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NSAID resistance in dysmenorrhea: epidemiology, causes, and treatment

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Abstract

Although non-steroidal anti-inflammatory drugs can alleviate menstrual pain, about 18% of women with dysmenorrhea are unresponsive, leaving them and their physicians to pursue less well-studied strategies. The goal of this review is to provide a background for treating menstrual pain when first-line options fail. Research on menstrual pain and failure of similar drugs in the antiplatelet category has suggested potential mechanisms underlying non-steroidal anti-inflammatory drug resistance. Based on these mechanisms, alternative options may be helpful for refractory cases. This review also identifies key pathways in need of further study to optimize menstrual pain treatment.

Keywords

Adenomyosis; Endometriosis; Menstrual Pain; Non-steroidal Anti-inflammatory Drugs; Oral Contraception; Primary Dysmenorrhea; Secondary Dysmenorrhea

Introduction

The scope of the clinical problem of menstrual pain was effectively communicated by former First Lady Michelle Obama, when she tweeted, “Why are girls still missing so many days of school because of their menstrual cycles?”[1] Too many women hide this personal stigma, and experience a physical and psychological burden of frequent, severely painful

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cramps occurring over several days every month, persisting for decades. The transcultural impact of this problem was highlighted when Chinese Olympic medalist Fu Yuanhui acknowledged that menstrual pain affected her Olympic swimming performance.[2] The etiology of menstrual pain remains inadequately characterized,[3] and this limited scientific understanding hinders adequate treatment for women who are unresponsive to first-line options including non-steroidal anti-inflammatory drug (NSAID) therapy. To optimize the management of menstrual pain, further studies of its pathophysiology are needed. This review summarizes current scientific knowledge and associated critical gaps in menstrual pain unresponsive to NSAIDs (Figure 1).

Epidemiology of NSAID-resistant dysmenorrhea

Menstrual pain, also known as dysmenorrhea, is common and affects nearly half of reproductive age women.[4–6] Before the advent of NSAID therapy, it was observed that 10% of high school girls in Los Angeles missed classes because of dysmenorrhea.[7] The development of NSAIDs in 1969 heralded a new era of pain management, and over-the-counter availability of this medication class in 1983 held the promise of resolving dysmenorrhea for many women. Indeed, for most women, NSAIDs are effective for treating dysmenorrhea as demonstrated by a meta-analysis of 35 randomized controlled trials.[8] However, dysmenorrhea still causes 10–20% of U.S. female high school students to miss class during their menses.[9,10] This phenomenon is also seen internationally,[11] with menstrual pain-induced absenteeism occurring at similar or greater rates.[12–14] Further, a review of 51 different clinical trials found that 18% of women report minimal or no relief of menstrual pain with NSAIDs.[15] This failure to relieve pain suggests multiple pathological mechanisms may contribute to treatment unresponsiveness. Clarifying these mechanisms is an obvious critical need in gynecological research.

What causes menstrual pain?

Preclinical research studies suggest prostaglandin-dependent mechanisms drive dysmenorrhea in a majority of women (reviewed by Maia et al. 2005).[16] The start of menstruation is marked by the simultaneous decrease in circulating progesterone and estradiol, initiating increased transcription of endometrial collagenases, matrix metalloproteinases (MMPs), and inflammatory cytokines (Figure 2). Upregulated MMPs specifically target and break down endometrial tissue, freeing phospholipids from the cellular membrane. Uterine phospholipases convert available phospholipids to arachidonic acid, which is then synthesized into prostaglandins (PG), prostacyclins, and thromboxane-2a via cyclooxygenase (COX)-1 and -2. Notably, COX-2 expression is highest during menses.[16] Although it is unclear whether increased COX-2 expression occurs in dysmenorrhea, the end products PGE_2 and $PGF_{2\alpha}$ are elevated in the menstrual effluent in dysmenorrheic women when compared to healthy controls.[17,18]

The identification of elevated PGE_2 and $PGF_{2\alpha}$ in dysmenorrhea has supported the strategy of inhibiting COX-2 with NSAIDs to treat menstrual pain. Non-specific NSAIDs (e.g. those listed in Table 1) bind to both COX-1 and COX-2 to inhibit prostaglandin synthesis. More selective NSAIDs known as COX-2 inhibitors alleviate menstrual pain by specifically

inhibiting COX-2 activity. Unlike COX-1, which is constitutively expressed, COX-2 is upregulated by stimuli associated with inflammation[19] and during progesterone withdrawal, [20,21] thus making COX-2 inhibitors an appropriate alternative to non-specific NSAIDs.

