn from the market by manufacturers [40,41].

All dosing regimens share a common approach, initiating a loading dose (e.g., ibuprofen, naproxen, mefenamic acid, or celecoxib) one to two days before the onset of menses and continuing for two to three days of bleeding, administered every 6–12 h depending on the specific medication.

5.1.2. Hormonal contraceptives

Hormonal contraceptives alongside the NSAIDs may as well be considered a first-line treatment for dysmenorrhea in females seeking contraception or in those with contraindications to NSAIDs [42,43].

They may include combined hormonal oral contraceptives, progestin-only pills, Levonorgestrel containing Intrauterine System (LNG-IUS), depot-injectables, implants, vaginal rings, or patches.

Combined estrogen-progestin oral contraceptives alleviate dysmenorrhea by reducing endometrial proliferation and suppressing ovarian hormone production. They may be administered cyclically or continuously to reduce the frequency of menstrual bleeding episodes [44].

The LNG-IUS is a recommended treatment for adolescents with laparoscopically confirmed endometriosis and is best inserted during the laparoscopic procedure [45].

The LNG-IUS is effective in reducing heavy menstrual bleeding, managing bleeding episodes in adolescents with coagulopathies such as von Willebrand disease, and may induce amenorrhea in certain patients with disabilities [46,47].

Progestin-only pills (POPs) are also recommended for the treatment of dysmenorrhea in individuals with contraindications to estrogen-containing components [48].

Pharmacologic treatment options that are not widely used due to limited high-quality clinical evidence include leukotriene antagonists used in asthma therapy (montelukast), calcium channel blockers (nifedipine), vasopressin inhibitors, and nitric oxide donors.

5.1.3. Complementary and alternative medicine (CAM)

At least 10-20% of patients with dysmenorrhea do not adhere to standard Western medical treatment due to contraindications or lack of efficacy. Alternative therapeutic approaches include the following.

5.1.3.1. · Herbal and dietary supplements. They are available without a prescription and are widely used. Randomized controlled trials (RCTs) evaluating their efficacy indicate that thiamine, pyridoxine, tocopherol, magnesium, vitamin D, fish oil, ginger, valerian, fenugreek, dill, zataria, fennel, and zinc sulfate may help reduce pain, although the supporting evidence remains limited [49–52].

5.1.3.2. ·Topical heat application. Studies suggest that applying hot compresses at 39 °C for 12 h daily produces effects comparable to 400 mg of ibuprofen administered every 8 h. Patients should be advised not to exceed the recommended temperature exposure to prevent heat-induced inflammation of the skin [53].

5.1.3.3. ·Physical activity. Both stretching and strength training enhance pelvic blood flow and stimulate the release of beta-endorphins, which act as nonspecific analgesics [54,55].

5.1.3.4. ·Transcutaneous electric nerve stimulation (TENS). It involves the application of electrical currents with varying intensities and frequencies to specific dermatomes and is considered a safe option for patients seeking nonpharmacological treatment [56,57].

5.1.3.5. ·Acupuncture, acupressure, and moxibustion. This traditional Chinese intervention is widely accepted in Western medicine. Needle stimulation enhances endorphin and serotonin interaction, thereby blocking pain transmission through neural pathways [58–60].

5.1.3.6. ·Spinal manipulation. Spinal manipulation is expected to enhance spinal mobility, improve pelvic blood flow, and reduce pain. Several techniques differ in speed, amplitude of movement, and applied pressure. Systematic reviews have demonstrated a lack of high-quality studies to support definitive recommendations [61,62].

5.1.3.7. ·Cannabis. The plant *Cannabis sativa* contains compounds such as cannabidiol (CBD), tetrahydrocannabinol (THC), terpenes, limonene, cannabichromene (CBC), cannabigerol (CBG), and other phytocannabinoids, with their concentrations varying by plant type. Although the anti-inflammatory, analgesic, and relaxing effects of CBD are documented [63,64], the psychoactive properties of THC classify the plant as a controlled substance in many countries. Nevertheless, ongoing research continues to expand in this field [65].

6. Surgical treatment

Laparoscopic ablation of the uterine nerve (LAUN) and laparoscopic presacral neurectomy (LPSN) are surgical techniques used to treat refractory pain, especially in deep infiltrating endometriosis, by disrupting sensory nerves. These procedures are rarely performed in adolescents. One study showed there is insufficient evidence to recommend these procedures of nerve interruption in management of dysmenorrhea, regardless of the cause [66].

