TITLE: Celecoxib versus Non-COX-2 Selective Non-steroidal Anti-inflammatory Drugs: A Review of the Clinical Effectiveness, Safety, and Cost Effectiveness

DATE: 07 December 2011

CONTEXT AND POLICY ISSUES

Osteoarthritis (OA) is a chronic condition involving degeneration of cartilage within the joints. It is the most common form of arthritis and is associated with pain, substantial disability and poor quality of life. Rheumatoid arthritis (RA) is a systemic auto-immune disorder, involving persistent joint inflammation. Non-steroidal anti-inflammatory drugs (NSAIDs) play an important role in controlling the symptoms of arthritis including OA and RA, lower back pain and soft tissue pain, by blocking cyclooxygenase (COX) enzymes. Two COX isoenzymes, COX-1 and COX-2, have important roles in the effects of NSAIDs. COX-1 mediates the mucosal protection of the gastrointestinal (GI) mucosa, while COX-2 is found throughout the body, including joint and muscle and mediates effects on pain and inflammation. By blocking COX-2, NSAIDs reduce pain from different etiologies, such as arthritis, lower back pain, minor injuries and soft-tissue rheumatism. NSAIDs that block both COX-1 and COX-2 enzymes are called 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. Studies found, however, that they may increase the risk of cardiovascular (CV) adverse events. A number of nsNSAIDs, such as naproxen, ibuprofen and diclofenac, have been available in Canada since 1994. Celecoxib was approved by Health Canada in 1999.

Celecoxib is a commonly used COX-2 selective inhibitor and is indicated for the relief of symptoms associated with OA, RA and ankylosing spondylitis (AS). In recent years, more patients with OA or RA, who require anti-inflammatory treatment, are treated with celecoxib than nsNSAIDs. It is also indicated for the short-term (less than or equal to seven days) management of moderate to severe acute pain in adults with conditions such as musculoskeletal or soft tissue trauma including sprains, postoperative orthopedic, and pain following dental extraction. Celecoxib therapy was associated with higher costs. A UK study showed that in the first two years of treating AS, the drug costs were £685 for celecoxib as compared with £114 and £128 for diclofenac and naproxen, respectively. The gaps became

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smaller in five years, when the costs for celecoxib, diclofenac and naproxen were £5,043, £3,764 and £3,724, respectively. This change may have occurred because patients, who received nsNSAIDs and experienced adverse events, switched to more expensive treatments.  

The purpose of this report is to review the evidence regarding the use of celecoxib in adult patients with OA, RA or other diseases that require pain management. Its clinical effectiveness, safety, and cost-effectiveness are compared with those of nsNSAIDs. This report is an upgrade of a previous summary of abstracts, “Celecoxib versus Non-Selective Non-Steroidal Anti-Inflammatory Drugs: Clinical Effectiveness, Safety, and Cost Effectiveness”.

RESEARCH QUESTIONS

1. What is the comparative clinical effectiveness of celecoxib versus non-COX-2 selective non-steroidal anti-inflammatory drugs for pain management in adult patients?

2. What is the evidence for the safety of celecoxib compared with non-COX-2 selective non-steroidal anti-inflammatory drugs for pain management in adult patients?

3. What is the cost-effectiveness of celecoxib compared with non-COX-2 selective non-steroidal anti-inflammatory drugs for pain management in adult patients?

KEY MESSAGE

Evidence from five systematic reviews and one health technology assessment found that celecoxib had similar effects as non-COX-2 selective NSAIDs in pain relief. The results of cost-effectiveness were inconsistent across the identified economic evaluations.

METHODS

Literature Search Strategy

This report makes use of a literature search conducted for a previous CADTH report. The original literature search was conducted in September 2011 on key resources including PubMed, The Cochrane Library (2011, Issue 9), 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, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies containing safety data, and economic studies. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2006 and September 7, 2011. For the current report, the PubMed database search was rerun on November 9, 2011 to capture any articles published since the initial search date. The search of major health technology agencies was also updated to include documents published since September 2011.

