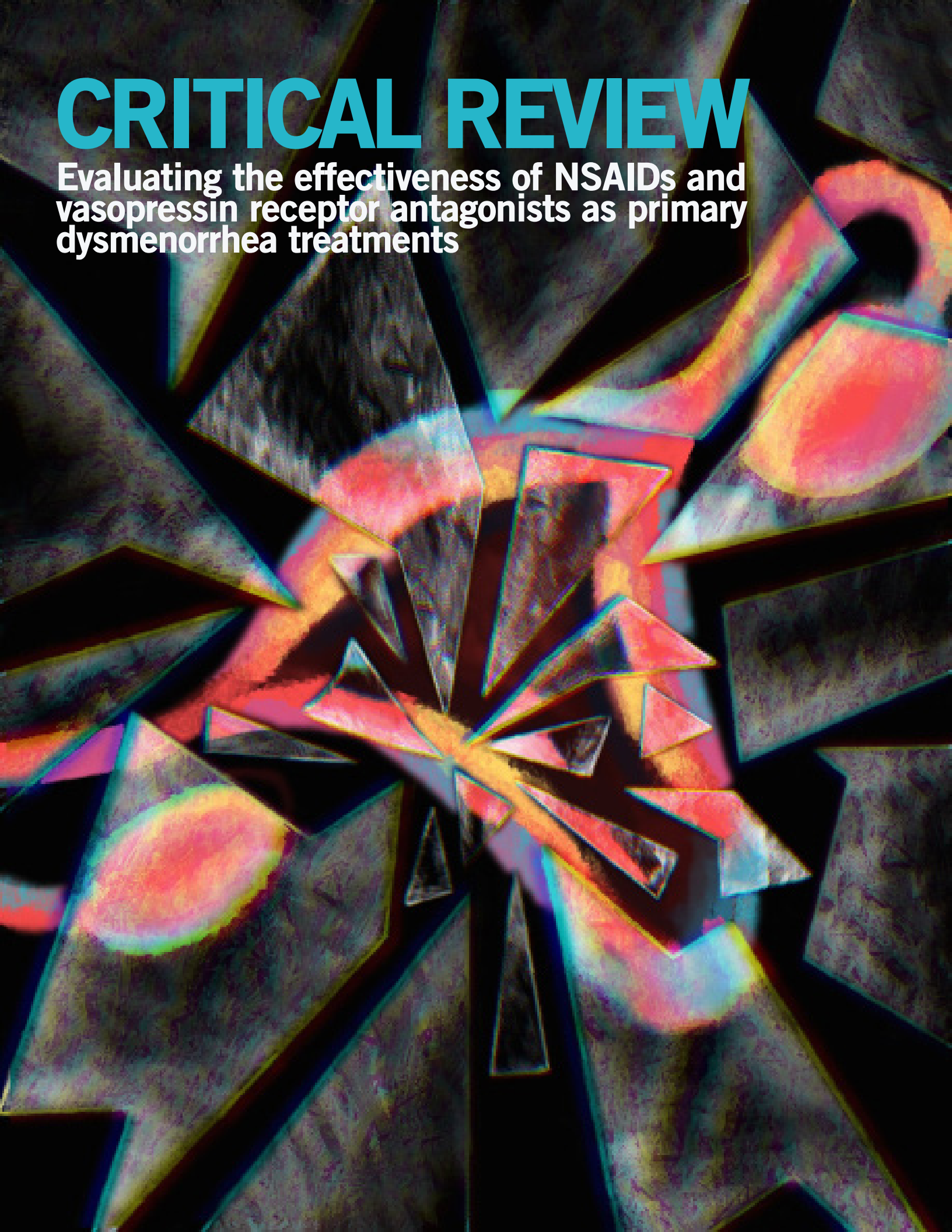
CRITICAL REVIEW

Evaluating the effectiveness of NSAIDs and vasopressin receptor antagonists as primary dysmenorrhea treatments



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ABSTRACT

Primary dysmenorrhea describes the intensely painful uterine contractions experienced during menstruation. It is associated with elevated prostaglandin production in the uterine area and primarily affects adolescents. There are several treatment options available for primary dysmenorrhea, however, there is a lapse in research assessing their efficacy and reliability. The purpose of this review is to provide an overview and evaluation of two forms of treatment for primary dysmenorrhea: non-steroidal anti-inflammatory drugs (NSAIDs) and vasopressin receptor antagonists. While studies conducted on the effectiveness of NSAIDs have shown consistent results, research conducted on vasopressin receptor antagonists remains contradictory. As such, the clinical efficacy of vasopressin receptor antagonists remains inconclusive, exposing several limitations and areas that require additional research. Furthermore, this review discusses the efficacy of promising novel treatments (i.e. levonorgestrel-releasing intrauterine devices, intravaginal rings, transdermal patches) and highlights the importance of additional studies for validation.