Although it is possible that prostaglandins could excite nociceptors and cause pain, it is believed that prostaglandins indirectly cause cramping pain by stimulating uterine contractility.[22] Preclinically, we have recently confirmed that $PGF_{2\alpha}$ administration increases uterine contractility and elicits visceral pain.[23] Conversely, drugs that inhibit prostaglandin synthesis, such as ibuprofen[24] and naproxen, [25] reduce uterine contractility in dysmenorrheic women. These findings suggest that prostaglandins increase uterine contractility and produce cramping pain via temporary elevations in uterine pressure.[22] Since not all women with dysmenorrhea have alterations in uterine pressure,[26] other mechanisms might contribute to menstrual pain. For example, impaired uterine perfusion has been observed in dysmenorrhea[27]; ischemia may also cause cramping pain. In our mouse model of dysmenorrhea, impaired uterine perfusion and hypoxemia also occurred.[23] Although these studies collectively suggest physiological mechanisms underlying dysmenorrhea, they fail to clarify why some women do not respond to NSAIDs.

Anatomical factors

A subset of women with dysmenorrhea, particularly those with delayed presentation after menarche, may harbor separate contributing anatomical factors such as endometriosis, leiomyoma, or adenomyosis; these cases are examples of ‘secondary dysmenorrhea’ that could underlie NSAID resistance. Undoubtedly, surgical interventions for these structural issues address dysmenorrhea. For example, in a meta-analysis, laparoscopic excision of endometriosis was shown to reduce menstrual pain.[28] The molecular contributions of anatomical factors to secondary dysmenorrhea are limited. Immunohistological studies investigating endometriosis demonstrated that lesions have increased COX-2 expression[29], which led to corresponding increased prostaglandins[30] and aromatase activity.[31] Ectopic endometrium from adenomyosis patients expressed increased levels of transient receptor potential vanilloid 1 (TRPV1 – a pain signaling protein) and oxytocin receptor.[32] Gene expression of myometrial regulators myostatin and MMP14 from leiomyoma biopsies were positively correlated to severe dysmenorrhea.[33] These in vitro studies provide insight into mechanisms that promote secondary dysmenorrhea, but more research is needed to unmask the complex pathophysiology associated with these anatomical factors.

The causal contribution of anatomical factors to dysmenorrhea, particularly those that exhibit NSAID unresponsiveness, is unclear. A meta-analysis has estimated as many as 29% of dysmenorrheic women may have moderate to severe endometriosis.[34] However, since many women do not undergo laparoscopic evaluation, it is difficult to identify the proportion of women with NSAID-resistant dysmenorrhea who have endometriosis. A small clinical study found that among 31 women with NSAID-resistant dysmenorrhea, 35% had endometriosis.[35] In a larger study (n=654), 25% of participants with NSAID-resistant dysmenorrhea had ultrasound or magnetic resonance imaging suggestive of endometriosis.[36] Conversely, it is important to note that dysmenorrhea symptoms are nonspecific for endometriosis,[37] and NSAIDs can be effective in relieving some cases of menstrual pain in

women with endometriosis.[38,39] In one observational study of leiomyomas, 70% of women with fibroids used NSAIDs and 51% reported a reduction in symptoms.[40] It is uncertain whether NSAIDs are useful for adenomyosis.[41] Since it is unknown whether anatomical factors contribute to NSAID unresponsiveness, further research is needed to determine whether treatment strategies targeting anatomical factors are sufficient for addressing the causes of NSAID-resistant dysmenorrhea.

