



TITLE: Non-steroidal Anti-inflammatory Drugs for Pain: A Review of Safety

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CONTEXT AND POLICY ISSUES

Non-steroidal anti-inflammatory drugs (NSAIDs) play an important role in the pain management in various clinical conditions such as headaches, menstrual disorders, postoperative pain, spinal and soft tissue pain, rheumatoid arthritis (RA), osteoarthritis (OA), and ankylosing spondylitis (AS) by blocking cyclooxygenase (COX) enzymes that are needed to produce prostaglandin.^{1,2} There are two COX isoenzymes, COX-1 and COX-2. COX-1 mediates the mucosal protection of the gastrointestinal (GI) mucosa, while COX-2 is found throughout the body, including joints and muscle, and mediates effects on pain and inflammation. By blocking COX-2, NSAIDs reduce pain from different etiologies.³

NSAIDs that block both COX-1 and COX-2 enzymes are classified as non-COX-2 selective NSAIDs (nsNSAIDs) and can cause GI bleeding. NSAIDs that target only the COX-2 enzyme, such as celecoxib, are called COX-2 selective NSAIDs and are deemed safer with regards to GI bleeding than nsNSAIDs.^{3,4} Studies have found, however, that COX-2 NSAIDs such as celecoxib may increase the risk of cardiovascular (CV) adverse events.^{5,6}

A number of factors, including the pending availability of generic versions of celecoxib, have prompted jurisdictions to reassess the formulary listings of all available NSAIDs. The purpose of this report is to review the safety evidence regarding the use of all NSAIDs with the focus of celecoxib and diclofenac in patients being treated for pain.

In this review, we included one COX-2 selective NSAID, celecoxib, as this is the only selective NSAID currently available in Canada. Partially selective NSAIDs (such as etodolac, meloxicam and nabumetone) and non-selective NSAIDs (such as diclofenac, ibuprofen, naproxen, diflunisal, fenoprofen, flurbiprofen, indomethacin, ketoprofen, ketorolac, meclofenamate sodium, mefenamic acid, oxaprozin, piroxicam and sulindac)³ were grouped as nsNSAIDs in this report.

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RESEARCH QUESTION

What is the comparative safety of non-steroidal anti-inflammatory drugs when used for the management of pain?

KEY FINDINGS

In pain management, celecoxib and non-selective NSAIDs seem to have a similar overall risk of major cardiovascular adverse events even though cardiovascular risk was reportedly statistically significantly higher in celecoxib compared with naproxen. Statistically significantly fewer gastrointestinal adverse events were reported with the use of celecoxib compared with non-selective NSAIDs in the short term. Different non-selective NSAIDs appear to be associated with similar risks of serious gastrointestinal events. All non-selective NSAIDs except for naproxen were associated with similar risks of serious cardiovascular events.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2013, Issue 6), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments (HTA), systematic reviews (SR), meta-analyses (MA), randomized controlled trials (RCT) and non-randomized studies containing safety data. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2008 and July 19, 2013.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications, and evaluated the full-text publications for the final article selection, according to the selection criteria present in Table 1.

Table 1: Selection Criteria

Population	Any patient being treated for pain
Intervention	Non-steroidal anti-inflammatory drugs (NSAIDs)
Comparator	Other NSAIDs
Outcomes	Clinical harm, safety (such as CV risk, GI events)
Study Designs	Health technology assessment, systematic review / meta-analysis, randomized controlled trial or non- randomized controlled trial.

CV = cardiovascular; GI = gastrointestinal; NSAIDs = non-steroidal anti-inflammatory drugs.

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria or if they were summarized in an included SR. In addition, SRs that were deemed to have incomplete reporting of adverse event outcomes, or were less current than other SRs included in this report, were excluded.

Critical Appraisal of Individual Studies

The quality of the included SR and HTA were assessed using the Assessment of Multiple Systematic Reviews (AMSTAR) tool.⁷ A numeric score was not calculated for each study. Instead, the strengths and weakness of each study were summarized and described.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search from January 1, 2008 and July 19, 2013, yielded 275 citations. Upon screening titles and abstracts, 270 citations were excluded, and 5 potentially relevant articles were retrieved for full-text review. In addition, eight potentially relevant reports retrieved from other sources (such as grey literature, hand search). Of the 13 potentially relevant reports, seven did not meet the inclusion criteria, and thus six reports were included in this review.^{1-3,8-10} The study selection process is outlined in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart (Appendix 1). Five SRs^{2,3,8-10} and one HTA¹ met the inclusion criteria. No additional relevant RCTs or non-RCTs were identified.

