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Guidelines in focus

Primary dysmenorrhea: treatment

Dismenorreia primária: tratamento

Federação Brasileira das Associações de Ginecologia e Obstetrícia
(Brazilian Federation of Gynecology and Obstetrics Associations)*

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Description of the evidence collection method
A literature review of relevant scientific articles was performed in the MEDLINE database. The search was conducted in actual clinical scenarios and included the key words (MeSH terms): Anti-Inflammatory Agents, Non-Steroidal AND Dysmenorrhea.

Degree of recommendation and strength of evidence
A: Experimental or observational studies of higher consistency
B: Experimental or observational studies of lesser consistency
C: Case reports (non-controlled studies)
D: Opinions without critical evaluation, based on consensuses, physiological studies, or animal models

Objective
To evaluate the benefits and the risks of primary dysmenorrhea treatment with anti-inflammatory drugs.

Introduction

Dysmenorrhea is one of the most prevalent gynecological problems among adolescents and young adults, whose condition is usually primary and not caused by any pelvic pathology[1] (**B**). It affects approximately 50% of women of reproductive age, and in 10% of them the symptoms are sufficiently intense to interfere with daily life[2] (**B**). It is believed that the underlying cause of primary dysmenorrhea is the over-production of uterine prostaglandins, derived from cyclooxygenase-2 (COX-2) activity[3] (**B**)[4] (**D**).

Primary dysmenorrhea is clinically characterized as colic pain in the lower abdomen in the beginning of the menstrual period that may continue for a few days, in the absence of any pelvic pathology. The etiology of primary dysmenorrhea is yet to be well understood, although many of the symptoms may be explained by prostaglandin action, particularly PGF2α, present in menstrual fluid, which causes abnormal uterine activity, reducing blood flow to the uterus and sensitizing nociceptors[3] (**B**). This explanation originates from the observation that women with primary dysmenorrhea have higher levels of prostaglandin in the endometrium and

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menstrual blood, with significant symptom improvement as prostaglandin levels decrease[2] (**B**). Thus, prostaglandin production inhibition in the endometrium, with the use of nonsteroidal anti-inflammatory drugs (NSAIDs), is a rational and effective treatment of primary dysmenorrhea[5,6] (**A**).

The synthesis of prostaglandins in humans is performed by two types of cyclooxygenases (COX), COX-1 and COX-2, which have different functions[7] (**B**). COX-1 is constitutively expressed in many tissues, such as platelets, and is related to the maintenance of the gastrointestinal mucosal integrity. COX-2, found with limited expression in basal conditions, undergoes up-regulation by several inflammatory mediators, and it is related to colorectal carcinogenesis[8,9] (**D**). The activity of non-steroidal anti-inflammatory drugs is related to COX-2 inhibition, and also determines COX-1 inhibition, therefore causing alterations in platelet function and predisposing patients to adverse gastrointestinal events. Thus, selective COX-2 inhibitors standout as drugs with an anti-inflammatory action that are effective against pain, and related to less adverse events[7] (**B**).

An important aspect to be considered regarding the use of anti-inflammatory drugs is related to their safety, especially for long-term use, as, for instance, in their prescription as part of a strategy to control inflammation and pain associated with osteoarthritis or rheumatoid arthritis, due to severe cardiovascular events involved, such as acute myocardial infarction, unstable angina, and venous thromboembolic events[10] (**D**). The mechanisms by which these events occur are not fully understood, but a few possibilities have been suggested, such as fluid retention caused by the inhibition of renal prostanoid synthesis (PGI2 and PGE2); reduction in PGI2 production by the vascular endothelium, which determines an increase in cardiovascular risk; and promotion of atherogenesis or atherosclerotic plaque destabilization[11,12] (**D**).

A multicenter randomized study using a selective COX-2 inhibitor (rofecoxib 25 mg/day) as the drug indicated for the chemoprevention of adenomatous colonic polyps was interrupted during follow-up, due to the increase in cardiovascular events associated with its use (2.6% *vs.* 4.6% for the control group and after treatment with rofecoxib, respectively, presenting hazard ratio (HR) = 1.79, 95% CI: 1.17 to 2.73)[13] (**A**).