Rapid Response reports are organized so that the evidence for each research question is presented separately.
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

<table>
<thead>
<tr>
<th>Population</th>
<th>Adult patients with osteoarthritis, rheumatoid arthritis or other conditions requiring pain management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Celecoxib</td>
</tr>
<tr>
<td>Comparator</td>
<td>Non-COX-2 selective NSAIDs</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Clinical effectiveness (for example, pain reduction)</td>
</tr>
<tr>
<td></td>
<td>Adverse events (for example, GI bleeding, ulcers, MI)</td>
</tr>
<tr>
<td>Study Designs</td>
<td>SR, HTA, RCT, non-RCT (safety only), and economic evaluations</td>
</tr>
</tbody>
</table>

| GI=gastrointestinal; HTA=health technology assessment; ICER=incremental cost-effectiveness ratio; MI=myocardial infarction; NSAID=non-steroidal anti-inflammatory drugs; RCT=randomized controlled trial; SR=systematic review |

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria, were duplicate publications, were abstracts or conference proceedings, were included in a selected systematic review, or were published prior to 2006.

Critical Appraisal of Individual Studies

The quality of the included SR and HTA were assessed using the Assessment of Multiple Systematic Reviews (AMSTAR) tool. Economic evaluation was assessed using the 35-item Drummond’s checklist. 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 November 9, 2011, yielded 38 citations. Upon screening titles and abstracts, nine citations were excluded, and 29 potentially relevant articles were retrieved for full-text review. Of the 29 potentially relevant reports, 23 did not meet the inclusion criteria, and thus six publications were included in this review. One additional relevant SR was identified from the grey literature search and was included. The study selection process is outlined in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart (Appendix 1). Five SRs, one HTA, and one cost-effectiveness analysis met the inclusion criteria. No relevant RCTs or non-randomized studies were identified.
Summary of Study Characteristics

Comparative Clinical Effectiveness and Safety of Celecoxib versus Nonselective COX-2 NSAIDs

Two of the SRs\textsuperscript{1,14} were conducted in the US, one HTA\textsuperscript{15} and one SR\textsuperscript{5} in the UK, one SR\textsuperscript{13} in Switzerland and one SR\textsuperscript{3} in Denmark. The study designs reviewed in these evidence-based studies included SRs, RCTs and non-RCTs. The quality assessment tools used were AMSTAR\textsuperscript{10} for SRs, the Jadad Scale\textsuperscript{17} for RCTs, the Downs and Black instrument\textsuperscript{18} for observational studies, or self-defined instruments\textsuperscript{3,14} to examine the completeness in data reporting, extent of heterogeneity of the primary study and whether there was a component of quality assessment in a certain SR.

The characteristics of the selected HTAs, SRs, and MAs are outlined in Appendix 2.

Trelle et al. evaluated the cardiovascular safety of different NSAIDs in a meta-analysis.\textsuperscript{13} Large scale RCTs that were published before July 2009 were identified from multiple sources. It is unclear whether there was a limit on language. The primary outcome was fatal or non-fatal myocardial infarction (MI), and 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 authors did not state whether quality assessment for each included study was performed. A Bayesian random effects model was used to calculate the pooled rate ratios. Celecoxib was investigated in 15 trials and compared with nsNSAIDs, other COX-2 selective inhibitors and placebo, for patients with OA or RA. The patients were followed for 12 to 65 weeks in these studies.

A comparative effectiveness review (CER) conducted by Agency for Healthcare Research and Quality (AHRQ)\textsuperscript{1} was an update of a previous report in 2006 that assessed the comparative efficacy and safety of nonopioid oral medications (selective and nonselective non-aspirin NSAIDs, aspirin, salsalate, and acetaminophen), over-the-counter supplements (chondroitin and glucosamine), and topical agents for OA. The authors replicated the comprehensive search of the scientific literature conducted for the original CER, with an updated date range from 2005 to January 2011 to identify relevant studies. Systematic reviews and controlled trials pertinent to the comparative efficacy and safety of the study drugs in patients with OA were evaluated for inclusion. Controlled trials included RCTs that compared one included drug to another, another active comparator, or placebo and non-RCTs, such as cohort and case-control studies, with at least 1,000 cases or participants that evaluated serious GI and CV endpoints that were inadequately addressed by RCTs. 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 effectiveness and safety profiles of various NSAIDs, including COX-2 inhibitors and nsNSAIDs, in the treatment of chronic pain from OA, RA, soft tissue pain, back pain, and AS.\textsuperscript{14} This review included controlled clinical trials and SRs for effectiveness assessment. Observational studies were included for the purpose of safety review only. 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 outcome measures of interest were pain control, functional status, discontinuations due to lack of effectiveness, risk of serious gastrointestinal (GI) events and serious cardiovascular
events. The internal validity was assessed based on predefined criteria. There were 31 studies included in the update.