Summary of Study Characteristics

Two SRs^{2,3} and were conducted in the USA; one SR⁹ in Canada, the UK and Australia; one HTA¹ and one SR⁸ in the UK, and one SR¹⁰ in Switzerland. The populations included in the SRs were patients with OA, RA or other conditions in need of pain management. Commonly studied NSAIDs included celecoxib, diclofenac, naproxen, ibuprofen, meloxicam and etodolac. Safety outcomes focused on cardiovascular risks and GI complications. The quality assessment tools used in the included SRs were AMSTAR⁷ for SRs,³ the Jadad Scale¹¹ for RCTs,¹ Newcastle–Ottawa Scale¹² for observational studies,⁹ or self-defined criteria.^{2,8,10} Two large RCTs, CLASS and SUCCESS-1, were included in four^{1-3,10} of six SRs. The characteristics of the included studies are outlined in Appendix 2 and briefly described below.

In a recently (May, 2013) published systematic review/meta-analysis by the Celecoxib and Traditional NSAID Trialists' (CNT) Collaboration,⁸ vascular and upper gastrointestinal (UGI) effects of NSAIDs were evaluated based on meta-analyses of individual participant data from randomized trials, including 474 trials comparing one NSAID with another (229,296 participants, 165,456 person-years). High-dose nsNSAIDs (diclofenac 150 mg daily, ibuprofen 2400 mg daily, or naproxen 1000 mg daily) were used in the included primary studies. The main outcomes were major cardiovascular (CV) events (non-fatal myocardial infarction, non-fatal stroke, or vascular death); major coronary events (non-fatal myocardial infarction or coronary death); stroke; mortality; heart failure; and UGI complications (perforation, obstruction, or bleed).

In 2011, McGettigan et al.⁹ performed a systematic review of community-based controlled observational studies. Comprehensive literature searches were conducted. Adjusted relative risk (RR) estimates were extracted and the estimates for major CV events (including acute

myocardial infarction, coronary heart disease–related death, or a composite of myocardial infarction and coronary heart disease death etc) associated with use of individual NSAIDs were pooled based on different doses of NSAIDs, and in populations with low and high background risks of CV events. The comparative safety of individual drugs were pooled and reported as ratios of RRs in pair-wise comparisons. Thirty case-control studies included 184,946 CV events, and 21 cohort studies described outcomes in more than 2.7 million exposed individuals.

In a network meta-analysis, Trelle et al.¹⁰ evaluated the cardiovascular safety of different NSAIDs. Large scale RCTs published before July 2009 were identified from multiple sources. The primary outcome was fatal or non-fatal myocardial infarction (MI). The secondary outcomes were hemorrhagic or ischemic fatal or non-fatal stroke, cardiovascular death, death from any cause, and a composite outcome of non-fatal MI, non-fatal stroke or cardiovascular death. The methodological quality of each included study was considered high. A Bayesian random effects model was used to calculate the pooled rate ratios using direct (head-to-head) and indirect evidence. The patients were followed for 12 to 65 weeks in these studies.

A comparative effectiveness review conducted by Agency for Healthcare Research and Quality (AHRQ)³ was an update of a previous report published in 2006 that assessed the comparative safety of NSAIDs for patients with OA. The authors replicated the comprehensive search of the scientific literature conducted for the original review to identify relevant studies published between 2005 and January 2011. Systematic reviews and controlled trials pertinent to the comparative efficacy and safety of the study drugs in patients with OA were evaluated for inclusion. RCTs that compared one included drug to another active comparator or placebo, and non-RCTs, such as cohort and case-control studies with at least 1,000 cases or participants and that evaluated serious GI and CV endpoints inadequately addressed by RCTs, were included. Non-English language studies were excluded. Thirty-three articles that compared the clinical benefits and harms of OA treatment with various oral medications were included.

An update of a previous Drug Effectiveness Review Project (DERP) review was conducted by Peterson et al. in 2010 to compare the safety profiles of various NSAIDs, including celecoxib and nsNSAIDs, in the treatment of chronic pain from OA, RA, soft tissue pain, back pain, and AS.² Systematic reviews, controlled clinical trials and observational studies were included for the purpose of the safety review. A comprehensive literature search was performed to identify relevant articles between 1996 and June 2010 from different sources. Non-English language publications were excluded. The safety outcomes included risk of serious GI events and serious CV events. The internal validity of included studies was assessed based on predefined criteria. There were 31 studies included in the update.

An HTA performed by Chen et al. assessed the adverse events associated with COX-2 selective NSAIDs and nsNSAIDs in patients with OA or RA.¹ Electronic databases were searched up to November 2003 for relevant RCTs. Celecoxib was compared with nsNSAIDs. Adverse events included CV risk and UGI events.

Summary of Critical Appraisal

The details on the critical appraisal of individual studies are presented in Appendix 3.

