

Flavocoxid is as effective as naproxen for managing the signs and symptoms of osteoarthritis of the knee in humans: a short-term randomized, double-blind pilot study^{☆,☆☆}

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Abstract

Flavocoxid (Limbrel), a proprietary mixture of flavonoid molecules (baicalin and catechin), was tested against a traditional nonsteroidal anti-inflammatory drug, naproxen, for the management of the signs and symptoms of moderate osteoarthritis (OA) in humans. Discomfort and global disease activity were used as the primary end points, and safety assessments were also taken for both treatments as a secondary endpoint. In this double-blind study, 103 subjects were randomly assigned to receive either flavocoxid [500 mg twice daily (BID)] or naproxen (500 mg BID) in a 1-month onset of action trial. Outcome measures included the short Western Ontario and McMaster University Osteoarthritis Index, subject Visual Analogue Scale for discomfort and global response, and investigator Visual Analogue Scale for global response and fecal occult blood. Both flavocoxid and naproxen showed significant reduction in the signs and symptoms of knee OA ($P \leq .001$). There were no statistically detectable differences between the flavocoxid and naproxen groups with respect to any of the outcome variables. Similarly, there were no statistically detectable differences between the groups with respect to any adverse event, although there was a trend toward a higher incidence of edema and nonspecific musculoskeletal discomfort in the naproxen group. In this short-term pilot study, flavocoxid was as effective as naproxen in controlling the signs and symptoms of OA of the knee and would present a safe and effective option for those individuals on traditional nonsteroidal anti-inflammatory drugs or cyclooxygenase-2 inhibitors. A low incidence of adverse events was reported for both groups.
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Keywords: Osteoarthritis; Flavocoxid; Limbrel; Flavonoid; Baicalin; Catechin; Medical food; Dual inhibition; Cyclooxygenase; Lipoxigenase; Randomized trial; Comparator; WOMAC; VAS; Nonsteroidal anti-inflammatory drugs; NSAID; Clinical trial

Abbreviations: AE, adverse event; BID, twice daily; COX, cyclooxygenase; K&L, Kellgren & Lawrence; LOX, lipoxigenase; NF- κ B, nuclear factor κ B; LTB₄, leukotriene B₄; NSAID, nonsteroidal anti-inflammatory drugs; OA, osteoarthritis; PGAD, physician's global assessment of disease activity; PLA₂, phospholipase A₂; SGAD, subject's global assessment of disease activity; SGADc, subject's global assessment of disease related discomfort; VAS, Visual Analogue Scale; WOMAC, Western Ontario and McMaster University Osteoarthritis Index.

MeSH: Osteoarthritis [05.550.114.606]; Anti-Inflammatory Agents [D27.505.954.158]; Flavonoids [D03.438.150.266.450].

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1. Introduction

Osteoarthritis is the most common form of joint disease in adults worldwide, affecting more than 25 to 40 million people in the United States alone [1–4] with similar data reported from other countries [5]. The disease results in impaired quality of life issues including pain, functional and social disability, and depression [6,7] and, when more severe, imposes a significant societal burden [8,9]. Despite multiple treatment modalities that have been used to manage the signs and symptoms of OA including physical therapy, analgesics; intra-articular injections of corticosteroids or hyaluronate preparations and surgical intervention; and nonsteroidal anti-inflammatory drugs (NSAIDs), including both non-selective NSAIDs and selective cyclooxygenase-2 (COX-2) inhibitors, remain the mainstay of most chemical therapeutic regimens. Although effective at relieving pain and inflammation, their use may be limited by toxic effects on the gastrointestinal tract, kidneys, platelets, heart, and liver. These adverse effects are mediated primarily by fatty acid metabolites generated via the primary inflammatory enzyme pathways in arachidonic acid (AA) metabolism, cyclooxygenase-1 (COX-1) and COX-2, as well as 5-lipoxygenase (5-LOX) (Fig. 1). All of the resulting metabolites serve important physiologic functions both within and beyond articular structures [10,11]. It is thought that imbalance in the levels of these end products from selective blocking of the cyclooxygenase (COX) metabolic enzymes may account for much of the toxicity of anti-inflammatory agents [12,13].