Gotzsche et al. conducted a systematic review to investigate the differences between oral NSAIDs in the management of musculoskeletal disorders. The literature was systematically searched from 1966 to September 2009. Published systematic reviews and RCTs were included. The quality of the selected studies was assessed using predefined criteria such as the completeness of data reporting, quality of the included trials in SR, and the extent of heterogeneity of included trials in MA. The primary outcomes were pain intensity and clinically significant GI complications. The ACR 20 criteria were adopted to measure the clinical effectiveness. The criteria represent a 20 percent improvement in tender and swollen joint counts, as well as a 20 percent improvement in three of the following five measurements: patient assessment of disease, physician assessment of disease, patient assessment of pain, function (degree of disability measured by a questionnaire), and an acute phase reactant (for example, C-reactive protein or erythrocyte sedimentation rate).

An HTA performed by Chen et al. assessed the clinical and cost-effectiveness of COX-2 selective NSAIDs for OA or RA. Electronic databases were searched up to November 2003 for relevant RCTs, and January 2004 for various economic evaluations. Each COX-2 selective NSAID was compared with placebo, nsNSAIDs, or another COX-2 selective NSAID. The primary outcomes in the clinical review were pain intensity and adverse events. In the economic review, published economic evaluations of COX-2 selective NSAIDs and nsNSAIDs were reviewed. The cost-effectiveness of NSAIDs from the National Health Service (NHS) perspective was analysed using a Markov model, and the clinical parameters were based on the meta-analysis in this HTA (see Appendix 3). The time horizon was five years. There were 12 RCTs that compared celecoxib with nsNSAIDs included in the clinical review; 18 published economic analyses and models were identified from the literature search or provided by manufacturers in the economic review.

A meta-analysis conducted by Chen et al. evaluated the risk of myocardial infarction associated with the use of COX-2 selective inhibitors (coxibs). A comprehensive literature search was performed to identify relevant studies published from 1966 to June 2006. Double-blind RCTs of at least four weeks duration that compared a coxib with placebo, nsNSAIDs, or another coxib were included, without limits on language. The studies had to have a score of at least 2 out of 5 on a Jadad scale, a commonly used tool that evaluates the quality of RCT from the aspects of methods of randomization and blinding, and withdraw or dropouts, with 5 representing the highest quality, in order to be included in the MA. The primary outcome in the MA was MI including fatal and non-fatal events. In total, 55 RCTs were included in this review. Among them, 45 trials enrolled patients with OA or RA. Other populations were AS, chronic low back pain, colorectal adenomas and mild cognitive impairment or early Alzheimer’s disease.

**Cost-Effectiveness of Celecoxib versus Nonselective COX-2 NSAIDs**

The characteristics of the selected economic studies are outlined in Appendix 3.

An economic evaluation was conducted in Mexico to identify the most cost-effective first line pharmacological treatment for pain control in patients with OA. A SR of the literature was performed to identify studies published from 1994 to 2004, in English or Spanish. The cost-effectiveness of celecoxib 200mg twice daily, naproxen 500mg twice daily, diclofenac 100mg twice daily, piroxicam 20mg per day and acetaminophen 1000mg twice daily were compared
using a decision tree model, from the perspective of a Mexican institution. An incremental cost-effectiveness ratio (ICER) was calculated to answer the research questions. The clinical effectiveness measure used for this evaluation was the number of patients with pain control and no adverse event per 1,000 patients treated with any of the study drugs. Direct medical costs related to the study treatment alternatives were estimated. The time horizon was six months in this study.

**Summary of Critical Appraisal**

The details on the critical appraisal of individual studies are presented in Appendix 4.

Overall, the included HTA, SRs and MAs were well-conducted, with explicit research questions and selection criteria. Multiple databases were searched. In most SRs (n=5), the quality of the primary studies was appraised using predefined quality assessment instruments. Conflicts of interests and funding sources were recorded. Three SRs were funded from non-industry research grants. The authors of the HTA report received funding from the manufacturer of celecoxib. The primary RCTs had study durations that ranged from two to 65 weeks. The results were not reported in sufficient details in some SRs. For instance, the characteristics of the primary studies were not described or the data were presented graphically without providing actual values. There were overlaps in the data reported between the SRs. For example, both the DERP and AHRQ reviews included similar studies and reported the same results.

In both cost-effectiveness analyses, sensitivity analyses were performed to test the validity of the assumptions and the robustness of the models. The Mexican cost-effectiveness study was funded by the manufacturer of celecoxib; however, the authors indicated that the manufacturer was blinded to the study planning and interpretation of the results. The incremental costs and incremental effectiveness for the study drugs were provided in this study, while the values of ICER were not reported. A reason for this was not given.