7. The approach to dysmenorrhea in adolescents

A presumption of primary dysmenorrhea should prompt initiation of first-line therapy [67,68].

(See Fig. 1. Flowchart for the treatment of Primary dysmenorrhea).

Over-the-counter NSAIDs are recommended for patients. After 3-6 months, the patient should be re-evaluated for adherence to therapy and response to treatment. A positive response indicates confirmation of the diagnosis of primary dysmenorrhea. If there is no response to NSAIDs, combined oral contraceptives should be initiated cyclically. If there is no response within three to six months of combined oral contraceptive use, secondary dysmenorrhea, most likely due to endometriosis, should be strongly suspected. In such circumstances, the therapeutic approach should be individualized to the patient. As a definitive diagnosis of endometriosis necessitates laparoscopic evaluation-a surgical intervention-it is often advisable to defer surgery until a later stage in life. In the interim, continuous use of combined oral contraceptives is recommended, as this regimen typically reduces menstrual frequency to two or three times per year, thereby decreasing the incidence of painful episodes. LNG-IUS is an excellent option, and it is advisable even in nulliparous females.

Other pharmacological treatment options should be considered after evaluating the underlying causes of dysmenorrhea.

Possible causes of non-adherence or poor therapeutic response may include adolescent attitude, forgetfulness, disorganization, lack of parental support, limited medication availability, high costs, restricted pharmacy access, peer influence, social network pressure, subtherapeutic dosing, and incorrect dosage intervals or timing.