Another multicenter study, designed to evaluate the cardiovascular safety and gastrointestinal tolerability of etoricoxib at oral doses of 60 or 90 mg/day and diclofenac at a dose of 150 mg/day in osteoarthritis patients for a mean period of 20 months, observed that the occurrence of cardiovascular events was similar both with the use of selective COX-2 and with the use of diclofenac (HR = 0.96 with 95% CI: 0.81 to 1.15)[14] (**A**).

However, this study demonstrated that, when compared to diclofenac, etoricoxib determined an increase in mean systolic blood pressure (when used at a dose of 60 mg/day, it was associated with a mean increase in systolic blood pressure of 3.2 mmHg, 2.5 mmHg, and 1.2 mmHg for 1 month, 12 months, and 36 months, respectively), establishing an association between treatment dropout and hypertension[14-16] (**A**).

Similar results were also reported in another randomized multicenter trial that evaluated the use of rofecoxib at a dose of 25 mg/day in patients with type II diabetes mellitus and hypertension during treatment for osteoarthritis. It was observed that, when compared to the use of rofecoxib, ambulatory blood pressure levels measured during 24 h were high (mean increase in systolic blood pressure of around 4.2 ± 1.2 mmHg after six weeks of treatment). When compared to the use of naproxen 1.0 g/day, a pressure difference of around 3.85 mmHg was observed (95% CI: 1.15 to 6.55; p = 0.005)[17] (**A**).

Subsequently, this guideline proposes some considerations regarding the use of non-steroidal anti-inflammatory drugs, both selective and non-selective, for COX-2, indicated for the treatment of primary dysmenorrhea, comparing drugs and evaluating mainly the analgesic and adverse effects, especially gastrointestinal disorders. It is also very important to consider that the comparisons among drugs for the treatment of primary dysmenorrhea were performed for a short time interval (mean of two days for four consecutive menstrual cycles, not exceeding 180 days).

It was therefore not possible to verify of this assessment of the aforementioned cardiovascular complications, which lead the Brazilian Health Surveillance Agency (Agência Nacional de Vigilância Sanitária – ANVISA) to disclose, on February 21, 2005, the article "Risks and benefits of selective inhibitors of COX-2: recommendations by the Technical Chamber of Medications (Câmara Técnica de Medicamentos – CATEME)", where several general and specific recommendations were made on COX-2 selective inhibitors (coxibs) to health professionals and consumers, demanding a more stringent oversight by ANVISA[18] (**D**).

Overall recommendations for health professionals:

- The use of coxibs should be considered only for patients with significantly increased risk of gastrointestinal bleeding risk and no concurrent risk of cardiovascular disease;
- There are no studies demonstrating the safety of these drugs in patients younger than 18 years;
- Patients treated with any selective COX-2 inhibitor that have ischemic heart disease or cardiovascular disease should have their treatment replaced, as soon as possible, with a nonselective COX-2 inhibitor;
- For all patients, alternative treatment with nonselective COX-2 inhibitors should be considered in the light of an individual assessment of risks and benefits of COX-2, particularly cardiovascular and gastrointestinal risk factors, among others;
- Prescribers should be advised that for all NSAIDs, including COX-2, the lowest effective dose should be used for the shortest time necessary for treatment;
- For patients whose treatment was replaced by nonselective NSAIDs, the possible need for gastroprotective drugs should be considered;
- The use of selective inhibitors of COX-2 is contraindicated in patients treated with acetylsalicylic acid as an anti-platelet agent;

Specific recommendations:

- The indication for use of celecoxib in the prophylaxis of familial adenomatous polyposis is excluded;

- The use of valdecoxib and parecoxib are contraindicated for patients submitted to surgical myocardial revascularization procedures;
- Valdecoxib discontinuation should be considered in the presence of skin rash, mucosal lesions, or other symptoms suggestive of hypersensitivity, as Stevens-Johnson syndrome and toxic epidermal necrolysis, which are severe skin reactions, have been observed with this drug, in patients with or without history of allergy to sulfonamides;
- Regarding celecoxib, daily doses > 400 mg should not be used, and treatments that consist of the administration of daily doses > 200 mg should be reviewed.