Cyclooxygenase-1 agents are generally known to cause gastrointestinal distress and ulceration when used chronically, accounting for thousands of deaths per year, especially in elderly populations [14,15]. Nitronaproxen, however, is currently in the final phases of a new drug application and has been shown in clinical trials to reduce the incidence of gastric distress due to a release of nitric oxide from the molecule in the gut which helps preserve tissue integrity

[16]. Cyclooxygenase-2 inhibitors have been shown to elevate hypertension and cardiovascular dysfunction in patients [17–20]. Both classes of NSAIDs have “black box” warnings assigned by the Food and Drug Administration (<http://www.fda.gov/bbs/topics/news/2005/NEW01171.html>). In addition, both traditional NSAIDs and COX-2 inhibitors have been shown to “shunt” AA metabolism down the 5-LOX enzymatic pathway producing vasoconstrictive and chemoattractive leukotrienes [21]. For example, the proinflammatory leukoattractant fatty acid metabolite leukotriene B₄ (LTB₄), a product of the 5-LOX pathway, is found in high concentrations in the walls of NSAID-induced gastric ulcers [22]. Therefore, safe products with the potential to regulate both COX and lipoxygenase (LOX) inflammatory enzyme pathways merit clinical investigations to determine their roles in the therapeutic management of osteoarthritis and other inflammatory diseases. Flavonoid compounds may represent new, safe therapeutics for inflammation.

Thousands of flavonoids have been isolated and many have been characterized for their antioxidant and anti-inflammatory effects [23]. Several different flavonoids have been shown to directly inhibit COX and LOX enzymes, suggesting that these natural compounds found in food can act as anti-inflammatory compounds [24]. In addition, a variety of flavonoid molecules have also been shown to modulate nuclear factor- κ B (NF- κ B), the controlling transcription factor of inducible inflammatory cytokines, probably via an antioxidant mechanism of action [25,26]. Though flavonoids were recognized as early as 1973 for their potential to treat joint inflammation [27], few clinical studies have been performed that assess their safety and efficacy for OA. However, recent pilot clinical trials utilizing *Garcinia kola* [28] and pine bark extract-derived bioflavonoids [29–31] have demonstrated a renewed interest in the use of natural molecules to manage OA.

Flavocoxid (Limbrel) is a proprietary prescription medical food product for the clinical dietary management of the metabolic processes underlying the pathogenesis of OA. Under US Food and Drug Administration law, flavocoxid is classified as a medical food, a therapeutic category distinct from drugs and supplements (defined in section 5(b) of the Orphan Drug Act and Amendments, 1988 [21 U.S.C. 360ee(b)(3)]). Flavocoxid is a concentrated and greater than 90% pure standardized blend of baicalin, a free-B-ring flavonoid extracted from *Scutellaria baicalensis*, and catechin, a flavan from *Acacia catechu* with the remaining content being excipient and water [32]. In Asia, these compounds have been used for more than 1000 years for the treatment of a variety of inflammatory conditions. In preclinical biochemical assays, more impure mixtures of baicalin and catechin were shown to possess significant activity against the primary enzyme pathways involved in arachidonic acid metabolism, that is, COX-1, COX-2, and 5-LOX [33]. Dual pathway inhibition greatly reduces the downstream production and imbalance of inflammatory mediators and is thought to result in an improved toxicity

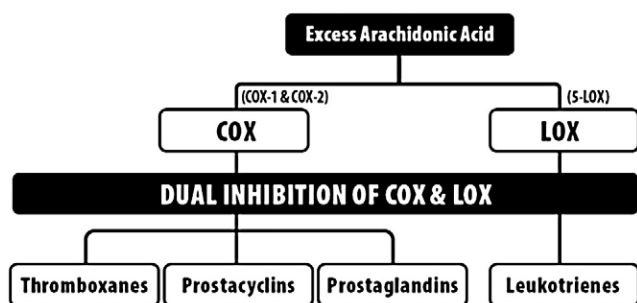


Fig. 1. Arachidonic acid liberated from membrane phospholipids upon cell damage or dietary omega-6 fatty acids is metabolized through one of 2 major enzymatic pathways, that is, COX (COX-1 or COX-2) or 5-LOX. Dual inhibition of COX and 5-LOX enzymes by flavocoxid regulates the production of prostaglandins and leukotrienes and their physiologic sites of action.

profile. Prior preclinical and exploratory clinical studies have suggested that flavocoxid may have a beneficial effect in the management of OA [33,34], and it is proposed here that a clinical trial on flavocoxid will establish suitable efficacy and safety in humans.

