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

Final Report Update 3 Evidence Tables

November 2006

Original Report Date: May 2002
Update 1 Report Date: September 2003
Update 2 Report Date: May 2004
A literature scan of this topic is done periodically

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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Note: A scan of the medical literature relating to the topic is done periodically(see http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm for scanning process description). Upon review of the last scan, the Drug Effectiveness Review Project governance group elected not to proceed with another full update of this report. Some portions of the report may not be up to date. Prior versions of this report can be accessed at the DERP website.

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Evidence Table 1. Systematic reviews

Author Year	(1) Aims	(2) Time period covered	(3) Eligibility criteria	(4) Number of patients	(5) Characteristics of identified articles: study designs
Chou, et al 2006	To assess the comparative effectivness and safety of analgesics in the treatment of osteoarthritis	1966-2005 (*some additional post-search studies included)	Systematic reviews and RCTs that compared one included drug to another, another active comparator, or placebo; cohort and case-control studies with at least 1,000 cases or participants that evaluated serious gastrointestinal and cardiovascular endpoints that were inadequately addressed by randomized controlled trials.	Not specified	Systematic reviews, RCTs, observational studies (for safety only) 351 publications, some relating to drugs outside the scope of this report (e.g. acetaminophen, topical analgesics)
Riedemann 1993	To assess the effect of tenoxicam vs other NSAIDs	1980-1990	Studies on OA treatment with tenoxicam and either prioxicam, diclofenac or indomethacin	4174: 3196 tenoxicam vs piroxicam; 757 tenoxicam vs diclofenac; 221 tenoxicam vs indomethacin	18 studies- all included studies had some of the following criteria: 1) random allocation 2) double-blinded 3) reported outcomes 4) sufficient numerica data for statistical analysis 5) min. 4 weeks of treatment

Evidence Table 1. Systematic reviews (cont.)

Author Year	(6) Characteristics of identified articles: populations	(7) Characteristics of identified articles: interventions	(8) Main results
Chou, et al 2006	Patients with OA for efficacy; any indication for safety	Oral analgesics. Agents of interest for this report include: celecoxib, diclofenac, diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate sodium, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, salsalate and sulindac	Efficacy: No statistically significant differences in efficacy were found when one non-selective NSAID was compared to another, or when a non-selective NSAID was compared to celecoxib Safety: Non-selective NSAIDs: No particular non-selective NSAID was associated with increased GI risk when compared to another non-selective NSAID; all non-selective NSAIDs appear to equally increase risk of serious GI events compared to non-use. For non-selective, non-naproxen NSAIDs, there was also no difference in CV risk. Based on limited evidence, the risk of CV events appears to be modestly lower for naproxen when compared to other non-selective NSAIDs and celecoxib. CV risk for naproxen was neutral compared to placebo based on indirect analysis. Celecoxib: Systematic reviews and many meta-analyses of short-term, low dose use celecoxib found fewer UGI complications when compared to non-selective NSAIDs. Data is mixed regarding CV risk and celecoxib. Some meta-analyses have found no increased risk associated with celecoxib use
Riedemann 1993	not reported	tenoxicam 20-40 mg/day vs. -piroxicam 20 or 40 mg/day (13 studies) or -diclofenac 100 mg/day (4 studies) or -indomethacin 75 mg/day	Efficacy: Tenoxicam vs piroxicam - Patients treated with tenoxicam were 1.46 (OR 1.46) times more likely to receive a "good" or "excellent" efficacy rating for outcome measures (generally Likert scale) than piroxicam patients (CI 1.08-2.03) Tenoxicam vs diclofenac - no SS difference between treatment groups (OR 1.23, 95% CI: 0.89-1.70) Tenoxicam vs indomethacin - no SS difference between treatment groups (rates not reported)

Evidence Table 1. Systematic reviews (cont.)

Author Year	(9) Subgroups	(10) Adverse events	(11) Comments
Chou, et al 2006	No evidence suggested a difference in efficacy based on age, gender or racial group For safety, there is an increased risk of GI and CV complications in elderly populations, however no particular non-selective NSAID appeared to be associated with an increased risk. One observational study found higher rate of death when celecoxib was compared to diclofenac and ibuprofen (compared to non-use, one additional death/year of treatment occurred for every 14 celecoxib pts, every 24 diclofenac pts, and every 45 ibuprofen pts)	see Main Results	
Riedemann 1993	not reported	Specific AEs were not reported for any interventions. There was no SS difference in percentages of patients reporting adverse events for tenoxicam vs. piroxicam or tenoxicam vs diclofenac. For tenoxicam vs indomethacin (2 studies) there was a SS lower rate of AEs for tenoxicam (pooled risk -0.27, p=0.0002.) Number of dropouts due to AEs was 17% lower with tenoxicam vs piroxicam. For tenoxicam vs diclofenac and tenoxicam vs indomethacin, so SS difference was reported in dropouts.	One study (tenoxicam 40 mg/day vs piroxicam 40mg/day) was excluded from efficacy anlysis for an unspecified reason

Evidence Table 1. Systematic reviews (cont.)