**Summary of Findings**

Two largest clinical trials, SUCCESS-1 (Successive Celecoxib Efficacy and Safety Study-1, n=13,274; celecoxib was compared with naproxen and diclofenac) and CLASS (the Celecoxib Long-term Arthritis Safety Study, n=7,968; celecoxib was compared with diclofenac and ibuprofen), were included in four of the six HTAs or SRs.

**Comparative Clinical Effectiveness of Celecoxib versus nsNSAIDs**

The results of clinical effectiveness of celecoxib versus nsNSAIDs are presented in Appendix 5.

**Pain Management**

In the AHRQ review, one SR published in 2002 that was included in the original CER evaluated pain relief of celecoxib versus nsNSAIDs. It was funded by the manufacturer of celecoxib and found similar effects between celecoxib and nsNSAIDs using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores. The results were based on data from published and unpublished RCTs in patients with either OA or RA.

In the DERP review, results from SRs also included the AHRQ review found comparable efficacy for pain relief between celecoxib and nsNSAIDs. Celecoxib 200mg per day to 800mg...
per day had similar pain reduction effect compared with nsNSAIDs in patients with OA, RA, soft tissue pain and AS, from 11 of 12 RCTs. A single study that was rated as poor quality by the authors reported significantly greater reduction in pain on walking in the diclofenac arm.

In the Gotzsche review\(^3\), three RCTs included in one systematic review found that celecoxib had similar effects on pain control as nsNSAIDs in patients with OA or RA.

In the HTA report\(^15\), celecoxib was found to have similar efficacy in pain control compared with nsNSAIDs (naproxen, diclofenac, ibuprofen or loxoprofen), based on the results from RCTs with treatment durations that ranged from two weeks to longer than 26 weeks.

Global Efficacy Assessment

In the systematic review by Gotzsche et al.\(^3\), three RCTs found that celecoxib had similar effects on participant- and physician-rated global assessment for disease and pain measured by ACR 20 criteria as nsNSAIDs in patients with OA or RA.

Withdrawal due to Lack of Efficacy

In the AHRQ review\(^1\), one SR published in 2005 that included in the original CER evaluated withdrawal due to lack of efficacy of celecoxib versus nsNSAIDs. This SR included unpublished manufacturer-held clinical trial reports. It found that celecoxib at doses of 200-400 mg was associated with slightly higher rates of withdrawals due to a lack of efficacy when compared with nsNSAIDs.

In the DERP review\(^14\), the differences between celecoxib and nsNSAIDs with respect to withdrawal due to lack of efficacy were statistically significant (relative risk 1.1, 95% confidence interval 1.02 to 1.23).

Comparative Safety of Celecoxib versus nsNSAIDs

The results of safety outcomes for celecoxib versus nsNSAIDs are presented in Appendix 6.

From the results of a meta-analysis by Trelle et al.\(^13\), celecoxib was related to higher risk of MI, cardiovascular death, death of any cause and composite outcomes but had a lower risk for stroke when compared with naproxen; ibuprofen and diclofenac were associated with higher risks of CV adverse events than celecoxib. However, the differences in all comparisons did not reach statistical significance. On the other hand, a significant difference in stroke was identified when celecoxib was compared with diclofenac and favored celecoxib. These results were reported graphically without providing actual data. The authors concluded that although uncertainty remains, little evidence existed to suggest that any of the study drugs in this review, including celecoxib, were safe in CV outcomes and CV risk needed to be taken into account when prescribing any NSAIDs.

The DERP review\(^14\) found that celecoxib may offer a short-term advantage over nsNSAIDs in terms of GI adverse events, yet this has not been confirmed in studies with longer than six months follow-up. As for CV adverse events, celecoxib was not significantly different from nsNSAIDs for rate of MI, other CV events, or cerebrovascular events.
In the Gotzsche review, three RCTs included in one systematic review found that celecoxib was associated with lower rates of GI ulcers than older nsNSAIDs.

The HTA showed that celecoxib was associated with superior GI tolerability but higher risk of MI. The between group differences were statistically significant.

In the meta-analysis by Chen et al., data from 13 RCTs showed no significant differences of MI risk when comparing celecoxib and nsNSAIDs (naproxen, ibuprofen or diclofenac) in patients with OA, RA or chronic low back pain. No separate results for individual nsNSAIDs were reported.

