

Drug Class Review on Cyclo-oxygenase (COX)-2 Inhibitors and Non-steroidal Anti-inflammatory Drugs (NSAIDs)



Update #4: Preliminary Scan Report

October 2007

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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OBJECTIVE:

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant only to assist with Participating Organizations' consideration of allocating resources toward a full update of this topic. Comprehensive review, quality assessment and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the FDA or Health Canada since the last report. Other important studies could exist.

Date of Last Update:

Final Report Update #3 November 2006 (searches from 1966 to February Week 2 2006)

Scope and Key Questions

The purpose of this review is to compare the benefits and harms of different pharmacologic treatments for beta2-agonists. The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

Scope and Key Questions

1. Are there differences in effectiveness between coxibs and other NSAIDs?
2. Are there clinically important differences in short-term safety or adverse effects between coxibs, other NSAIDs, and the combination of an NSAID plus antiulcer medication when used for musculoskeletal pain?
3. Are there clinically important differences in long-term safety or adverse effects between coxibs, other NSAIDs, and the combination of an NSAID plus antiulcer medication when used chronically?
4. Are there subgroups of patients based on demographics, other medications (e.g., aspirin), or co-morbidities for which one medication is more effective or associated with fewer adverse effects?

Several aspects of the key questions merit comment:

1. Patients. We focused on patients with chronic pain from osteoarthritis, rheumatoid arthritis, soft-tissue pain, or back pain. We included ankylosing spondylitis. COX-2 inhibitors are also used to treat dysmenorrhea and acute pain (e.g., dental or surgical pain), and to prevent the formation of colorectal

polyps. We did not examine studies of the use of coxibs for these indications.

2. *Efficacy*. The main efficacy measures are pain, functional status, and discontinuations due to lack of efficacy. Measures vary among studies.

Frequently used measures are:

Visual analogue scale (VAS): The patient indicates their level of pain, function, or other outcome by making a mark on a scale labeled with numbers (such as 0 to 100) or descriptions (such as “none” to “worst pain I’ve ever had”).

The *Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)* is a 24-item questionnaire used to assess the functional status of patients with osteoarthritis of the knee and hip. A lower score indicates better function.

Patient Global Assessment of Disease Status and *Investigator Global Assessment of Disease Status*. The patient or investigator answers questions about the overall response to treatment, functional status, and pain response, using a VAS or Likert scale.

American College of Rheumatology (ACR) criteria measure disease activity and response to treatment. ACR 20, ACR 50, or ACR 70 reflect either an improvement to the 20%, 50%, or 70% level in the parameters outlined.

3. *Safety and adverse effects*. The following events were included in the review:

a. Serious GI events (GI bleeding, symptomatic ulcer disease, perforation of the GI tract, and death).

b. Serious cardiovascular events (myocardial infarction, angina, stroke, transient ischemic attack, cardiovascular death, and related measures).

c. Tolerability and adverse events. We recorded discontinuation due to any adverse event, any serious adverse event, the overall rate of adverse events, the rate of GI adverse events, and the combined rate of adverse events related to renal and cardiovascular function, including increased creatinine, edema, hypertension, or congestive heart failure. We also recorded the frequency of, and discontinuations due to, abnormal laboratory tests, primarily elevated transaminases (liver tests).

Several types of adverse events were excluded:

d. The main non-clinical, or intermediate, outcome measure for GI adverse effect is *endoscopic ulcer*. Ulcers in the stomach or small intestine can be seen in up to 40% of patients taking NSAIDs. (Hawkey, Laine et al. 2000; Laine, Maller et al. 2004) Up to 85% of these ulcers can only be found by endoscopy because they do not cause symptoms or bleeding. All three COX-2 inhibitors in the US market significantly reduce the incidence of these asymptomatic ulcers. Based on input from the subcommittee, we did not include endoscopic ulcer as an outcome measure, since our focus is on clinically significant adverse events.

e. *Case reports associated with celecoxib*: anaphylaxis, (Grob, Pichler et al. 2002) fatal (Schneider, Meziani et al. 2002) and nonfatal allergic vasculitis, (Gscheidel, Daspert et al. 2002; Jordan, Edwards et al. 2002) interstitial nephritis with (Alper, Meleg-Smith et al. 2002) and without (Henao, Hisamuddin et al. 2002) nephritic syndrome, cholestatic hepatitis, (Alegria, Lebre et al. 2002) toxic epidermal necrolysis, (Berger, Dwyer et al. 2002; Friedman, Orlet et al. 2002; Verbeiren, Morant et al. 2002; Giglio 2003)

erythema multiforme,(Ernst and Egge 2002) migratory pulmonary infiltrates,(Mehandru, Smith et al. 2002) acute pancreatitis,(Nind and Selby 2002) torsade de pointes,(Pathak, Boveda et al. 2002) and renal papillary necrosis.(Akhund, Quinet et al. 2003)

4. *Drugs.* We sought evidence about the following NSAIDs currently available in the US or Canada:

Table 1. Included NSAIDs

Generic Name	Proprietary Name	Dosage Forms
CELECOXIB	Celebrex	100, 200, 400 mg
DICLOFENAC SODIUM	Voltaren, Voltaren-XR	25, 50, 75, 100 mg
DICLOFENAC POTASSIUM	Cataflam	25, 50 mg
DIFLUNISAL	Dolobid	250, 500 mg
ETODOLAC	Lodine, Lodine XL	200, 300, 400, 500 mg
FENOPROFEN	Nalfon	200, 300, 600 mg
FLURBIPROFEN	Ansaid	50, 100 mg
IBUPROFEN	Motrin	300, 400, 600, 800 mg
INDOMETHACIN	Indocin, Indocin SR	25, 50, 75 mg
KETOPROFEN		25, 50, 75 mg
KETOPROFEN XR	Oruvail	100, 150, 200 mg
KETOROLAC	Toradol	10 mg
MECLOFENAMATE		50, 100 mg
MEFENAMIC ACID		250 mg
MELOXICAM	Mobic	7.5, 15 mg
NABUMETONE	Relafen	500, 750 mg
NAPROXEN		250, 375, 500 mg
NAPROXEN delayed release		375, 500 mg
NAPROXEN SODIUM	Anaprox, Anaprox DS	250, 500 mg
	Naprelan	375, 500, 750 mg
OXAPROZIN	Daypro	600 mg
PIROXICAM	Feldene	10, 20 mg
SALSALATE	Disalcid	100, 500 mg
SULINDAC	Clinoril	150, 200 mg
TIAPROFENIC ACID	Surgam	200, 300, 600 mg
TENOXICAM	Mobiflex	20, 40 mg
TOLMETIN	Tolectin	200, 400, 600 mg

METHODS

Literature Search

To identify relevant citations for this scan update, we searched MEDLINE (January 2006 to September week 2 2007). We used terms for included drugs and limits for humans, English and randomized clinical trials or controlled clinical trials. We also searched the FDA (<http://www.fda.gov/cder/Offices/DDI/pathfinder.htm>) and Health Canada (http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2007/index_e.html) websites for identification of

new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote 9.0).

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

Overview

We identified 38 potentially relevant citations. Of those, there are 2 new potentially relevant controlled clinical trials (Appendix A).

New FDA-approved Drugs

No new drugs have been approved since our last update of this review.

New Indications

In December 2006, use for juvenile rheumatoid arthritis (JRA) in patients 2 years of age and older was FDA-approved for celecoxib as an additional labeled indication.

New Safety Alerts

No new safety alerts have been reported since January 2006 when the FDA mandated the addition of a boxed warning to all NSAIDs' product labels regarding the potential risks of cardiovascular and gastrointestinal adverse effects.

APPENDIX A

Pincus, T., X. Wang, et al. (2005). "Patient preference in a crossover clinical trial of patients with osteoarthritis of the knee or hip: face validity of self-report questionnaire ratings.[erratum appears in J Rheumatol. 2005 May;32(5):966]." Journal of Rheumatology **32**(3): 533-9.

OBJECTIVE: To analyze correlational validity of self-report responses regarding patient preference between 2 drugs at the conclusion of a crossover double-blind clinical trial in patients with osteoarthritis (OA) of the knee or hip. **METHODS:** Patients were randomized to 6 weeks' treatment of diclofenac/misoprostol or acetaminophen, followed by crossover to 6 weeks of the other drug. Patient preference was queried at the final visit: "Please compare control of your arthritis during the first and second periods as 'much better' or 'better' in the first period, 'no different' or 'better' or 'much better' in the second period." Patient preference ratings were evaluated in comparisons with 4 independent self-report measures within each treatment period: (1) change in Western Ontario McMaster (WOMAC) questionnaire scores; (2) change in pain visual analog scale (VAS) on a multidimensional Health Assessment Questionnaire (MDHAQ); (3) patient ratings of drug efficacy; and (4) patient report of change in arthritis status, as well as investigator ratings of the more efficacious drug. **RESULTS:** Among 173 patients, diclofenac/misoprostol was rated as "much better" by 54 and "better" by 45, acetaminophen was rated as "better" by 18 and "much better" by 17, and "no difference" by 39 patients. Spearman rank correlations for patient preferences were significant for changes in WOMAC scores, pain VAS, and independent patient ratings of drug efficacy and changes in arthritis status within each treatment period, as well as with physician ratings of the more efficacious drug ($p < 0.001$). **CONCLUSION:** Significant correlational validity is documented for patient self-report of preferences between 2 drugs compared to independent measures within each treatment period in this crossover clinical trial in patients with OA of the knee or hip.

Soininen, H., C. West, et al. (2007). "Long-term efficacy and safety of celecoxib in Alzheimer's disease." Dementia & Geriatric Cognitive Disorders **23**(1): 8-21.

BACKGROUND/AIMS: Cyclooxygenase-2 (COX-2) may play an important role in the neuropathology of Alzheimer's disease (AD). The efficacy and safety of celecoxib (200 mg bid), a COX-2 selective inhibitor, were assessed in patients $> \text{ or } = 50$ years with established mild-to-moderate AD to determine whether treatment was effective in retarding deterioration of cognitive function. **METHODS:** This was a 52-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. The primary efficacy end points were the change from baseline to week 52 in the Alzheimer's Disease Assessment Scale-Cognitive Behavior (ADAS-cog) composite score and the week 52 Clinician's Interview-Based Impression of Change Plus (CIBIC+). **RESULTS:** At 52 weeks, change in ADAS-cog scores from baseline was similar for placebo and celecoxib 200 mg bid groups (5.00 and 4.39, respectively). CIBIC+ scores were also similar (4.83 and 4.92). Two extension studies were conducted but were terminated early based on these efficacy results. Safety data from all 3 studies indicated that celecoxib was generally well-tolerated. **CONCLUSION:** Celecoxib 200 mg bid did not slow the progression of AD in this study, and the occurrence of adverse events was as expected for

an elderly population with a complex chronic medical condition. Copyright 2007 S. Karger AG, Basel