Molecular mechanisms

Therapeutic alternatives for NSAID-resistant dysmenorrhea will be developed quicker once mechanistic characterization progresses. NSAIDs collectively elicit non-specific inhibition of COX isoforms (Table 1). COX-1 and COX-2 are homologous, share 63% identical amino acid sequences and have a similar catalytic binding site.[19] Although NSAIDs bind non-selectively to both COX isoforms, they vary in isoform-specific inhibition. As seen in Table 1, NSAIDs such as aspirin and ibuprofen are more selective for COX-1, while diclofenac preferentially targets COX-2.[42] Genetic polymorphisms have been shown to disrupt COX-1 inhibition with aspirin. For example, Ulehlova et al demonstrated that COX-1 polymorphism *rs10306114* was correlated with high platelet aggregation in aspirin-resistant individuals.[43] Although multiple single nucleotide polymorphisms (SNPs) that contribute to aspirin resistance have been identified, they have only been replicated in some studies and remain an active area of research (reviewed by Weng and colleagues).[44] Although there are no documented COX polymorphisms directly associated with NSAID binding, there are several COX SNPs within the promoter regions that may alter NSAID efficacy.[45] Notably, *rs20417* is a SNP in the promoter region of COX-2 associated with aspirin resistance.[41] Further research is needed to determine if the identified SNP have a transcriptional effect contributing to NSAID-resistant dysmenorrhea.

Another molecular factor that contributes to treatment resistance is drug bioavailability. The drug formulation alongside an individual's metabolic profile may alter the efficacy of both antiplatelet and NSAID therapy. One study found a significant relationship between total naproxen serum levels and a reduction in rheumatoid arthritis symptoms[46]; the range of oral dosages used (250mg, 500mg, 1500mg), however, makes it difficult to determine whether variable absorption significantly contributed to inadequate pain relief. Other mechanisms affecting NSAID metabolism could also greatly impact COX inhibition. Cytochrome P450 (CYP) enzymes, specifically CYP1A2, CYP2C8, and CYP2C9, are responsible for metabolizing NSAIDs. CYP "gain of function" variants are associated with increased metabolism, resulting in decreased drug effect.[47] For example, the CYP2C9*2/*2 polymorphism was associated with increased total clearance of celecoxib and diclofenac.[48] More research is necessary to determine if other gain-of-function variants exist and alter NSAID metabolism.

Other molecular contributors to NSAID-resistant dysmenorrhea

In addition to COX and prostaglandin-mediated pathways, other molecular mechanisms could drive NSAID-resistant dysmenorrhea. Leukotrienes, a class of eicosanoids synthesized via 5-lipoxygenase, should be considered candidate mediators,[49] as their increased

expression is found in the endometrium,[50] urine,[51] and menstrual effluent[52] of women with dysmenorrhea. However, leukotriene receptor inhibition did not successfully alleviate menstrual pain.[53,54] Another potential COX-independent mechanism is the platelet activating factor (PAF) pathway. PAF mediates inflammatory states unaffected by NSAIDs and is elevated in the menstrual effluent of women with NSAID-resistant dysmenorrhea.[52] Alterations in PAF synthesis have been found in women with endometriosis.[55,56] In a mouse model, we have recently confirmed a PAF receptor agonist is capable of increasing uterine hypercontractility and impairing perfusion, causing uterine hypoxemia and pain.[23] The effects on uterine physiology were blocked with a PAF receptor antagonist in our mouse model, but PAF-targeting treatments have not yet been conducted in women with dysmenorrhea. Additional research is needed to elucidate the possible roles of leukotrienes and PAF in NSAID-resistant dysmenorrhea.

Peripheral and central sensitization within dysmenorrhea

The aforementioned molecules are readily implicated in mechanisms that would increase peripheral nerve sensitivity. Prostaglandins can sensitize primary afferents[57] via the modulation of tetrodotoxin-resistant sodium channels[58] and TRPV1 receptors.[59] Local neurogenesis is another element of peripheral sensitization, and has been demonstrated to contribute to secondary dysmenorrhea.[60–62,32] However, the role of local neurogenesis in NSAID-resistant dysmenorrhea has not yet been demonstrated.

Alternatively, wide-spread increases in pain sensitivity known as central sensitization could contribute dysmenorrhea.[63] Although it has not been demonstrated directly, evidence of central sensitization within dysmenorrhea includes increased referred pain,[64] and heightened experimentally evoked thermal, ischemic, muscular, and pressure pain sensitivity.[65–68] Dysmenorrheic women also exhibit altered grey matter volume in key cortical regulatory pain regions.[69–71] Since NSAIDs are not known to affect central sensitization,[72] further research is needed to confirm whether dysfunctional central sensitization occurs in NSAID-resistant dysmenorrhea.

Mechanisms driving peripheral or central sensitization could also lead to increased referred pain. In rat models, uterine inflammation led to neurogenic plasma extravasation the abdominal musculature and adjacent organs.[73,74] Although some women with dysmenorrhea may also have superficial abdominal muscular pain, it is not predictive of endometriosis.[75] Thus, it remains unclear whether women with abdominal muscle cramps during menses are more or less likely to respond to NSAIDs.