This present study was conducted in a group of individuals with clinically diagnosed moderate to severe OA of the knee. The hypothesis was that the prescription nutritional compound, flavocoxid, is a viable alternative to NSAIDs and COX-2 inhibitors in managing the inflammatory processes of OA in humans and providing a benefit to those suffering from this painful and dysfunctional disease. The objective used to test this hypothesis was to compare the short term effectiveness of flavocoxid to a full therapeutic dose of naproxen using validated instruments for efficacy as the primary endpoint with safety as a secondary end point. This initial study provides guidance for future larger studies in humans and suggests that this combination of naturally derived flavonoid molecules, baicalin and catechin, is a novel new therapy for the management of OA.

2. Methods and materials

A 4-week, multicenter, double-blind, active comparator controlled pilot study was performed in the Russian Federation. Subjects were chosen from investigators' hospital clinic practices and were required to have Kellgren & Lawrence (K&L) grade 2 to 3 OA of a knee in need of anti-inflammatory therapy. Subjects were required to discontinue use of NSAIDs (including selective COX-2 inhibitors) at least 2 weeks before the screening visit. Subjects were then randomly assigned to receive either flavocoxid 500 mg BID [32] or naproxen 500 mg BID. Acetaminophen (up to 3 g daily) was provided for rescue analgesia.

The study was conducted under ethical review board oversight and according to International Congress of Harmonization and Good Clinical Practices guidelines. Subjects were required to sign an informed consent document and were free to discontinue their participation in the study at any time and for any reason. Efficacy parameters included subject Visual Analogue Scale (VAS) for discomfort and global disease activity, investigator global assessment of disease activity VAS and Western Ontario and McMaster University Osteoarthritis Index (WOMAC) short form (validated in Russian). The WOMAC has been repeatedly shown to be a valid and reproducible instrument for assessing OA [35,36]. The short form WOMAC has been validated as a surrogate for the full WOMAC [37]. The VAS instruments for discomfort and global disease activity are routinely used to assess management of pain and discomfort [38].

Major inclusion criteria were:

1. Grade 2 to 3 K&L OA in at least 1 knee [39]
2. Age 35 to 85 years, inclusive

3. In general good health
4. Not pregnant or breast feeding

Major exclusion criteria were:

1. Grade 1 or 4 K&L OA in target knee
2. Grade 4 K&L OA in any knee or hip
3. Any form of arthropathy other than OA
4. Any musculoskeletal or neurologic condition that might alter gait or confound evaluation of discomfort in the target knee
5. Use of any gastroprotective medication whether by prescription or over the counter within 2 weeks of the screening visit
6. Intra-articular corticosteroids within 3 months or hyaluronate preparations within 6 months of the screening visit
7. Use of mechanical ambulation aids
8. History of bleeding disorder or use of anticoagulant medications
9. History of chronic upper gastrointestinal disease or upper gastrointestinal bleeding within 3 years of screening
10. Positive fecal occult at screening
11. Significant renal, cardiovascular, or neoplastic disease or any other disease that, in the opinion of the investigator, might put the subject at undue risk during the study
12. History of allergy to aspirin, NSAIDs, or flavonoids

2.1. Statistical analyses

Fisher exact test was computed for improved vs not improved (sum of unchanged and worsened) for all 4 efficacy parameters. For each adverse event (AE), a 2×2 contingency table was formed with values for each group representing the number (and percent) of patients reporting the given condition and the number of those not reporting the condition. These values were analyzed to determine if significantly different proportions of individuals reported each condition in the flavocoxid and the naproxen groups. Proportions were analyzed using the Fisher exact test, and

Table 1
Baseline characteristics

	Flavocoxid 500 mg BID	Naproxen 500 mg BID
N per group	52	51
Age (mean [\pm SEM])	60.3 (9.7)	57.5 (14.4)
Sex (men;women)	7;45	6;45
Weight (kg) (mean [\pm SEM])	82.3 (14.1)	83.0 (15.8)
Body mass index: mean (\pm SEM)	30.4 (6.3)	30.7 (5.1)
WOMAC (composite score) (mean [\pm SEM])	55.3 (17.0)	55.8 (15.1)
PGAD (mm on VAS) (mean [\pm SEM])	57.1 (16.7)	57.7 (14.2)
SGAD (mm on VAS) (mean [\pm SEM])	33.2 (16.1)	36.3 (15.2)
SGADc (mm on VAS) (mean [\pm SEM])	56.8 (19.4)	58.2 (18.2)

Baseline characteristics of subjects in both flavocoxid and naproxen groups were similar.