CATEME also recommended the following actions to be taken by ANVISA:

- To require the manufacturers of drugs classified as selective COX-2 inhibitors to follow the ANVISA protocol "Change in Package Insert Text Notification", to add recommendations and warnings related to cardiovascular risks and other risks discussed in that document;
- To remove from celecoxib's package insert text the possibility of using doses > 400 mg;
- To produce an informative document aimed at the prescriber/dispenser and other health professionals recommending the rational use of these drugs. The release of this document may be made through the professional boards and class associations;
- Review the instructions for use of the approved coxibs registered in Brazil;
- Review the advertisement on coxibs released by Brazilian laboratories.

Other recommendations, more general, aimed at preventing similar situations in the future, but that do not apply only to the case of coxibs were as follows:

- To create and add a symbol to the packaging/labeling/package insert of innovative drugs indicating that it is a new drug and that the knowledge of the safety profile is limited, requiring special attention;
- To encourage voluntary reporting of adverse reactions by health professionals, particularly for new drugs;
- To promote the rational use of medications;
- To encourage studies that are independent from the pharmaceutical industry;
- To continuously update systematic reviews of adverse events based on published and unpublished data of randomized controlled trials and observational studies.

1. Is etoricoxib more effective than naproxen in the treatment of women with primary dysmenorrhea?

The use of NSAIDs (ibuprofen, naproxen) is the main therapy for primary dysmenorrhea; their efficacy results mainly from COX-2 inhibition[19,20] (**D**). In turn, etoricoxib is a selective inhibitor for this enzyme, showing more than 100-fold selectivity for COX-2 over COX-1[21] (**C**).

When evaluating women with a mean age of 30.5 years, history of primary dysmenorrhea of moderate to severe intensity in at least four of the last six menstrual cycles, without gynecological abnormalities (at physical examination), and not allergic to NSAIDs, undergoing therapy with etoricoxib at a dose of 120 mg/day, and/or naproxen 550 mg/day for three consecutive menstrual cycles, it was observed that the use of etoricoxib or naproxen did not show significant difference concerning analgesic efficacy assessed by pain relief scores for an eight-hour period (TOPAR-8h) ($p = 0.326$).

When analyzing the necessary time to achieve analgesia, it was observed that a single dose of 120 mg of etoricoxib had a similar effect to naproxen 550 mg/day (1.5 h *versus* 1.0 h, respectively $p = 0.767$),[22] (**A**).

Recommendation 1

In women with primary dysmenorrhea, the use of etoricoxib at the dose of 120 mg/day and naproxen 550 mg/day for three consecutive menstrual cycles presented similar results regarding analgesic efficacy assessed by pain relief scores for an eight-hour period.

2. Is valdecoxib more effective then naproxen for the treatment of women with primary dysmenorrhea?

Valdecoxib is a NSAID with potent inhibitory action specific to COX-2. It has an *in vitro* selectivity 28,000 times superior for COX-2 recombinant enzyme than for COX-1[23] (**C**).

In women aged 18 to 35 years, with primary dysmenorrhea of moderate to severe intensity (76% and 24%, respectively), occurring in at least four of the last six menstrual cycles, undergoing therapy with valdecoxib 40 mg/day or 80 mg/day, and compared to the use of naproxen 1,100 mg/day, it was observed that the analgesia provided by the use of valdecoxib at both doses was similar to the analgesia provided by naproxen after the administration of the initial dose.