The importance of medical adherence

Medication adherence likely contributes to NSAID-resistant dysmenorrhea. A quarter to half of dysmenorrheic women do not take the correct medication or dosage.[10,12] Side effects associated with NSAIDs such as gastrointestinal discomfort also limit medication adherence.[8] Along with medication type, dosage, and side effects, the timing of NSAID administration may affect efficacy. Notably, biochemical analyses demonstrated that naproxen administration prior to initiating the COX-2 cascade results in nearly complete suppression

of prostaglandin synthesis; attempting to block synthesis afterwards only produced a gradual and incomplete suppression.[76] However, a single, but underpowered trial, comparing menstrual pain relief between prophylactic versus abortive treatment with ibuprofen did not find a difference.[77] It is possible that differences in prophylactic use of naproxen and ibuprofen could be due to different preferential binding to COX-1 and COX-2 (Table 1). Aside from this trial, clinical investigators have not sufficiently investigated prophylactic NSAIDs use prior to the onset of menses. Although an educational trial regarding prophylaxis did demonstrate increased patient knowledge, reduction of menstrual pain was not evaluated.[78]

Treatments for NSAID-resistant dysmenorrhea

Until it can be determined why some women with dysmenorrhea are unresponsive to NSAIDs, it is essential that clinicians be aware of adequate alternative treatments. Below, we present a list of candidate pharmacological and non-pharmacological treatments previously investigated for use in dysmenorrhea. We have noted where generic medications are available, but insurance coverage for off-label use needs to be considered in terms of patient costs.

Hormone-based Treatments

Hormonal treatments, specifically oral contractive pills (OCPs), are widely used for NSAID-resistant dysmenorrhea.[22,79,80] OCPs thin the endometrial lining, resulting in reduced COX-2 and prostaglandin production.[16,81] The bulk of research examining OCPs and dysmenorrhea focuses on the effect of different hormonal regimens and combinations. A systematic review suggested continuous regimens are generally more effective at reducing dysmenorrhea symptoms than cyclic regimens.[82] Cyclic regimens often improve dysmenorrhea, but studies have rarely found differences between different hormone combinations.[83] Nomegestrol acetate/17β-estradiol was more effective in treating menstrual pain when compared to drospirenone/ethinylestradiol oral contraceptive.[84] A comparison of 20μg ethinyl estradiol/150μg desogestrel to 20μg ethinyl estradiol/100μg levonorgestrel suggested each improved dysmenorrhea similarly (23 and 26% of women respectively).[85] Combination OCPs with estradiol valerate/dienogest and ethinyl estradiol/levonorgestrel both reduced experienced time of dysmenorrhea pain by four days, but significant differences between the regimens were not observed.[86] A systematic review concluded that levonorgestrel-releasing intrauterine devices are as effective as OCPs at alleviating menstrual pain.[87] A critical limitation of the above studies of comparing hormonal regimens and combinations in primary dysmenorrhea is that they have not specifically evaluated their utility in NSAID-resistant dysmenorrhea.

Hormonal treatments are also used for women with secondary dysmenorrhea unresponsive to NSAIDs and do not wish to undergo surgery. A randomized placebo-controlled trial demonstrated that OCPs were an effective treatment for secondary dysmenorrhea associated with endometrosis.[88] Continuous OCP regimens improve dysmenorrhea better than cyclical regimens after surgery for endometriosis[89], although there are concerns that the estradiol

component of OCPs could exacerbate endometriosis.[90] In any case, hormonal suppression is still recommended for treatment of dysmenorrhea in current consensus guidelines.[91]

Other studies on secondary dysmenorrhea treatment have focused on gonadotropin-releasing hormone (GnRH) agonists. A randomized placebo-controlled trial showed GnRH agonist leuprolide almost completely eliminated menstrual pain in 44 patients with suspected endometriosis.[92] Although effective in treating secondary dysmenorrhea, GnRH agonist-induced reduction of estrogen promotes bone density loss over time.[93,94] Pairing GnRH agonists with 'add-back' or replacement estrogen therapy[95–97] or utilizing low GnRH agonist dosages[98] are capable of alleviating menstrual pain associated with endometriosis without bone loss. The utilization of these drugs is recommended by the American Society for Reproductive Medicine guidelines only after laparoscopic diagnosis of endometriosis given these risks.[99] Alongside its side-effect profile, patients may find monthly injections of GnRH agonists inconvenient.