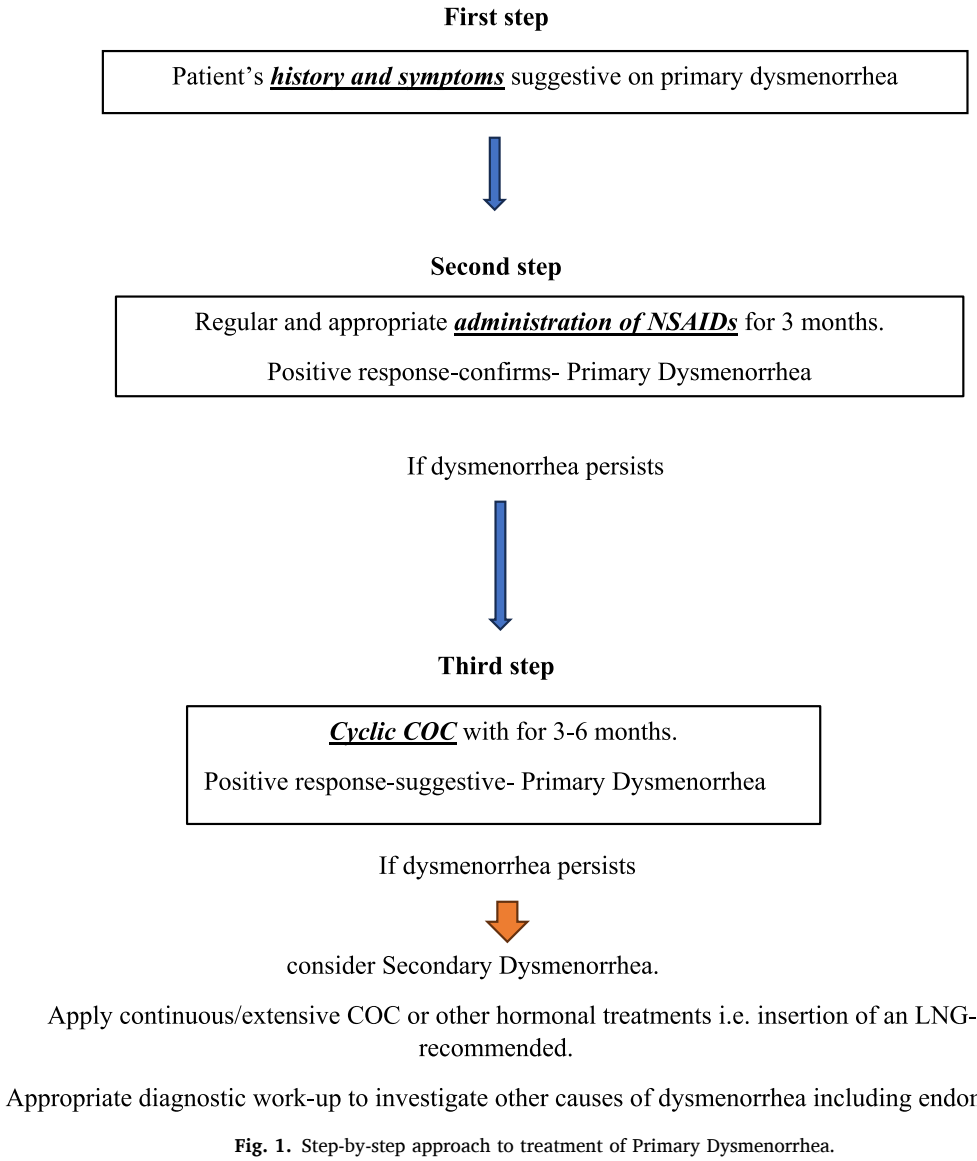

Fig. 1. Step-by-step approach to treatment of Primary Dysmenorrhea.

8. Prognosis

Most cases of mild to moderate dysmenorrhea subside with NSAID therapy, and the prognosis is favorable. Cases unresponsive to NSAIDs and/or oral hormonal contraceptives should be re-evaluated for secondary dysmenorrhea, most commonly due to endometriosis. A delay in diagnosis can lead to disease progression.

9. Discussion and conclusion

Although not life-threatening, dysmenorrhea should be taken seriously, as it may have lifelong consequences such as endometriosis and adenomyosis.

An adolescent with a history of primary dysmenorrhea should be provided with information about available treatments, including NSAIDs and hormonal contraceptive options. A shared and informed decision-making process is essential for patient satisfaction and treatment adherence. Nevertheless, first-line treatment with NSAIDs may be initiated once the patient has been appropriately informed about their correct use. When NSAIDs are used as prescribed, the risk of adverse effects is minimal; however, the patient should still be counseled regarding potential side effects. During the same consultation, the healthcare provider should encourage the adolescent to adhere to treatment and schedule a follow-up appointment after three months to assess adherence and treatment effectiveness. At that point, if there is no response to treatment, the patient should undergo a gynecological evaluation to identify potential pathological causes of secondary dysmenorrhea. If such pathology is identified, dysmenorrhea should be classified as secondary and managed accordingly. In cases where there is no response to NSAIDs, OHC therapy should be initiated. Again, providing detailed explanations and dedicating time to addressing questions, concerns, and misconceptions should be prioritized to ensure successful treatment outcomes.

What if an adolescent presenting with painful menstrual periods, diagnosed as primary dysmenorrhea, indeed has endometriosis? If not properly managed, this patient may experience lifelong pain, development of pain-related psychological changes, infertility, and ongoing physical and emotional distress. Hence, this article can serve as a call to action to policy makers to raise awareness of menstrual health as an integral component of overall public health as well as to incorporate reproductive health education into school curricula.

The professionals like medical doctors, nurses, and pharmacists united in their professional societies should recognize and promote menstrual periods as a vital sign of reproductive health. They should educate patients to recognize and promptly report early-onset dysmenorrhea unresponsive to initial treatment and identify and rule out possible underlying causes of dysmenorrhea which may be first sign of endometriosis. Gynecologists should reassess cases of dysmenorrhea unresponsive to treatment to determine whether the issue results from non-adherence to the prescribed regimen or treatment resistance due to an underlying pathology.

Finally, the patients and caregivers should increase their awareness that a familial pattern of painful menstruation should not be considered normal and the girls should develop self-management skills and promptly report any menstrual irregularities or abnormal levels of pain to a gynecologist.

CRediT authorship contribution statement

Daniela Ivanova Panova: Writing – original draft, Data curation, Conceptualization. **Aleksandra Atanasova Boshku:** Writing – review & editing, Conceptualization. **Zoran B. Stankovic:** Writing – review & editing, Conceptualization.

Practice points

- Most adolescent dysmenorrhea cases are primary, without an organic cause.
- Based only on history, treatment with non-steroidal anti-inflammatories should be initiated with regard on correct dosage and proper timing for 3-6 months.
- If non-responsive the patient should be advised cyclical hormonal treatment for 3-6 months.
- Persistent dysmenorrhea suggests a diagnosis other than primary dysmenorrhea and should be investigated.

Research agenda

- We should rely only on history until an easy and affordable laboratory testing for diagnosis is invented.
- Professionals who work with adolescents should bear in mind that diagnostic delay could bring low quality of life for the young person.
- Furthermore, as research into the neuropsychological aspects of dysmenorrhea progresses, it remains essential to continue basic societal education for girls and to enhance healthcare professionals' awareness of this issue.

Declaration of competing interest

The authors report no conflicts of interest.

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