Overall, the included HTA, SRs and MAs were well-conducted, with explicit research questions and selection criteria. Multiple databases were searched. In three SRs,^{2,6,10} the quality of the primary studies was appraised using predefined quality assessment instruments. Conflicts of

interests and funding sources were recorded. Three^{2,3,10} SRs were funded from non-industry research grants. The authors of the HTA reported receiving funding from the manufacturer of celecoxib. The results were not reported in sufficient detail in two SRs.^{4,10} For instance, the characteristics of the primary studies were not described⁸ or the data were presented graphically without providing actual values.¹⁰ Two SRs^{8,9} provided synthesized data (pooled data). The remaining reviews presented a narrative summary of the results from each included study.¹⁻³

Summary of Findings

Comparative safety of celecoxib versus nsNSAIDs

The results of safety outcomes for celecoxib versus nsNSAIDs are presented in Table 2, Table 3 and Appendix 4.

Celecoxib vs. diclofenac:

In the systematic review of RCTs by the CNT Collaboration,⁸ no statistically significant differences were identified between celecoxib and high dose diclofenac in major vascular events (relative risk [RR] 0.97, 95% confidence interval [CI]: 0.84 to 1.12); heart failure (RR: 1.23, 95%CI: 0.87 to 1.73), all-cause mortality (RR: 1.02, 95%CI: 0.84 to 1.24) and UGI complications (RR: 0.94, 95%CI: 0.72 to 1.24) (Table 2). Similarly, the network meta-analysis of RCTs conducted by Trelle et al.¹⁰ reported no statistically significant differences between groups in total CV adverse events, but diclofenac had a statistically significantly higher risk for stroke when compared with celecoxib

In the systematic review of observational studies by McGettigan et al.⁹ a marginal statistically higher risk of adverse CV events (acute MI, coronary heart disease [CHD]–related death, composite of MI and CHD death or stroke only) was reported in the patients treated with diclofenac compared with celecoxib. The pooled ratio of RR for diclofenac versus celecoxib was reported as 1.15 (99%CI: 1.02 to 1.30) (Table 3).

Celecoxib vs. ibuprofen:

There were no statistically significant differences identified between celecoxib and ibuprofen in major vascular events (RR: 0.92, 95%CI: 0.58 to 1.46); heart failure (RR: 0.83, 95%CI: 0.42 to 1.64) and all-cause mortality (RR: 0.78, 95%CI: 0.43 to 1.42) based on pooled data from RCTs.⁸ However, the overall risk of UGI complications was 60% less those treated with celecoxib than ibuprofen (RR: 0.40, 95%CI: 0.25 to 0.64) (Table 2).⁸

No statistically significant difference was found between celecoxib and ibuprofen in the risk of CV adverse events in the network meta-analysis, by Trelle et al.¹⁰

Celecoxib vs. naproxen:

The overall combined risk of major vascular events was statistically significantly higher in celecoxib than that in naproxen (RR 1.49, 95%CI: 1.16 to 1.92) in one SR of RCTs.⁸ Of the major vascular events, the risk of MI or CHD death was higher for celecoxib versus naproxen (RR: 2.11, 95%CI: 1.44 to 3.09), while no statistically significant difference was found between groups in terms of the other individual CV risks, such as non-fatal MI, coronary death, non-fatal

stroke, stroke death, any stroke or other vascular death (Table 2).⁸ The risk of UGI complications was 63% lower in the patients treated with celecoxib compared with naproxen (RR :0.37, 95%CI: 0.28 to 0.49) (Table 2).⁸

The network meta-analysis by Trelle et al.,¹⁰ reported no statistically significant increased risk of MI, cardiovascular death, death of any cause or composite CV outcomes for celecoxib versus naproxen. (See Appendix 4).

Celecoxib vs. nsNSAIDs (as a drug class):

In the AHRQ and DERP reviews, it was reported that celecoxib may offer a short-term advantage over nsNSAIDs in terms of GI adverse events; however this has not been confirmed in studies with duration longer than six months. As for CV adverse events, celecoxib was not significantly different from nsNSAIDs in the incidence of MI, other CV events, or cerebrovascular events.^{2,3}

Table 2: Comparative CV and GI adverse events based on pooled RCTs: Celecoxib vs. nsNSAIDs