When evaluating pain relief using the scale consisting of five points and assessed through TOTPAR (which evaluates the achieved analgesia magnitude according to the elapsed period), it was observed that treatment with valdecoxib at doses of 40 mg/day or 80 mg/day and naproxen 1,100 mg/day were similar regarding pain relief in the first eight hours as well as after 12 hours (TOTPAR-8h = 19.3, 20.4, and 20.3; and TOTPAR-12h = 30.0, 32.1, and 31.2, for valdecoxib 40 mg/day, valdecoxib 80 mg/day, and naproxen 1100 mg/day, respectively; $p < 0.001$)[24] (**A**).

The percentage of women that required rescue analgesia in the first 12 hours was similar among naproxen 1,100 mg and valdecoxib at 40 mg and 80 mg doses (20%, 15%, and 20%), respectively[24] (**A**).

Regarding adverse events, similar rates were observed between treatment with valdecoxib and naproxen (14.1%, 17.6%, and 12.9% for valdecoxib 40 mg/day, valdecoxib 80 mg/day, and naproxen 1,100 mg/day), respectively[24] (**A**).

Recommendation 2

The use of valdecoxib at doses of 40 mg/day or 80 mg/day had a similar effect to that of naproxen 1,100 mg/day to relieve primary dysmenorrhea, both in the first eight hours and after 12 hours; the treatments are well tolerated.

3. Is rofecoxib more effective than naproxen for the treatment of women with dysmenorrhea?

Rofecoxib, a selective inhibitor of COX-2 or prostaglandin H2 synthase has a low effect on the inhibition of COX-1 isoenzyme, even at doses > 1,000 mg/day. Clinical trials have evaluated its effect at different doses (12.5 mg to 500 mg/day) in the treatment of osteoarthritis and rheumatoid arthritis, as well as its effectiveness in the treatment of primary dysmenorrhea[25] (**D**)[7] (**B**).

When evaluating women with a mean age of 26.9 years (SD ± 5.58 years) presenting abdominal pain related to the menstrual flow (75% diagnosed as primary dysmenorrhea), without systemic diseases or use of medications that may promote analgesia (antidepressants, hypnotics, corticosteroids), submitted to treatment of dysmenorrhea with rofecoxib at doses of 25 mg/day or 50 mg/day, compared to naproxen 550 mg/day, when pain intensity is evaluated through a score with four levels of intensity (0 = no pain, 1 = weak pain, 2 = moderate pain, 3 = severe pain), no significant difference was observed between the treatment of dysmenorrhea using naproxen 550 mg/day and rofecoxib 25 mg/day.

When comparing naproxen with rofecoxib 50 mg/day, there was a significant decrease in pain intensity score within 30 minutes ($p < 0.001$), but the same difference was not observed after the period of 1 hour. When comparing the use of rofecoxib 25 mg/day or 50 mg/day, no significant difference was observed between the doses ($p > 0.05$)[26] (**B**).

Regarding adverse events, especially gastrointestinal, there is a greater frequency when using naproxen 550 mg/day (63.6%) when compared to rofecoxib 25 mg/day or 50 mg/day[26] (**B**).

Recommendation 3

The use of rofecoxib for the treatment of dysmenorrhea (primary or secondary) at doses of 25 mg/day and 50 mg/day was shown to be as effective in relieving pain as naproxen 550 mg/day. When evaluating the rofecoxib doses employed, there was no significant difference between 25 mg/day and 50 mg/day.

4. Is dexibuprofen more effective than ibuprofen for the treatment of women with primary dysmenorrhea?

Ibuprofen, a racemic mixture of S- and R-enantiomers, is a safe and effective NSAID for the relief of pain caused by primary dysmenorrhea. Its anti-inflammatory and analgesic effects have been attributed mainly to the S-enantiomer, called dexibuprofen; the R-enantiomer takes effect only after being converted to S-enantiomer[27,28] (**D**).

In women with a mean age of 31.1 years (SD ± 6.7 years) and recurrent episodes of primary dysmenorrhea (four consecutive menstrual cycles, with pain of moderate to severe intensity, distribution of 40.2% and 59.7%, respectively), undergoing therapy with dexibuprofen at doses of 200 mg/day or 300 mg/day, or 400 mg ibuprofen/day for three menstrual cycles, it was observed that the administration of dexibuprofen 200 mg/day or 300 mg/day was as effective as ibuprofen 400 mg/day for the relief of pain assessed through a scale with four degrees of intensity[29] (**B**).