A recent review has suggested that oral progestins may be a better first-line option for menstrual and pelvic pain associated with endometriosis.[90] Oral progestins such as norethindrone acetate and dienogest, target the progesterone receptor, and have regulatory approval for endometriosis. A randomized placebo-controlled trial demonstrated that dienogest reduced dysmenorrhea in women with endometriosis.[100] Dienogest was also as effective in reducing menstrual pain when compared to the GnRH agonist leuprolide.[101] An open-label study found norethindrone acetate was as effective at reducing menstrual pain as OCPs.[102] Despite their efficacy, it is important to consider the frequent irregular bleeding associated with oral progestins.[103] Although a meta-analysis supports oral progestin usage for endometriosis,[104] it remains to be investigated whether it is an effective empirical option for NSAID-resistant dysmenorrhea.

Another class of hormonal treatment used for secondary dysmenorrhea is aromatase inhibitors.[105] Aromatase is an enzyme that is expressed in the ovarian follicle and endometriotic stromal cells and converts androgens to estrogen.[106] Aromatase inhibitors, primarily used to reduce endometriomas[107] and myomas[108] in women, may be beneficial for secondary dysmenorrhea by rendering patients amenorrheic. Due to concern regarding its effects on bone mineral density and other adverse side effects, add-back regimens may be necessary.[109] Further research is needed to determine if aromatase inhibitors are appropriate of NSAID-resistant dysmenorrhea.

Surgical Interventions

Although excision of endometriotic lesions are routinely recommended,[99] some symptomatic patients that do not have identified anatomical factors following diagnostic surgical evaluation may benefit from alternative surgical strategies. Laparoscopic uterine nerve ablation (LUNA) and laparoscopic presacral neurectomy (PSN) are two surgical interventions historically employed for the treatment of secondary dysmenorrhea (reviewed by Proctor, Lathe and colleagues).[110,111] However, a large multi-site randomized controlled trial conducted by Daniels and colleagues determined that LUNA for chronic pelvic pain did not have a significant effect on dysmenorrhea, regardless of time accrued following surgery,[112] and has led to this procedure largely being abandoned. However, this trial and many of

the other negative trials did not study the effects of LUNA or PSN in NSAID-resistant dysmenorrhea in women without chronic pelvic pain and endometriosis.

Clinical trials have examined the efficacy of surgical interventions on primary dysmenorrhea. A double-blinded randomized controlled trial of LUNA demonstrated menstrual pain relief in half of women with primary dysmenorrhea.[113] A trial comparing LUNA and LUNA plus PSN reported 69% and 73% of primary dysmenorrhea patients respectively had improvements in menstrual pain.[114] Chen et al found that 77% of primary dysmenorrhea patients benefited from PSN.[115] Although it is unknown whether these patients with primary dysmenorrhea were NSAID-resistant, it is quite possible that surgery was performed since NSAID management was not feasible. Thus, further research is needed to clarify the utility of LUNA and PSN as treatments for NSAID-resistant dysmenorrhea, particularly in the absence of endometriosis and chronic pelvic pain.

Vasodilators

Another potential treatment for dysmenorrhea is sildenafil citrate. Sildenafil specifically blocks cyclic guanosine monophosphate degradation, thus promoting smooth muscle relaxation in the uterus and surrounding blood vessels.[116] In a randomized placebo-controlled trial, sildenafil reduced menstrual pain in women with primary dysmenorrhea.[117] Similar to sildenafil, nitric oxide (NO) donor drugs also promote vasodilation and myometrial muscle relaxation, and are capable of reducing menstrual pain. Transdermal nitroglycerin or glyceryl trinitrate administration on the first day of menstruation was sufficient to reduce reported menstrual pain for the duration of menses.[118,119] Glyceryl trinitrate and nitroglycerin are available as generic medications. A limiting factor of glyceryl trinitrate and similar vasodilators are their side effects that impair tolerability including headaches.[120] Therefore, the utility of glyceryl trinitrate or other vasodilators for NSAID-resistant dysmenorrhea remains to be determined.