Table 2
Improvements in WOMAC and VAS

	Flavocoxid 500 mg BID (n = 52)		Naproxen 500 mg BID (n = 51)		Within-group <i>P</i>	Between-group <i>P</i>
	Patients with improvement	Improvement	Patients with improvement	Improvement		
	n (%)	Mean (±SEM)	n (%)	Mean (±SEM)		
WOMAC	41 (79%)	32% (33)	45 (88%)	36% (36)	<.001	.67
PGAD	43 (83%)	31% (32)	38 (75%)	38% (35)	<.001	.34
SGAD	45 (87%)	162% (249)	45 (88%)	130% (188)	<.001	.46
SGADc	45 (87%)	28% (39)	45 (88%)	38% (39)	≤.001	.20

Fisher exact test: approximately 85% of both flavocoxid and naproxen groups showed improvement.

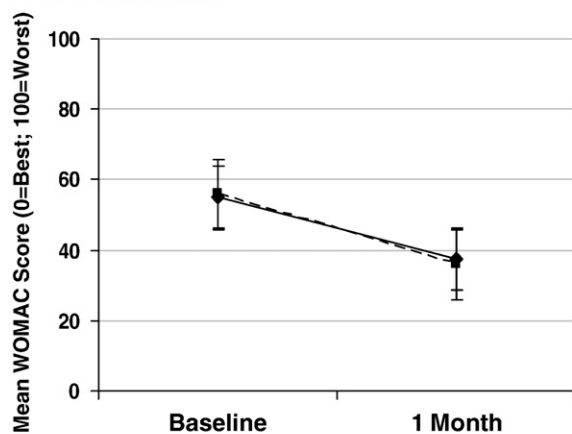
any probability of a significant difference is reported. The mean and SEM were calculated for all efficacy measures.

3. Results

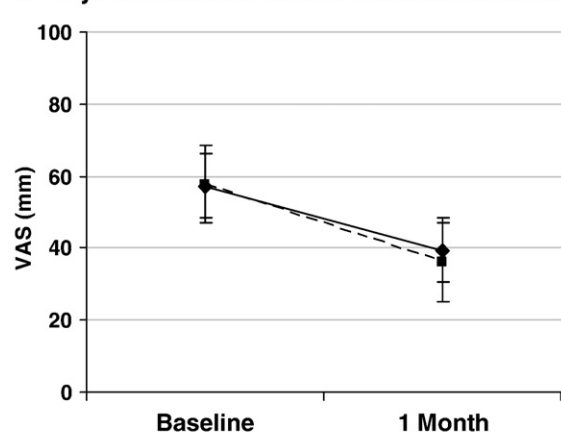
One hundred three subjects were randomized to the trial. Two subjects, both in the naproxen arm, failed to complete the full month of study product, one for increasing upper

gastrointestinal discomfort, the other for personal reasons unrelated to the trial. Both subjects completed 3 weeks of therapy and were included in the efficacy and safety analyses. The baseline characteristics of the 2 groups are shown in Table 1. There were no differences in demographic or symptomatic disease severity as measured by WOMAC or several VAS scores between the 2 groups. The population was, in general, moderately obese with a mean body mass index of 30.4 (flavocoxid) and 30.7 (naproxen).