Recommendation 4

Dexibuprofen at doses of 200 mg/day and 300 mg/day, or 400 mg of ibuprofen/day have equivalent effects regarding pain relief in the treatment of primary dysmenorrhea.

5. Is lumiracoxib more effective than naproxen for the treatment of women with primary dysmenorrhea?

In women with a mean age of 28.7 years (SD ± 7.61 years) and a positive history of primary dysmenorrhea of moderate to severe intensity in at least four of the last six menstrual cycles, after exclusion of other causes of dysmenorrhea (secondary dysmenorrhea), in the absence of chronic abdominal pain, undergoing therapy with lumiracoxib at a dose of 200 mg/day, lumiracoxib 200 mg/day followed by a further dose of 200 mg on the first day after a period of one to 12 hours, with treatment extention for three more days if necessary, and the use of naproxen 1,000 mg/day, no significant difference was observed at the SPID-8h evaluation (difference in pain intensity calculated within the eight-hour period after treatment administration, in which pain intensity is assessed either through the four-point scale or through of the visual analogue scale) for the use of naproxen and two lumiracoxib administration regimens (12.07, 12.0, and 12.11 for lumiracoxib 200 mg/day, lumiracoxib 200 mg/day combined with another dose of 200 mg on the first day, and naproxen 1000 mg/day, respectively; $p < 0.001$[30] (**B**).

Regarding pain relief, assessed through the five-point scale with for a period of 8 and 12 hours (TOTPAR-8h and TOTPAR-12h), no significant difference was observed between the two regimens with lumiracoxib or between these schemes and naproxen (19.65, 19.39, and 19.56 for lumiracoxib 200 mg/day, lumiracoxib 200 mg/day associated with a further dose of 200 mg, and naproxen 1,000 mg/day, respectively, in the period of eight hours; and 29.23, 30.59, and 30.35, for the period of 12 hours, respectively)[30] (**B**).

Regarding adverse events (nausea, headache, abdominal pain, diarrhea), it was observed that the treatments were well tolerated (19%, 19.7%, and 22.6% for lumiracoxib 200 mg/day, lumiracoxib 200 mg/day combined with

a further dose of 200 mg, and naproxen 1,000 mg/day, respectively)[30] (B).

Recommendation 5

The use of lumiracoxib at a dose of 200 mg/day, with or without a new dose of 200 mg on the first day of treatment in women with primary dysmenorrhea of moderate to severe intensity had an analgesic efficacy similar to that of naproxen.

6. Is dexketoprofen more effective than ketoprofen in the treatment of primary dysmenorrhea?

Dexketoprofen is an S (+) enantiomer of ketoprofen, which is a racemic compound resulting from the mixture of R- and S-enantiomers. As in derivatives of propionic acid, S (+) enantiomer is the compound responsible for the inhibitory effect of ketoprofen on COX isoenzymes[31] (C). In animal models, it has been demonstrated that the anti-inflammatory potency of dexketoprofen is equivalent to twice the dose of ketoprofen. The R (–) enantiomer exhibits a much lower potency, and its analgesic action apparently occurs only through its metabolic inversion to the S (+) enantiomer[27] (D). Thus, the selective administration of the active enantiomer, S-enantiomer, apparently has advantages over the racemic mixture.

In women with a mean age of 24.6 years (SD ± 5.2 years) diagnosed as having primary dysmenorrhea (after ruling out secondary causes of dysmenorrhea), of moderate to severe intensity, lasting for at least four months, submitted to therapy for three days in four consecutive menstrual cycles with dexketoprofen at doses of 50 mg/day or 100 mg/day, or ketoprofen 200 mg/day, it was observed that in the TOTPAR-6h evaluation (assessed by verbal scale of pain relief consisting of five points, six hours after receiving the drug), the active treatments did not present significant difference (15.8 ± 7.4, 15.9 ± 6.9, and 17.7 ± 5.9 for dexketoprofen 50 mg/day, dexketoprofen 100 mg/day, and ketoprofen 200 mg/day, respectively, $p < 0.05$).