Sorkin EM, Brogden RN 1985	Review of pharmacological properties and therapeutic efficacy in RA, OR and other rhuematic diseases	? - 1985	Not specified, although all published studies of tiaprofenic acid appear to be included	Not specified	Open label and randomized controlled trials - unspecified number of short-term (< 3 mos) studies

Evidence Table 1. Systematic reviews (cont.)

Sorkin EM, Brogden RN 1985	Patients with RA, OA, "other rheumatic diseases"	tiaprofenic acid 600 mg/day vs: aspirin 3600 mg/day diclofenac 150 mg/day ibuprofen 1200 mg/day indomethacin 75-105 mg/day naproxen 500 mg/day piroxicam 20 mg/day sulindac 300 mg/day placebo	Similar effectiveness vs. all comparators except placebo - more effective that placebo Pooled data not provided; absolute values not provided

Evidence Table 1. Systematic reviews (cont.)

Sorkin EM, Brogden RN 1985	not reported	Statistically significant percentage of patients reported fewer GI side effects with tiaprofenic acid v indomethacin (3.7% v 7.8% nausea and vomiting; 9.5% v 23.4% dyspepsia or other GI) Similar rates of AEs for other comparators	

Evidence Table 2. Randomized controlled trials

(limited to studies not included in Chou, et al 2006)

Trial	Subjects	Interventions	Duration (weeks)	Aspirin permitted?	Efficacy measures
Scott, et al 2000	812 randomized patients with knee OA: 307 tiaprofenic acid; 202 indomethacin; 303 placebo.	tiaprofenic acid (300 mg BID) indomethacin (25 mg TID) placebo	4 wks - 5 yrs	yes (dose not specified)	VAS and Likert scale
Calin, et al 1988	109 randomized patients with OA, followed by crossover	tiaprofenic acid SR 600 mg/day indomethacin SR 75 mg/day	4 wks each intervention with min 3 day washout	not stated	VAS

Evidence Table 2. Randomized-controlled trials (cont.)

Trial	Withdrawals	Other outcomes
Scott, et al 2000	All indomethacin patients were withdrawn at an unspecified point due to significantly higher rates of radiologic progression when compared to tiaprofenic acid and placebo Withdrawal rates were similar for tiaprofenic acid (47%), indomethacin (50%) and placebo (46%) at 48 wks.	No serious AEs reported. Most common AE was GI events, experienced by 46% of tiaprofenic acid patients, 47% of indomethacin patients and 32% of placebo patients. No SS differences in efficacy were observed for tiaprofenic acid vs indomethacin. Both were similarly efficacious short-term (at 4 wks, 43% and 45% pf patients showed improvement respectively) and both showed decreased efficacy in the long-term (at 1 yr, 39% and 36% respectively.)
Calin, et al 1988	19.6% of tiaprofenic acid patients and 13.3% of indomethacin patients- 58% of TA withdrawals and 77% of indomethacin withdrawals due to side effects 68% of TA withdrawals and 31% of indomethacin withdrawals also cited lack of efficacy	No serious AEs reported. Non-serious AEs were similar for both interventions including GI, central nervous system and dermatological events were most common.

Evidence Table 2. Randomized controlled trials (cont.)

Trial	Subjects	Interventions	Duration (weeks)	Aspirin permitted?	Efficacy measures
Maccagno, et al 1988	80 randomized knee OA patients: 40 TA patients, 39 piroxicam patients and 1 not stated	tiaprofenic acid 300 mg tid piroxicam 40 mg/day	2 wks - evaluation at 7 and 14 days	not stated	physician evaluated pain relief

Evidence Table 2. Randomized controlled trials (cont.)

Trial	Withdrawals	Other outcomes
Maccagno, et al 1988	The tiaprofenic acid group had a higher percentage of patients with "marked or complete" alleviation/recovery (68.5% for pain, 68.6% for functional recovery) compared to the piroxicam group that had a higher percentage of patients with no or slight alleviation/recovery (64.7% for pain and 63.6% for functional recovery)	Similar number of patients reported side effects (20% TA and 20.5% piroxicam) with no serious AEs reported

Evidence Table 3. Observational studies

(limited to studies not included in Chou, et al 2006)

Author, Year Data source Sample size	Population	Exposure (days)	Dose	Outcome
Buchbinder, 2000 Australian Adverse Drug Reactions Advisory Committee 190 (case-control study: 81 cases and 109 controls)	81 cases of suspected tiaprofenic-induced cystitis; 109 matched controls (based on tiaprofenic acid use within the previous 12 mos	Median 6.3 mos (0.1 - 47.1 mos)	Median cumulative dose 196.4 g (33.6 - 604.8 g)	Based on controls, cystitis likely tiaprofenic acid induced