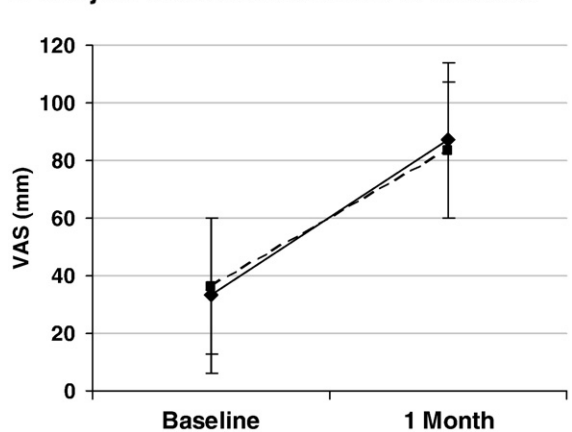
A Short WOMAC^a



B Physician Global Assessment of Disease^a



C Subject Global Assessment of Disease^b



D Subject Global Assessment of Discomfort^a

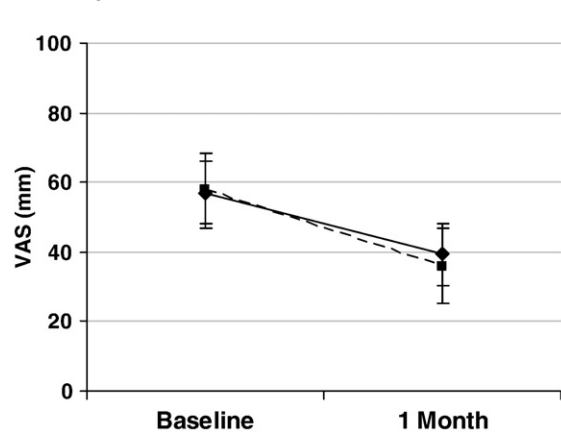


Fig. 2. Efficacy measurements. Within group improvements were all significant for both flavocoxid and naproxen groups ($P \leq .001$) for WOMAC, PGAD, SGAD, and SGAD. The means and \pm SEM are shown for each efficacy measurement. Differences between groups were not statistically significant ($P > .2$). \blacklozenge — \blacklozenge Indicates flavocoxid 500 mg BID; \blacksquare — \blacksquare , naproxen 500 mg BID. ^aDecreasing trends indicated improvement ($P \leq .001$). ^bIncreasing trends indicated improvement ($P \leq .001$).

Table 3
Adverse events^a

	Flavocoxid	Naproxen
	500 mg BID (n = 52)	500 mg BID (n = 51)
Cardiovascular	4 (8%)	6 (12%)
Worsening hypertension	2	2
Edema	2	4
Dermal (itching)	1 (2%)	0 (0%)
Dizziness/insomnia	1 (2%)	1 (2%)
Vertigo	1	0
Insomnia	0	1
Gastrointestinal	11 (21%)	11 (22%)
Abdominal pain	3	4
Constipation	0	1
Diarrhea	3	2
Heartburn	2	1
Nausea	1	3
Vomiting	2	0
Musculoskeletal (increased knee pain)	3 (6%)	6 (12%)
Respiratory (cold, upper respiratory infection [URI])	3 (6%)	0 (0%)
Other (facial swelling)	1 (2%)	2 (4%)
Total	24 (46%)	26 (51%)

^a No serious AEs were reported for either group. One subject discontinued in the naproxen group due to increased upper gastrointestinal discomfort. Percentage of AEs are shown out of the total population in each arm.

Four efficacy parameters were followed: WOMAC short form (validated in Russian), physician's global assessment of disease activity (PGAD), subject's global assessment of disease activity (SGAD), and subject's global assessment of disease related discomfort (SGADc). A significant average improvement of approximately 85% from baseline for all efficacy measurements were noted in both groups ($P < .001$) (Table 2, Fig. 2). No significant differences in any efficacy parameter were found between the flavocoxid and naproxen groups although there appeared to be a slight trend toward a larger reduction of discomfort in the naproxen group and a greater overall improvement of disease activity in the flavocoxid group.

Adverse events were similar in both study groups. There were 24 (46%) AEs in the flavocoxid group and 26 (51%) in the naproxen group (Table 3). Neither the numbers nor kinds of AEs differed significantly between the groups with the exception of a slight, but not statistically significant, trend toward more frequent edema and nonspecific musculoskeletal events in the naproxen group. No serious AEs were reported. No significant changes were observed within or between groups for weight, systolic blood pressure, or diastolic blood pressure. No positive fecal occult bloods were recorded.

4. Discussion

Currently prescribed NSAIDs and selective COX-2 inhibiting agents are often effective for controlling pain and inflammation associated with OA but may be associated with poor patient tolerance and/or significant physiologic

side effects [40]. Agents that block all 3 major metabolic pathways of AA metabolism (COX-1, COX-2, and 5-LOX), the so-called "dual pathway inhibitors," are thought to have better safety profiles because of their more balanced inhibition of production of the end products of this important regulatory system [12,41].

Baicalin, as well as baicalein, the resulting aglycone bacterial digestive product of baicalin in the small intestine, have both been shown to reduce prostaglandin E₂, COX-2 and cytokine generation in cell assays and animal models suggesting a direct modulation of COX activity and cytokine production either by gene regulation or a direct inhibition of enzyme activity [42–44]. Baicalein was also shown to inhibit synthesis of leukotrienes in stimulated macrophages in vitro [45]. Tea derived catechins have also been shown to decrease COX-2 gene expression in human chondrocytes via NF- κ B modulation [46,47] and to inhibit ex vivo degradation of human cartilage [48].