Regarding pain intensity assessed by the SPID-6h (difference in pain intensity after treatment administration, assessed through verbal pain scale consisting of four points and the visual analogue scale – VAS 0-100 mm), 6 hours after treatment, a significant difference was not observed between treatments (8.6 ± 5.3, 8.0 ± 5.2, and 9.3 ± 4.4 for dexketoprofen 50 mg/day, dexketoprofen 100 mg/day, and ketoprofen 200 mg/day, respectively[32] (A).

Regarding adverse events, no significant difference was observed between treatments[32] (A).

Recommendation 6

When analyzing the scores for pain relief, no significant analgesic difference was observed between treatments; dexketoprofen at doses of 50 mg/day and 100 mg/day were shown to be as effective in relieving pain as ketoprofen 200 mg/day.

7. Is bromfenac more effective than naproxen for the treatment of women with primary dysmenorrhea?

Bromfenac, a 2-amino-3 phenyl acetic acid derivative, is a potent PGF2α-inhibitor that has shown analgesic properties in animal models[33] (C). Pharmacodynamics studies have shown that, after its administration, the drug reaches maximum concentration within a time period ranging from 20 to 40 minutes, and its analgesic and anti-inflammatory actions persist for over 24 hours.

When evaluating women of a mean age of 32.2 years (SD ± 7.3 years) with primary dysmenorrhea (positive dysmenorrhea history in at least four consecutive months, with moderate to severe pain intensity), undergoing therapy with bromfenac at doses of 50 mg/day or 10 mg/day, and naproxen 550 mg/day over the course of one to three days for a period of five months, it was observed that the doses of 10 mg/day and 50 mg/day of bromfenac were as effective as naproxen 550 mg/day for pain relief when assessed through TOPAR-3h and 6h (total score of pain relief after the first dose of medication as well as three to six hours after treatment, $p < 0.001$)[34] (B).

Recommendation 7

The use of bromfenac at doses of 10 mg/day and 50 mg/day is as effective in relieving pain of primary dysmenorrhea as naproxen 550 mg/day.

8. Is piroxicam more effective than ibuprofen for the treatment of primary dysmenorrhea?

Piroxicam, which belongs to the oxican group, has advantages regarding treatment adherence over other anti-inflammatory due to its prolonged serum half-life, which allows for a single daily dose administration[35] (D).

When evaluating women of a mean age of 24.4 years, with primary dysmenorrhea of moderate to severe intensity, with at least six months of history, after ruling out secondary causes for secondary dysmenorrhea, undergoing treatment for a minimum of three and maximum of five days, with piroxicam 20 mg/day for five days; piroxicam 40 mg/day on the first day, followed by administration of piroxicam 20 mg/day from the second to the fifth days; piroxicam 40 mg/day on the first two days followed by piroxicam 20 mg/day from the third to fifth days; and ibuprofen 1,600 mg/day, it was observed that the relief of overall discomfort measured within 24 hours after treatment administration and evaluated through the five point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe) showed no significant difference between treatments.

When analyzing the use of rescue medication for the treatment of pain within the first 24 hours, it was observed that the administration of piroxicam 40 mg/day on the first two days followed by piroxicam 20 mg/day from the third to fifth day significantly reduced the need for drug

supplementation compared to women treated with piroxicam 20 mg/day for five days (p = 0.035)[36] (**A**).

Recommendation 8

In women with primary dysmenorrhea treated with a single daily dose of piroxicam (40 mg/day for two days followed by 20 mg/day for three more days; 40 mg/day for one day, followed by 20 mg/day for four more days; and 20 mg/day for five days) it was observed that discomfort and pain relief within 24 hours is comparable to the administration of 400 mg ibuprofen four times a day.

Conflicts of interest

All the authors declare to have no conflicts of interest.