CONTEXT

Primary dysmenorrhea, one of the most common gynecological conditions in the world, adversely affects the quality of life of more than half of menstruating individuals.[1,2] It is characterized by severe menstrual pain associated lower abdominal cramps and is often accompanied by nausea, vomiting, sweating, headaches, diarrhea, and tremulousness. It specifically refers to pain that is not caused or aggravated by an underlying pathological or physical condition, and typically persists for 2-3 days after the onset of menstrual flow. This time period is consistent with that of maximal prostaglandin (PG) release into the menstrual fluid via cyclooxygenases (COX), a process that induces uterine contractions. Alongside PGs, the hormone vasopressin is a notable uterine stimulant that induces menstrual pain.[3] For this reason, COX inhibitors (commonly known as NSAIDs) and vasopressin receptor antagonists have been used to reduce dysmenorrhea symptoms.

Primary dysmenorrhea is relatively common in adolescents, with prevalence estimates ranging from 67-90% in those aged 17-24. It is also typically more severe within this relative age group, with 41% of dysmenorrheic individuals aged 26 or under experiencing intense, daily activity-limiting pain.[4] Alongside age, other risk factors for primary dysmenorrhea include beginning menstruation before the age of 11, experiencing heavy blood flow during cycles, having irregular periods, and never having given birth. In addition, menstruating individuals who are obese or underweight, have low vegetable intake, experience high stress, or have a history of smoking are at greater risk of primary dysmenorrhea.[4,5]

PATHOPHYSIOLOGY

Advances made in the past decades propose that primary dysmenorrhea is characterized by an abnormal increase in vasoactive PGs. The increase in endometrial secretion prostaglandin F2 (PGF2) during menstruation induces abnormal uterine contractions, which subsequently cause uterine hypoxia. Thus, menstrual cramps and associated symptoms of primary dysmenorrhea are directly proportional to the amount of PGF2 released.[6]

At the start of the menstrual cycle, a decrease in progesterone and estradiol concentrations in the blood upregulates transcription of endometrial collagenases, matrix metalloproteinases (MMPs), and pro-inflammatory cytokines. MMPs target endometrial tissue and subsequently break it down, allowing previously membrane-bound phospholipids to be released and converted to arachidonic acid (AA) by uterine phospholipases. AA is converted into PGs, which then undergo transformations to yield PGF2 and PGF2α. These metabolites are thought to directly stimulate uterine nociceptors to induce pain, as well as indirectly cause cramps by stimulating uterine contraction.[7,8]

EVALUATING THE EFFECTIVENESS OF NSAIDS

Given that PGs are relevant mediators in the intense, painful uterine contractions prevalent in primary dysmenorrhea, PG production is a common therapeutic target.[8] NSAIDs aim to alleviate painful contractions by reducing PG production through the inhibition of the enzymes COX-I and COX-II. Through the abundance of supportive cost-effectiveness and harm-benefit analyses, ibuprofen, a non-selective COX inhibitor, has become the most widely

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accepted treatment for primary dysmenorrhea.[4] Ibuprofen induces a significant reduction in PGF2 production when compared to placebo, which reduces self-reported pain duration and severity. It was also found that ibuprofen restores uterine hypercontractility to that of eumenorrheic menstruating individuals (those with normal menstrual cycles).[9] A study investigating the efficacy of ibuprofen, in which participants ingested the drug on the first day of their menstrual cycle, found a reduction in pain scores when comparing pre- and post-treatment pain (pre-treatment: 5.30±2.23; first cycle: 1.48±1.62; second cycle: 1.68±2.13).[8] Several other studies corroborated these results, reporting a corresponding reduction in total menstrual fluid PGF2 during treatment (placebo: 36.2±6.1 µg; ibuprofen: 14.8±3.0 µg).[10]

EVALUATING THE EFFECTIVENESS OF VASOPRESSIN ANTAGONISTS

Although the role of PGs in primary dysmenorrhea is well elucidated in the literature, the role of vasopressin is less understood. Several studies have found that elevated levels of circulating vasopressin during menstruation caused dysrhythmic uterine contractions, inducing uterine hypoxia through reduced blood flow. However, few studies have employed vasopressin antagonists as a potential therapy for primary dysmenorrhea, and many findings are either inconclusive or contradictory.[11] For example, studies by Liedman et al. and Brouard et al. have shown that the vasopressin/oxytocin receptor antagonists, atosiban and SR49059, may reduce uterine contractions in dysmenorrheic individuals.[11,12] In contrast, a study by Valentin et al. showed that intravenous administration of atosiban during the menstrual cycle did not reduce pain or uterine contractions.[13] Additionally, Valentin et al. demonstrated that dysmenorrheic individuals had levels of vasopressin comparable to non-dysmenorrheic individuals.[11,13] Due to conflicting evidence, vasopressin antagonist therapies are not widely used among the public.