The combination of baicalin and catechin has been shown previously to act as a "dual-inhibitor" of COX and LOX enzymatic activity as well as inhibiting the production of prostaglandin E₂ and LTB₄ production in cell models [33] as well as inhibit the induction of interleukin-1 β , interleukin-6, and tumor necrosis factor- α gene expression [32]. Recently, flavocoxid itself has been shown in lipopolysaccharide-induced macrophages to inhibit the NF- κ B production, restore Ikappa-Balpa (IkB α), reduce COX-2 and 5-LOX but not COX-1 protein expression damping prostaglandin E₂ and LTB₄ generation as a consequence, decrease inducible nitric oxide synthase and tumor necrosis factor- α production, and finally, blunt intracellular nitrite and malondialdehyde levels [32]. These data suggest that baicalin and catechin, when mixed together, not only inhibit AA processing to inflammatory fatty acids by direct inhibition of COX-2 and 5-LOX enzymes but also by modulating NF- κ B presumably via an antioxidant mechanism of action, a well-documented activity of flavonoids [49]. There may be other mechanisms of action, however, by which flavocoxid exerts its anti-inflammatory effects.

A number of flavonoid compounds have been shown to inhibit phospholipase A₂ (PLA₂), the enzyme which processes cell membrane phospholipids to AA [50]. Tea catechins, baicalin, and the aglycone baicalein all have been shown to inhibit PLA₂ both cell and animal models [42,50–52]. Thus, flavocoxid may also inhibit the production of AA via inhibition of PLA₂. Similarly, platelet activating factor, another inflammatory eicosanoid, has been shown to stimulate bone resorption [50,53], and proteoglycan degradation in cartilage [54] may be modified by flavonoids. Balestrieri et al [55] have shown that the flavonoids hesperedin, naringin, and quercetin all act through an antioxidant mechanism of action to stimulate transacetylase transfer of an acetyl group to platelet activating factor which has been shown to reduce the activation of neutrophils. A great deal is known about the anti-inflammatory activities of flavonoids on a variety of molecular targets to down-regulate

inflammation, but only limited human clinical data exists regarding the use of these molecules in chronic disease states such as OA.

Recently, the results of a small pilot clinical study ($n = 21$ per arm) demonstrated that flavonoid extracts from *G kola* were equivalent to naproxen and celecoxib, as assessed by WOMAC, and significantly better than placebo in addressing the pain, stiffness, and mobility of OA patients [28]. Similarly, in a 37-subject randomized, double-blind study, Farid et al [31] showed that pine bark extracts (Pycnogenol) improved WOMAC composite scores for pain, stiffness, and mobility compared to the placebo control group, which showed no improvement. These results were extended for Pycnogenol showing improvement of WOMAC scores in 2 separate pilot studies of 100 and 143 subjects [29,30]. The placebo comparator again showed no improvement.

Our pilot study is the first formal clinical trial investigating the efficacy of flavocoxid. This well-controlled clinical trial confirms the anti-inflammatory effect seen for baicalin and catechin in a number of experimental models [32,33] and extends these findings to humans. In this study, flavocoxid was shown to be as effective as naproxen in managing the signs and symptoms of OA of the knee.

There are a few limitations in this study. First, the study length of 30 days was too short to allow for any potential differences in AEs between the flavocoxid and naproxen groups, particularly those of a gastrointestinal nature, to manifest. Second, biochemical blood markers should be included in a longer study (eg, 3 months) to test for specific safety on hepatic, renal, and gastrointestinal function. And third, the study size needs to be increased and these results replicated to assure that flavocoxid is an acceptable therapy for OA. Still, the significant efficacy of flavocoxid in this trial supports the need for more extensive clinical studies in larger populations and longer duration.

Flavocoxid and naproxen appear to be equally effective therapies for symptomatic OA of the knee when administered in full therapeutic doses for the short duration of 30 days, a typical course of therapy administered by physicians to test the effectiveness anti-inflammatory compounds in patients. A larger, long-term clinical trial of flavocoxid vs naproxen is therefore warranted and currently being conducted to confirm the long-term safety and clinical efficacy vs naproxen.

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