REFERENCES

1. Nor Azlin MI, Maryasalwati I, Norzilawati MN, Mahdy ZA, Jamil MA, Zainul Rashid MR. The efficacy of etoricoxib *vs* mefenamic acid in the treatment of primary dysmenorrhoea: a randomised comparative trial. J Obstet Gynaecol. 2008;28:424-6.
2. Daniels SE, Talwalker S, Torri S, Snabes MC, Recker DP, Verburg KM. Valdecoxib, a cyclooxygenase-2-specific inhibitor, is effective in treating primary dysmenorrhea. Obstet Gynecol. 2002;100:350-8.
3. Chan WY, Dawood MY. Prostaglandin levels in menstrual fluid of nondysmenorrheic and of dysmenorrheic subjects with and without oral contraceptive or ibuprofen therapy. Adv Prostaglandin Thromboxane Res. 1980;8:1443-7.
4. Dawood MY. Dysmenorrhea. Clin Obstet Gynecol. 1990;33: 168-78.
5. Zhang WY, Li Wan Po A. Efficacy of minor analgesics in primary dysmenorrhoea: a systematic review. Br J Obstet Gynaecol. 1998;105:780-9.
6. Marjoribanks J, Proctor ML, Farquhar C. Nonsteroidal anti-inflammatory drugs for primary dysmenorrhoea. Cochrane Database Syst Rev. 2003;(4):CD001751.
7. Morrison BW, Daniels SE, Kotey P, Cantu N, Seidenberg B. Rofecoxib, a specific cyclooxygenase-2 inhibitor, in primary dysmenorrhea: a randomized controlled trial. Obstet Gynecol. 1999;94:504-8.
8. Gupta RA, Dubois RN. Colorectal cancer prevention and treatment by inhibition of cyclooxygenase-2. Nat Rev Cancer. 2001;1:11-21.
9. Baron JA. Epidemiology of non-steroidal anti-inflammatory drugs and cancer. Prog Exp Tumor Res. 2003;37:1-24.
10. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. Arthritis Rheum. 2000;43:1905-15.
11. Patrono C, Dunn MJ. The clinical significance of inhibition of renal prostaglandin synthesis. Kidney Int. 1987;32:1-12.
12. Houston MC. Nonsteroidal anti-inflammatory drugs and antihypertensives. Am J Med. 1991;90:42S-47S.
13. Baron JA, Sandler RS, Bresalier RS, Lanas A, Morton DG, Riddell R. Cardiovascular events associated with rofecoxib: final analysis of the APPROVEe trial. Lancet. 2008;372:1756-64.
14. Combe B, Swergold G, McLay J, McCarthy T, Zerbini C, Emery P, et al. Cardiovascular safety and gastrointestinal tolerability of etoricoxib *vs* diclofenac in a randomized controlled clinical trial (The MEDAL study). Rheumatology (Oxford). 2009;48:425-32.
15. Cannon CP, Curtis SP, FitzGerald GA, Krum H, Kaur A, Bolognese JA, et al. Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. Lancet. 2006;368:1771-81.
16. Cannon CP, Curtis SP, Bolognese JA, Laine L; MEDAL Steering Committee. Clinical trial design and patient demographics of the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) study program: cardiovascular outcomes with etoricoxib *versus* diclofenac in patients with osteoarthritis and rheumatoid arthritis. Am Heart J. 2006;152:237-45.
17. Sowers JR, White WB, Pitt B, Whelton A, Simon LS, Winer N, et al. The effects of cyclooxygenase-2 inhibitors and nonsteroidal anti-inflammatory therapy on 24-hour blood pressure in patients with hypertension, osteoarthritis, and type 2 diabetes mellitus. Arch Intern Med. 2005;165:161-8.
18. Agencia Nacional de Vigilância Sanitária [accessed Dec 2009]. Available from: http://www.anvisa .gov.br.
19. Dawood MY. Nonsteroidal antiinflammatory drugs and reproduction. Am J Obstet Gynecol. 1993;169:1255-65.
20. Vane JR, Botting RM. New insights into the mode of action of anti-inflammatory drugs. Inflamm Res. 1995;44:1-10.
21. Riendeau D, Percival MD, Brideau C, Charleson S, Dubé D, Ethier D, et al. Etoricoxib (MK-0663): preclinical profile and comparison with other agents that selectively inhibit cyclooxygenase-2. J Pharmacol Exp Ther. 2001;296:558-66.
22. Malmstrom K, Kotey P, Cichanowitz N, Daniels S, Desjardins PJ. Analgesic efficacy of etoricoxib in primary dysmenorrhea: results of a randomized controlled trial. Gynecol Obstet Invest. 2003;56:65-9.
23. Talley JJ, Brown DL, Carter JS, Graneto MJ, Koboldt CM, Masferrer JL, et al. 4-[5-methyl-3-phenylisoxazol-4-yl]-benzenesulfonamide, valdecoxib: a potent and selective inhibitor of COX-2. J Med Chem. 2000;43:775-7.
24. Daniels SE, Torri S, Desjardins PJ. Valdecoxib for treatment of primary dysmenorrhea. A randomized, double-blind comparison with placebo and naproxen. J Gen Intern Med. 2005;20:62-7.
25. Matheson AJ, Figgitt DP. Rofecoxib: a review of its use in the management of osteoarthritis, acute pain and rheumatoid arthritis. Drugs. 2001;61:833-65.
26. Sahin I, Saraçoğlu F, Kurban Y, Türkkani B. Dysmenorrhea treatment with a single daily dose of rofecoxib. Int J Gynaecol Obstet. 2003;83:285-91.
27. Evans AM. Pharmacodynamics and pharmacokinetics of the profens: enantioselectivity, clinical implications, and special reference to S (+)-ibuprofen. J Clin Pharmacol. 1996; 36(12 Suppl):7S-15S.
28. Caldwell J, Hutt AJ, Fournel-Gigleux S. The metabolic chiral inversion and dispositional enantioselectivity of the 2-arylpropionic acids and their biological consequences. Biochem Pharmacol 1988;37:105-14.
29. Kollenz C, Phleps W, Kaehler ST. ADIDAC trial: analgesia with dexibuprofen *versus* ibuprofen in patients suffering from primary dysmenorrhea: a crossover trial. Gynecol Obstet Invest. 2009;67:25-31.
30. Bitner M, Kattenhorn J, Hatfield C, Gao J, Kellstein D. Efficacy and tolerability of lumiracoxib in the treatment of primary dysmenorrhoea. Int J Clin Pract. 2004;58;340-5.
31. Carabaza A, Cabré F, Rotllan E, Gómez M, Gutiérrez M, García ML, Mauleón et al. Stereoselective inhibition of inducible