PRACTICAL LIMITATIONS

Several practical limitations hinder the advancement of therapeutics for primary dysmenorrhea, one of which is the gap in the current literature surrounding the condition's pathogenesis. The present body of knowledge concerning the relevance of vasopressin in the pathogenesis of primary dysmenorrhea remains controversial, with several studies yielding conflicting and outdated findings. As such, the commercial use of vasopressin antagonists as a method of treatment may prove to be ineffective. Thus, researchers should continue to explore the pathogenesis of primary dysmenorrhea to uncover novel therapeutic targets and points of intersection for the development of novel treatments.

One practical limitation in using NSAIDs is the associated health risks. Although NSAIDs can be taken alongside a variety of prescription drugs, they are contraindicated with birth control medications and anticoagulants.[14] Several adverse effects can be seen with the concurrent use of these medications, including an increased risk of bleeding and an increase in blood potassium levels, both of which put the patient at risk for cardiovascular complications.[15]

Finally, studies currently lack a well-established set of standards to measure pain and discomfort. The amendment of this issue would ensure consistently referenced metrics in literature and increased reliability, therefore opening up the opportunity for better comparisons between treatment methods in terms of pain relief.[16] Furthermore, numerous studies overlook the importance of appropriate dosage size and frequency when measuring the efficacy of treatments. Studies have found that up to 25% of adolescents used less than the recommended dosage of NSAIDs and that almost half did not reach the maximum daily frequency, reducing the effectiveness of NSAIDs in treating inflammatory conditions.[17]

FUTURE DIRECTIONS

Most existing and emerging therapies for primary dysmenorrhea, especially those concerning vasopressin antagonists, require further trials before drawing conclusions on their clinical effectiveness. Aside from vasopressin receptor antagonists and NSAIDs, another emerging treatment is levonorgestrel-releasing intrauterine devices (IUDs), which were introduced in Europe as a possible treatment for dysmenorrhea.[4] Although available, utilization rates remain quite low in North America due to the Dalkon Shield intrauterine controversy during the 1970s, which continues to negatively influence the opinions of both health care providers and users.[18] The IUDs decrease pelvic pain by releasing 20 µg of progesterone into the uterine cavity daily, which reduces the synthesis of endometrial PGs.[19] Subsequently, this decreases menstrual blood flow and can be used as an effective contraceptive. This preferential method of pain relief for those wishing to take a contraceptive eliminates the risks associated with usage of NSAIDs and is a more suitable long-term option.[20] However, for menstruating individuals not seeking to use a contraceptive, NSAIDs are currently the most effective method of reducing primary

Researchers may also choose to shift towards equally prevalent alternatives to NSAIDs and vasopressin. Recent studies have demonstrated that treatments, such as vaginal rings and transdermal patches, may have similar efficacies to oral contraceptives in the treatment of primary dysmenorrhea.[21] Through differing mechanisms, both devices release estrogen and progestin in order to prevent the egg from fully developing each month, thereby preventing the onset of menstruation and the associated dysmenorrhea. Transdermal patches release progestin and estrogen daily into the systemic circulation for one week, after which it can be removed, and a new patch can be added. After the use of three patches, no patch is added for the fourth week to allow for withdrawal bleeding. Vaginal rings are flexible, transparent rings that also release estrogen and progestin into the vaginal epithelium. Patient adherence may be better with these devices because they are applied weekly or monthly, rather than daily like oral contraceptives.[22]

Overall, primary dysmenorrhea presents a pressing problem to menstruating individuals, and a strong, consistent treatment should be made widely accessible. Although significant progress has been made in the treatment of primary dysmenorrhea, there are still significant barriers and limitations to overcome before the widespread implementation of emerging treatments. Current research suggests that the reduction of PGs and vasopressin in dysmenorrheic individuals should reduce pain. However, further research needs to be conducted in order to determine how to improve COX inhibition through NSAIDs. Specifically, future developments need to avoid the risks associated with consuming a combination of NSAIDs, birth control, and anticoagulants, and further reduce uterine contractions through vasopressin receptor antagonists. Through an improved understanding of the pathogenesis of primary dysmenorrhea, new developments in clinical therapeutics can be made to alleviate symptoms and improve patient quality of life.

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