Outcome	Relative risk (95%CI)		
	Celecoxib vs. diclofenac	Celecoxib vs. ibuprofen	Celecoxib vs. naproxen
Major vascular events			
Non-fatal MI	1.09 (0.87–1.36)	0.91 (0.43–1.94)	2.02 (1.35–3.02)
Coronary death	0.71 (0.38–1.32)	0.41 (0.06–2.95)	2.46 (0.71–8.50)
MI or CHD death	1.04 (0.84–1.28)	0.81 (0.41–1.61)	2.11 (1.44–3.09)*
Non-fatal stroke	0.86 (0.65–1.15)	1.00 (0.43–2.33)	1.19 (0.76–1.86)
Stroke death	1.47 (0.78–2.80)	NE	0.89 (0.21–3.81)
Any stroke	0.92 (0.71–1.20)	1.00 (0.44–2.25)	1.14 (0.74–1.73)
Other vascular death	0.93 (0.68–1.27)	1.11 (0.32–3.84)	1.49 (0.74–3.00)
Subtotal: major vascular events	0.97 (0.84–1.12)	0.92 (0.58–1.46)	1.49 (1.16–1.92)*
Heart failure	1.23 (0.87–1.73)	0.83 (0.42–1.64)	1.17 (0.76–1.79)
Cause-specific mortality			
Vascular	0.96 (0.74–1.23)	0.83 (0.32–2.16)	1.53 (0.89–2.62)
Non-vascular	1.05 (0.75–1.46)	0.49 (0.03–9.27)	1.61 (0.54–4.77)
Unknown cause	1.96 (0.71–5.42)	0.79 (0.34–1.84)	0.90 (0.52–1.57)
Subtotal: Any cause mortality	1.02 (0.84–1.24)	0.78 (0.43–1.42)	1.23 (0.86–1.75)
Upper gastrointestinal complications			
Bleed	1.01 (0.75–1.36)	0.55 (0.24–1.30)	0.34 (0.23–0.49)*
Perforation	0.42 (0.13–1.37)	NE	0.78 (0.17–3.61)
Obstruction	1.18 (0.20–7.00)	NE	NE
Unknown	0.76 (0.22–2.68)	0.32 (0.18–0.58)*	0.39 (0.25–0.60)*
Subtotal: any UGI complication	0.94 (0.72–1.24)	0.40 (0.25–0.64)*	0.37 (0.28–0.49)*

CHD = coronary heart disease; CI=confidence interval; MI = myocardial infarction; NE=not estimated; nsNSAIDs=non-specific non-steroidal anti-inflammatory drugs; RCT=randomized controlled trials; UGI=upper gastrointestinal

*Indicates statistically significant
Data source: CNT Collaboration⁸

Comparative Safety of nsNSAIDs versus other nsNSAIDs

In terms of overall CV risk including acute MI, CHD-related death, composite of MI and CHD death or stroke only, McGettigan et al.⁹ reported that diclofenac had a statistically significantly higher risk than ibuprofen and naproxen (Table 3). The pooled ratio of RR (99%CI) were 1.13 (1.03 to 1.24) and 1.22 (1.11 to 1.35) for diclofenac versus ibuprofen and naproxen,

respectively.⁹ Etodolac was not significantly different from diclofenac, naproxen or ibuprofen in CV risk. Naproxen had a significantly lower risk of CV events than diclofenac, ibuprofen, [ratio of RR (99%CI): 0.92 (0.87 to 0.99)] and indomethacin (Table 3). The RR estimates were consistent across different subgroups based on background risks for cardiovascular disease in the SR of observational studies.⁹

In AHRQ’s systematic review, it was reported that meloxicam (7.5 mg/day) and etodolac (600 mg/day) were associated with a statistically significantly lower risk of ulcer complications or symptomatic ulcers (RR 0.53, 95% CI: 0.29 to 0.97 and RR 0.32 95% CI: 0.15 to 0.71) for meloxicam and etodolac respectively, compared to nsNSAIDs as a drug class.³

Table 3: Comparative CV adverse events based on observational studies

Intervention	Intervention vs. comparators (ratio of RR [99%CI])			
	Diclofenac	Ibuprofen	Naproxen	Celecoxib
Etodolac	0.95 (0.78, 1.16)	1.04 (0.88, 1.24)	1.10 (0.96, 1.26)	NR
Diclofenac	--	1.13 (1.03, 1.24)	1.22 (1.11, 1.35)	1.15 (1.02, 1.30)
Naproxen	--	0.92 (0.87, 0.99)	--	0.96 (0.81, 1.13)
Meloxicam	NR	NR	1.11 (1.0, 1.23)	NR
Indomethacin	NR	NR	1.23 (1.10, 1.39)	NR

CI=confidence interval; NR=not reported; RR = relative risk; Values are pooled ratio of RRs and 99% CIs.

* CV adverse events included pooled risk of acute myocardial infarction, coronary heart disease–related death, or a composite of myocardial infarction and coronary heart disease death etc).