Calcium Channel Blockers

Calcium channel blockers, available as generic medications, are primarily indicated to treat hypertension by reducing contractility in vascular smooth muscle and cardiac muscles; they also inhibit uterine contractions in pregnant and non-pregnant women.[121] Observational studies from the late seventies demonstrated that 20–40mg of calcium channel blocker nifedipine provided menstrual pain relief but was associated with side effects such as tachycardia, flushing, and headache.[122,123] These findings are supported in a controlled trial showing that 14 out of 19 patients obtained menstrual pain relief with nifedipine.[124] Although one research study suggested efficacy of nifedipine in women that unresponsive to salicylates,[125] future research is needed to establish efficacy for women unresponsive to NSAIDs.

Vasopressin and Oxytocin Receptor Antagonists

Vasopressin and oxytocin, hormones known to stimulate myometrial contractions, have also been implicated in primary dysmenorrhea.[126] There is conflicting evidence, however, on the effects of vasopressin/oxytocin receptor antagonists on dysmenorrhea. Several studies have shown that vasopressin-induced contractions in dysmenorrheic women were reduced by

vasopressin/oxytocin receptor antagonists atosiban[127,128] and SR49059.[129] In contrast, Valentin and colleagues demonstrated that when compared to healthy controls, dysmenorrheic women did not show elevated levels of vasopressin and that the intravenous administration of atosiban did not attenuate menstrual pain or uterine contractility.[130] It is important to note that the Valentin study administered atosiban intravenously after menses onset, while the Brouard study administered SR49059 orally at least 4 hours prior to menses onset. Thus, more evidence is needed to examine how the time and type of administration impacts the efficacy of vasopressin/oxytocin receptor antagonists on NSAID-resistant dysmenorrhea.

Anti-spasmodics

Although infrequently used in the United States, anti-spasmodics such as hyoscine butylbromide are used globally to treat abdominal pain, including menstrual pain. Hyoscine butylbromide is an anticholinergic drug that targets muscarinic receptors to relax smooth muscle.[131] In the United States, a similar drug, hyoscyamine sulfate is available as a generic medication. Common adverse effects include dry mouth, constipation and dizziness. Although it is frequently prescribed for visceral spasms, it is not FDA indicated for dysmenorrhea.

In a double-blind crossover study, Kemp and colleagues demonstrated that hyoscine butylbromide was just as effective as aspirin in treating dysmenorrhea.[132] Questionnaire-based studies have shown that women used hyoscine butylbromide to self-treat their dysmenorrhea with a similar frequency as paracetamol and NSAIDs.[133–136] A randomized controlled trial compared a combination of an anti-spasmodic (drotaverine) and an NSAID (aceclofenac) versus aceclofenac alone, and found the combination provided superior pain relief for primary dysmenorrhea.[137] Since the addition of drotaverine provided better pain relief than aceclofenac alone, these results support the use of an adjunct anti-spasmodic to treat refractory menstrual pain. These findings also suggest that muscle spasm pain in dysmenorrhea may contribute to NSAID-resistant pain.

Complementary and Non-Pharmacological Medical Treatments

Herbal and dietary supplements have been proposed as alternative treatments for dysmenorrhea. Although many varieties are currently used to treat dysmenorrhea, inconsistencies between various studies make it difficult to determine the efficacy of supplements (reviewed by Pattinitum and colleagues).[138] Ginger, the most commonly reported effective remedy in randomized controlled trials, only reduced pain 1.5 cm on a 10 cm visual analog scale.[139] Thus more high-quality trials demonstrating superior effectiveness of herbal and dietary supplements are needed to provide viable options for patients unresponsive to NSAIDs.

Many non-pharmacological remedies for dysmenorrhea have been investigated. Limited evidence suggests acupuncture,[140] hot water bottles,[141] yoga,[142] massage,[143] physiotherapy,[144] and exercise[145] may be helpful for menstrual pain, but as with many traditional pharmaceuticals, effects have not been consistently repeated or verified with large randomized controlled trials. In contrast, transcutaneous electrical nerve stimulation (TENS)

has been shown to reduce menstrual pain in several randomized[146–148] and observational[149,150] trials. Since trans-abdominal application of TENS has no effect on uterine contractility,[25] TENS may affect associated abdominal muscle contractility instead. The role of abdominal muscle cramping in dysmenorrhea would be consistent with the utility of antispasmodic agents described above. The findings obtained with TENS are consistent with the hypothesis that prostaglandin-independent pathways contribute to dysmenorrhea, and suggest that the attenuation of these alternative pathways may be effective.