cyclooxygenase by chiral nonsteroidal anti-inflammatory drugs. J Clin Pharmacol. 1996;36:505-12.
32. Ezcurdia M, Cortejoso FJ, Lanzón R, Ugalde FJ, Herruzo A, Artigas R, et al. Comparison of the efficacy and tolerability of dexketoprofen and ketoprofen in the treatment of primary dysmenorrhea. J Clin Pharmacol. 1998;38(12 Suppl): 65S-73S.
33. Sancilio LF, Nolan JC, Wagner LE, Ward JW. The analgesic and anti-inflammatory activity and pharmacologic properties of bromfenac. Arzneimittelforschung. 1987;37:513-9.
34. Mehlisch DR, Fulmer RI. A crossover comparison of bromfenac sodium, naproxen sodium, and placebo for relief of pain from primary dysmenorrhea. J Womens Health. 1997;6:83-92.
35. Wiseman EH, Lombardino JG. Oxicams – a novel family of non-steroidal anti-inflammatory drugs. Eur J Rheumatol Inflamm. 1981;4:280-97.
36. Pasquale SA, Rathauser R, Dolese HM. A double-blind, placebo-controlled study comparing three single-dose regimens of piroxicam with ibuprofen in patients with primary dysmenorrhea. Am J Med. 1988;84:30-4.