Data source: McGettigan et al⁹

Limitations

The HTAs, MA, and SRs included in this report examined data from numerous primary studies or systematic reviews of RCTs and non-randomized studies. While the methodological quality of most included SRs are good, the various important limitations of the body evidence presented in this report do exist. Firstly, there were some overlap of primary studies or SRs due to the similar selection criteria (population: adult patients with OA or RA; intervention: COX-2 selective NSAIDs; comparators: nsNSAIDs; outcome measures: adverse events) adopted by these SRs. For example, two large RCTs, CLASS and SUCCESS-1, were included in four^{1-3,10} of six studies. It is challenging to summarize such data due to the possibility of overestimating the benefits or harms of celecoxib if these data were repeatedly used. To help avoid this issue, we focused our summary on the results of three high quality reports that used different data sources.^{3,8,9} Secondly, the classification of NSAIDs was inconsistent between the systematic reviews, and agents such as etodolac and meloxicam were classified as COX-2 NSAIDs in the HTA report by Chen.¹ However, both etodolac and meloxicam were classified as partially selective NSAIDs in the SRs by AHRQ³ and DERP.² Thirdly, some COX-2 agents, such as rofecoxib, etoricoxib, valdecoxib and lumiracoxib, which were discontinued or were never marketed in Canada, were presented in some of the included SRs.^{1,9} Furthermore, the study durations in the primary clinical trials were generally less than three months. The lack of long-term data regarding GI, CV and other serious adverse events limited our ability to accurately determine the true risk of harms. Finally, high-dose nsNSAIDs (diclofenac 150 mg daily, ibuprofen 2400 mg daily, or naproxen 1000 mg daily) was used in the SR/MA by the Celecoxib and traditional NSAID Trialists' (CNT), which might constitute a potential bias in favor of celecoxib in terms of evaluating comparative safety between celecoxib and nsNSAIDs.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Numerous studies have been conducted that examined the safety of celecoxib and non-selective non-steroidal anti-inflammatory drugs (nsNSAIDs) in the past five years. In total, five systematic reviews and one health technology assessment were included in this review. Most of these studies evaluated the use of celecoxib and nsNSAIDs in patients with osteoarthritis and rheumatoid arthritis.

It was found that the combined risk of major vascular events (including non-fatal myocardial infarction, non-fatal stroke or vascular death) were similar for celecoxib, diclofenac or ibuprofen, but there was some evidence of increased risk for celecoxib compared with naproxen. Celecoxib compared with nsNSAIDs (as a drug class) seems to be associated with a similar risk of cardiovascular adverse events, heart failure, or all-cause mortality.

Compared to nsNSAIDs, celecoxib was reportedly associated with statistically significantly fewer gastrointestinal (GI) adverse events including GI bleeding or ulcers, within 6 months of treatment. Comparisons between individual nsNSAIDs showed similar risks of serious GI events, and all except naproxen (with lower serious CV risk), were associated with similar risks of serious CV events.

These findings should be interpreted with caution given the important limitations of the body evidence, such as short study duration (< 3 months) and different nsNSAID doses used in the primary studies. The systematic reviews used different inclusion criteria (randomized controlled trials vs. observational studies) and different pooling methods which produced inconsistent results for some comparisons. In addition, overlapping included studies among the systematic reviews may overestimate confidence in findings.

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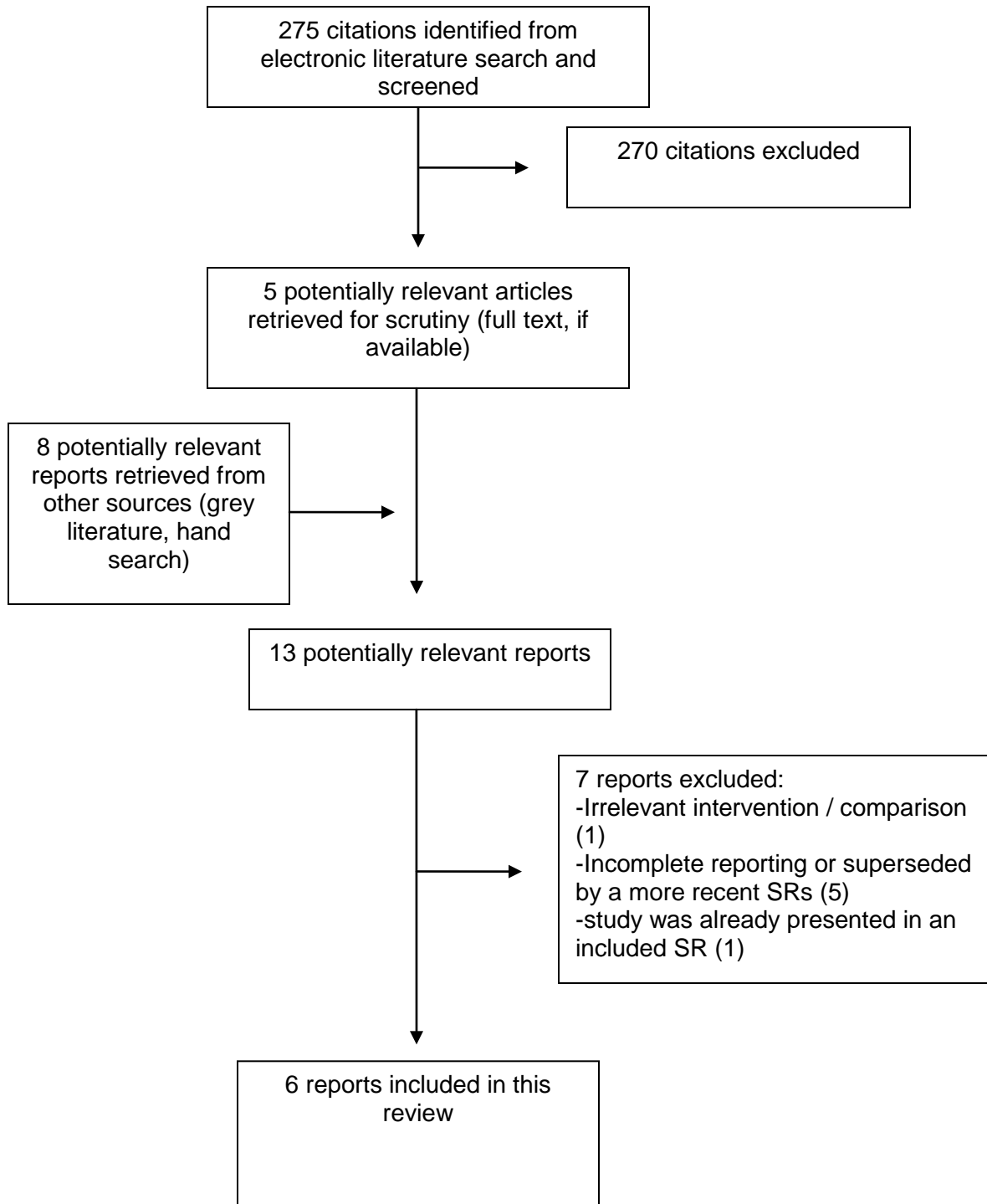
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APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included studies