Future Directions

As mentioned above, most studies investigating various treatments for dysmenorrhea have not examined the prevalence of NSAID resistance amongst their participants. Since dysmenorrhea patients may choose treatments based on preference rather than previous NSAID treatment failure, the overall efficacy of treatments for NSAID-resistant dysmenorrhea is unknown. Validated electronic tools which track menstrual pain and the use of rescue medication[151] would be useful for clinical trials. It is likely that multiple phenotypes of dysmenorrhea exist reflecting different underlying causes. However, since the abandonment of classifying spasmodic and congestive menstrual pain phenotypes,[152] a replacement classification scheme has not been popularly accepted, and should possibly be reconsidered for the diagnosis for NSAID-resistant dysmenorrhea.

Pharmacological and gene assays could help identify forms of NSAID-resistant dysmenorrhea that may respond to alternative treatment strategies. A similar research strategy has revolutionized the understanding of aspirin resistance observed in antiplatelet therapy. The utilization of ex-vivo assays that detect mechanisms of aspirin resistance has led to the identification of polymorphisms,[43,44] absorption impairments,[153] or other factors that limit drug bioavailability.[154, 46] The translation of these tests for NSAID-resistant pain could similarly clarify why some patients are unresponsive and provide avenues for adequate therapeutic development.

Conclusion

A significant proportion of women who suffer from dysmenorrhea obtain no relief from NSAIDs. Opportunities to characterize NSAID resistance with diagnostic testing and enroll women with resistance phenotypes into novel clinical trials have not been pursued. We suggest that future studies explore molecular targets that could explain resistance and evaluate novel therapies in these patients. Given that cyclooxygenases are implicated in other acute (e.g., muscle soreness, inflammation, burn pain) and chronic pain conditions (e.g., migraine, arthritis) studying the mechanisms of NSAID resistance has the broad potential to improve pain relief in patients with multiple types of refractory pain conditions.

Prior treatment algorithms suggest that symptomatic patients with NSAID-resistant dysmenorrhea that do not respond to OCPs undergo diagnostic laparoscopic examination [22,79]. Recent consensus guidelines suggest trials of levonorgestrel-releasing intrauterine devices, with surgery being the last diagnostic and therapeutic option.[91] Although surgery

for symptomatic patients is often effective and recommended[155–157], some patients may be not willing to undergo surgery. For these patients, until research establishes the underlying mechanisms, some of the options described here could partially ameliorate their unremitting monthly pain.

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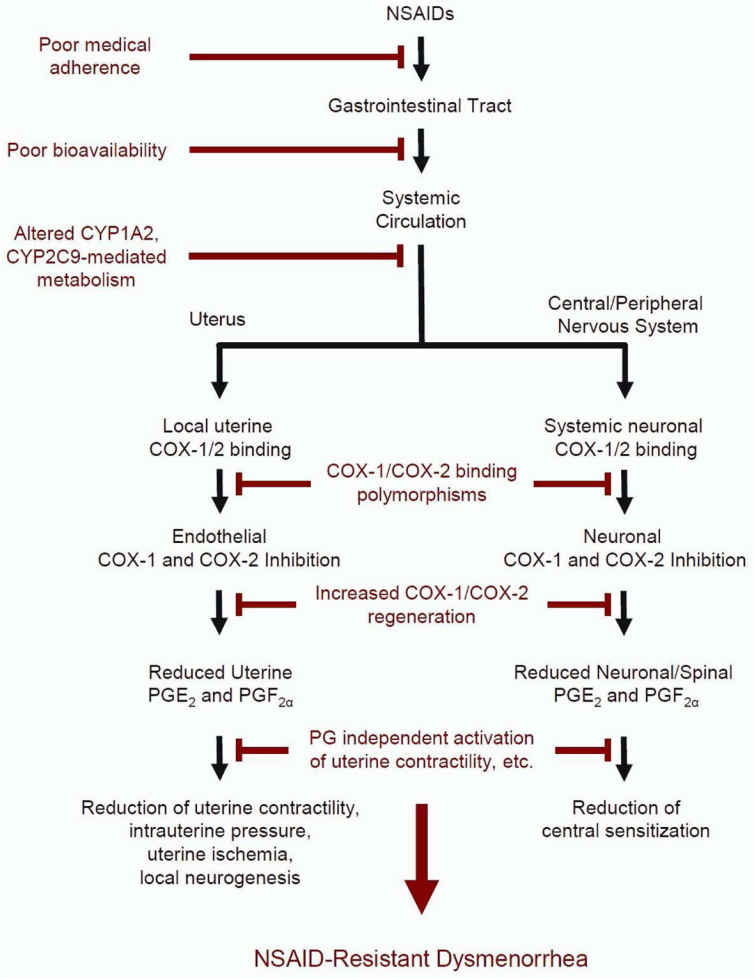

Figure 1.