First Author, Publication Year, Country	Study Design (Numbers of trials and patients)	Patient Characteristics	Intervention	Comparator(s)	Main Outcomes
Celecoxib and traditional NSAID Trialists' (CNT) Collaboration, 2013, UK ⁸	SR (474 RCTs including 229, 296 patients).	Patients using NSAIDs	Celecoxib nsNSAIDs	Diclofenac Ibuprofen Naproxen	CV risk GI risk mortality heart failure
McGettigan, 2011, Canada, UK, Australia ⁹	SR (30 case-control studies included 184,946 CV events, and 21 cohort studies included 2.7 million patients)	Patients using NSAIDs	Celecoxib, nsNSAIDs	nsNSAIDs	CV risk
Trelle, 2011, Switzerland ¹⁰	SR (31 trials in 116,429 patients)	Patients with OA or RA	Celecoxib nsNSAIDs	nsNSAIDs	CV risk All-cause mortality
AHRQ, 2011, US ³	SR (including SRs, RCTs, cohort and case control studies)	Adults with OA	Celecoxib nsNSAIDs	nsNSAIDs,	AEs (CV and GI events, etc.)
Peterson, 2010, US ²	SR (SRs, controlled trials; observational studies)	Patients with OA, RA, soft tissue pain, back pain and AS	Celecoxib nsNSAIDs	nsNSAIDs	AEs (CV and GI, events, etc.)
Chen, 2008, UK ¹	HTA (SR of RCTs)	Patients with OA or RA	Celecoxib nsNSAIDs	nsNSAIDs	AEs (CV and GI events)

AHRQ=Agency for Healthcare Research and Quality; AS=ankylosing spondylitis; CV=cardiovascular;; GI=gastrointestinal; HTA=health technology assessment; MA=meta-analysis; MI=myocardial infarction; NSAID=non-steroidal anti-inflammatory drug; nsNSAID=non-COX-2 selective NSAID; OA=osteoarthritis; RA=rheumatoid arthritis; RCT=randomized controlled trial; SR=systematic review.

APPENDIX 3: Critical Appraisal of Included Studies

First Author, Publication Year	Strengths	Limitations
Celecoxib and traditional NSAID Trialists' (CNT) Collaboration, 2013, UK ⁸	<ul style="list-style-type: none"> • Research questions and selection criteria were defined and presented • Comprehensive literature search • Two independent investigators performed study selection, and data extraction • Appropriate methods for data synthesis • Conflict of interests declared 	<ul style="list-style-type: none"> • List of included and excluded studies not provided • Unclear if there was a limit on language in literature search • Quality assessment of the included studies was not described
McGettigan, 2011, Canada, USA, Australia ⁹	<ul style="list-style-type: none"> • Research questions and selection criteria were defined and presented • Comprehensive literature search • Two independent investigators performed study selection, and data extraction • List of included studies provided • Appropriate methods for data synthesis • Conflict of interests declared 	<ul style="list-style-type: none"> • Excluded studies not listed • Quality assessment of the included studies was not provided
Trelle, 2011, Switzerland ¹⁰	<ul style="list-style-type: none"> • Research questions and selection criteria were defined and presented • Comprehensive literature search • Two independent investigators performed study selection and data extraction • List of included studies provided • Appropriate methods for data synthesis • Conflict of interests declared 	<ul style="list-style-type: none"> • Unclear if there was a limit on language in literature search • List of excluded studies not provided • Quality assessment of the included studies was not described • Results were not reported in sufficient details
AHRQ, 2011, USA ³	<ul style="list-style-type: none"> • Research questions and selection criteria were defined and presented • Comprehensive literature search based on pre-defined criteria • Quality assessment on the included studies • At least 2 independent investigators performed study selection, and quality assessment • Results were reported in sufficient details • Conflict of interests declared 	<ul style="list-style-type: none"> • Most of the RCTs in SRs evaluated short-term use of celecoxib • Non-English language studies were excluded
Peterson, 2010, USA ²	<ul style="list-style-type: none"> • Research questions and selection criteria were defined and presented • Comprehensive literature search based on pre-defined criteria • Quality assessment on the included studies • At least 2 independent investigators performed study selection, and quality assessment • Conflicts of interest declared 	<ul style="list-style-type: none"> • Non-English language studies were excluded • No description of trial characteristics
Chen, 2008, UK ¹	<ul style="list-style-type: none"> • Research questions and selection criteria were defined and presented 	<ul style="list-style-type: none"> • The last search date was 2003 which may be considered out of date

First Author, Publication Year	Strengths	Limitations
	<ul style="list-style-type: none"> • Comprehensive literature search with no limit on language • Quality assessment on the included studies • Two reviewers conducted the study selection; data extraction and quality assessment were carried out by 1 reviewer and verified by another • Conflict of interests declared 	<ul style="list-style-type: none"> • Some trial data that were commercial-in-confidence were removed; therefore not all the data were available for review

APPENDIX 4: Main Study Findings and Authors' Conclusions – Safety

First Author, Publication Year	Main Study Findings	Authors' Conclusions
CNT Collaboration, 2013, UK ⁸	<p>CV risks: Detailed data was reported in Table 2</p>	<p><i>On page. 1</i> (interpretation): "The vascular risks of high-dose diclofenac, and possibly ibuprofen, are comparable to celecoxib, whereas high-dose naproxen is associated with less vascular risk than other NSAIDs."</p>
McGettigan, 2011, Canada, USA, Australia ⁹	<p>CV risk: Ratio of RR (99% CI) DIC vs. IBU: 1.13 (1.03 - 1.24) DIC vs. NAP: 1.22 (1.11- 1.35) DIC vs. Celecoxib: 1.15 (1.02 - 1.30)</p> <p>NAP vs. IBU : 0.92 (0.87- 0.99); NAP vs. Celecoxib: 0.96 (0.81-1.13)</p> <p>MEL vs. NAP : 1.11 (1.0 - 1.23)</p> <p>IND vs. NAP: 1.23 (1.10 - 1.39)</p>	<p><i>On page. 1:</i> "This review suggests that among widely used NSAIDs, naproxen and low-dose ibuprofen are least likely to increase CV risk. Diclofenac in doses available without prescription elevates risk..."</p>
Trelle, 2011, Switzerland ¹⁰	<p>Results were reported graphically. <u>Celecoxib vs. nsNSAIDs</u> The figures showed that there were no statistically significant differences between celecoxib vs. naproxen, ibuprofen or diclofenac with respect to MI, CV death, all-cause death and stroke (except that celecoxib group had significantly fewer strokes compared with diclofenac). <u>nsNSAID vs. other nsNSAIDs:</u> data not extractable</p>	<p><i>On page. 1:</i> "Although uncertainty remains, little evidence exists to suggest that any of the investigated drugs are safe in cardiovascular terms. Naproxen seemed least harmful. Cardiovascular risk needs to be taken into account when prescribing any NSAID."</p>
AHRQ, 2010, USA ³	<p><u>Celecoxib vs. nsNSAIDs:</u> GI harms: Overall: Ulcer complications (RR 0.23, 95%CI: 0.07 - 0.76) Ulcer complications or symptomatic ulcers: (RR 0.39, 95%CI: 0.21 - 0.73) In the CLASS RCT: celecoxib vs. DIC or IBU for ulcer complications or symptomatic ulcers at 6-month follow-up (2.1% vs. 3.5%, p=0.02): no significant differences at 12-month follow-up. In SR of RCTs: celecoxib vs. nsNSAIDs: -Risk of GI AEs: RR 0.75 (95% CI: 0.70 - 0.80) -Withdrawals due to GI AEs: RR 0.45 (95% CI: 0.33 - 0.56) -Difference in risk of any AE or withdrawal due to any AE did not reach statistical significance.</p> <p>CV harms: No increase in the rate of CV events with celecoxib vs. ibuprofen or diclofenac in CLASS RCT (0.5% vs. 0.3%). A network meta-analysis of RCTs and 3 large observational studies did not find difference in risk of MI compared to naproxen, ibuprofen or diclofenac.</p> <p><u>One nsNSAID vs. another nsNSAIDs: (RR [95%CI])</u> GI harms: Reported in a SR: <i>MEL (7.5 mg/day) vs. other nsNSAIDs:</i></p>	<p><i>On page. VI:</i> "Each of the analgesics evaluated in this report was associated with a unique set of risks and benefits. Choosing the optimal analgesic for an individual with osteoarthritis requires careful consideration and thorough discussion of the relevant tradeoffs."</p>