A proposed pathway examining NSAID-resistant dysmenorrhea. Many complex mechanisms contribute to the development of NSAID-resistant dysmenorrhea. NSAIDs normally reduce menstrual pain via the suppression of peripheral and systemic prostaglandins and corresponding downstream effects (shown in black). Elements on the left branch highlight uterine mechanisms while the right branch highlights central and peripheral neural mechanisms. Various physiological factors, ranging from poor medical adherence to the involvement prostaglandin-independent cascades, may disrupt NSAIDs' efficacy to ameliorate menstrual pain and promote NSAID resistance (shown in red).

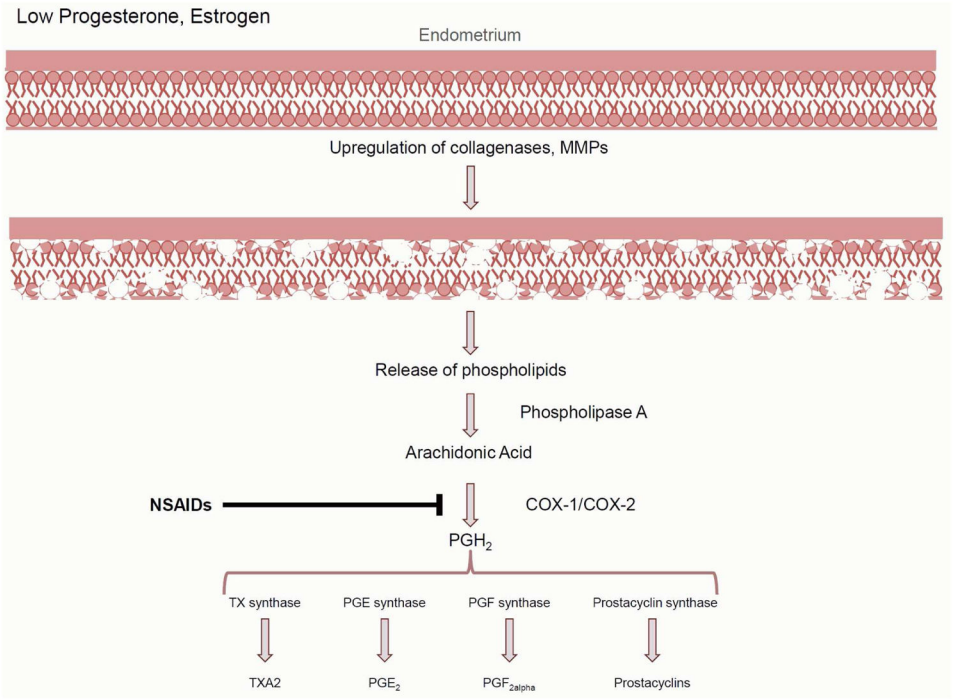

Figure 2.

The production of prostaglandins via the onset of menstruation. Decreased progesterone and estrogen levels at the end of the luteal phase initiate a cascade that results in the breakdown of the endometrial tissues, the release of cellular phospholipids, and the subsequent production of prostaglandins. COX: cyclooxygenase, MMP: matrix metalloproteinases, NSAIDs: non-steroidal anti-inflammatory drugs, PG: prostaglandin, TX: thromboxane.

Table 1

Commonly used NSAIDs and concentrations that inhibit COX activity in blood.

NSAID	COX-1 IC_{50} (μM)	COX-2 IC_{50} (μM)	COX-1: COX-2 IC_{50} Ratio*
Diclofenac	0.26	0.01	0.05
Aspirin	4.45	13.88	3.12
Ketorolac	0.27	0.18	0.68
Naproxen	32.01	28.19	0.88
Ibuprofen	5.90	9.90	1.69

Ratios greater than 1 indicate drug is more selective for COX-1. Ratios lesser than 1 indicate drug is more selective for COX-2.