First Author, Publication Year	Main Study Findings	Authors' Conclusions
	<p>- Risk of ulcer complications or symptomatic ulcers: RR 0.53 (95% CI: 0.29 - 0.97); - Risk of ulcer complications alone: RR 0.56 (95% CI: 0.27 - 1.2).</p> <p><i>ETO (600 mg/day) vs. other nsNSAIDs:</i> -Risk of ulcer complications or symptomatic ulcer: RR 0.32, (95% CI: 0.15 - 0.71); -Risk of ulcer complications alone: RR 0.39 (95% CI: 0.12 - 1.2)</p> <p>In large observational studies: naproxen was associated with a higher risk of serious GI harms than ibuprofen in 7 studies. Comparative data on GI harms with other nonselective NSAIDs was less consistent.</p> <p>CV harms: data not extractable.</p>	
<p>Peterson, 2010, USA²</p>	<p>Celecoxib vs. nsNSAIDs GI AEs: Short-term advantage for celecoxib, yet this has not been conclusively demonstrated in studies with ≥6 months follow-up: Serious GI complications (bleeding, perforations, stricture) at 6-month (CLASS): Celecoxib vs. nsNSAIDs: 2.08% vs. 3.54%, p=0.02; At 12-month, celecoxib, diclofenac and ibuprofen were associated with similar rates of ulcers (in the CLASS RCT)</p> <p>CV AEs: Celecoxib vs. nsNSAIDs: RR for risk of MI ranged from 1.51-1.60, 95%CI contained value of 1(MAs of RCTs that were primarily 12-week in duration).</p> <p>Risk of MI in 1 case-control study Celecoxib vs. naproxen: OR 0.95, 95%CI 0.74 -1.21; Celecoxib vs. ibuprofen: OR 0.98, 95%CI 0.76 -1.26;</p> <p><u>One nsNSAID vs. another nsNSAID</u></p> <p>No significant short-term (< 6 months) differences were found among oral NSAIDs,</p>	<p><i>On page 3:</i> "...for serious harms, celecoxib does not appear to be associated with higher risk of cardiovascular events and is gastroprotective in the short term compared with nonselective NSAIDs. These findings vary by subgroup, depending on age, recent history of gastrointestinal bleeding, and concomitant use of antiulcer medication. Different nsNSAIDs were associated with similar increased risks of serious gastrointestinal events, and all but naproxen was associated with similar increased risk of serious cardiovascular events..."</p>
<p>Chen, 2008, UK¹</p>	<p>Celecoxib vs. nsNSAIDs: All AEs: RR (95%CI): 0.90 (0.78 -1.04) Clinical upper GI events: RR (95%CI): 0.55 (0.40 - 0.76) Complicated UGI events: RR (95%CI): 0.57 (0.35 - 0.95) Risk of MI: RR(95%CI): 1.77 (1.00 - 3.11)</p> <p><u>One nsNSAID vs. another nsNSAID</u> Pooled analysis did not show a difference in complicated UGI events: RR (95%CI) :0.39 (0.12 - 1.24)</p> <p>ETO vs. nsNSAIDs: -UGI events: RR (95%CI): 0.32 (0.15 - 0.71) MI: NO MI were reported</p>	<p><i>On page. Xi:</i> "...Although COX-2 selective NSAIDs offer protection against serious GI events (i.e. perforation, ulcer or bleed: refers to symptomatic ulcers and complicated UGI events combine) the amount of evidence for this protective effect varied considerably across individual drugs. The volume of trial evidence with regard to cardiovascular safety also varied substantially between COX-2 selective NSAIDs. Increased risk of MI compared to non-selective NSAIDs was observed among those drugs with</p>

First Author, Publication Year	Main Study Findings	Authors' Conclusions
	MEL vs. nsNSAIDs: clinical UGI events: RR (95%CI): 0.53 (0.29 - 0.97) MI: insufficient events to be analyzed	greater volume of evidence in terms of exposure in patient-years."

AE = adverse event; CI = confidence interval; CNT=Celecoxib and Traditional NSAID Trialists' collaboration; CV = cardiovascular; DIC = diclofenac; ETO = Etodolac; HR = hazard ratio; MEL = Meloxicam; MI = myocardial infarction; NSAID = non-steroidal anti-inflammatory drug; nsNSAID = non-COX-2 selective NSAID; OR = odds ratio; RCT = randomized controlled trial; RRR = ration of relative risk. UGI = upper gastrointestinal.