**Cost-Effectiveness and Safety of Celecoxib versus nsNSAIDs**

One HTA report included an economic review. The review of the published economic evaluations of COX-2 selective NSAIDs and nsNSAIDs were inconsistent. Some economic analyses suggested that COX-2 selective NSAID was dominant and supported the widespread use of COX-2 selective NSAIDs, whereas others reported very high ICERs and concluded that COX-2 selective NSAIDs were not optimal given the limited healthcare resources. In addition to the systematic review of economic studies, a cost-effectiveness analysis of NSAIDs was conducted. COX-2 selective NSAIDs were individually compared with nsNSAIDs using the Assessment Group Model (AGM) developed from an existing Markov model. Based on the findings from the AGM, where patients had no opportunity to switch NSAID, with ibuprofen or diclofenac alone as the comparator, celecoxib was associated with higher costs and small increases in effectiveness, measured by quality-adjusted life-years (QALYs). When compared with ibuprofen, the base-case incremental costs per QALY were £98,400 for low dose celecoxib, and £215,000 for high dose celecoxib. When compared with diclofenac the base-case incremental costs per QALY were £68,400 for low dose celecoxib and £151,000 for high dose celecoxib. The economic model showed a wide range of possible costs per QALY gained in patients with OA and RA, while a firm conclusion regarding the cost-effectiveness of COX-2 selective NSAIDs was not provided.

In the Mexican cost-effectiveness analysis, celecoxib (652.5 Mexican pesos, equivalent to US$652.5 in 2008) had the lowest cost of OA drug versus nsNSAIDs (US$658.7) and acetaminophen (US$702.6) during a 6-month treatment period. The number of patients with pain control without developing adverse events was 371 in the celecoxib group, 274 in the nsNSAIDs group, and 270 in the acetaminophen. The lower use of resources with celecoxib was associated mainly with a lower rate of adverse events that resulted in a decrease in healthcare cost. Celecoxib, therefore, was found to be more cost-effective compared with the other treatment arms. The ICERs were not reported in this study. The authors concluded that from a Mexican institutional perspective and likely in other Social Security Institutions in similar developing countries, the most cost-effective option for treatment of knee or hip OA was celecoxib.

**Limitations**

The HTAs, MAs, and SRs in this report examined data from numerous primary studies or systematic reviews of RCTs and non-randomized studies. There were some overlapping of primary studies due to the similar selection criteria (population: adult patients with OA or RA; intervention: COX-2 selective NSAIDs; comparators: nsNSAIDs; outcome measures: effectiveness and adverse events) adopted by these SRs. Two large RCTs, CLASS and
SUCCESS-1, were included in four of six SRs. It could be challenging when summarizing such data, due to the possibility of overestimating the benefits or harms of celecoxib if these data were repeatedly used.

In general, the study durations in the primary clinical trials were 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 balance of overall benefits and harms.

The identified economic evaluations were conducted in the UK and Mexico. The conclusions from these two studies were inconsistent. The Mexican study indicated that celecoxib was cost-effective in treating OA; however, this may not apply to a Canadian population due to the diverse health care systems between the two countries.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

Numerous studies have been conducted that examined the clinical benefits and safety of celecoxib in the past five years. In total, five SRs, one HTA and two cost-effectiveness analyses are included in this review. Most of these studies evaluated the use of celecoxib in patients with osteoarthritis and rheumatoid arthritis.

According to the results from the six studies in our report, celecoxib was as effective as the conventional nsNSAIDs in pain relief. Diclofenac, naproxen and ibuprofen were the most common nsNSAIDs in the published studies. There was no significant difference in the number of patients who withdrew from the celecoxib therapy due to a lack of efficacy compared with nsNSAIDs. As for the drug safety, the HTA, MAs and SRs indicated that celecoxib was related to less GI toxicities, such as ulcers. The results regarding CV-related adverse events were inconsistent. Some studies suggested that there was no difference between celecoxib and nsNSAIDs, while others reported a higher risk of MI or lower risk of stroke associated with celecoxib. The cost-effectiveness of celecoxib compared with conventional nsNSAIDs is inconsistent based on the results from two cost-effectiveness analyses, conducted in the UK and Mexico, while the difference in settings may be a factor.

Even though celecoxib has been used for many years in patients with arthritis or other diseases that require pain management, there is still a need for long-term studies that evaluate its clinical benefits and safety profiles. This is particularly important for the cardiovascular risks, which may not been observed in the first few years of treatment. Furthermore, the cost-effectiveness of celecoxib compared with nsNSAIDs in a Canadian setting remains unknown.

PREPARED BY:
Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439
www.cadth.ca
REFERENCES


APPENDIX 1: Selection of Included Studies

38 citations identified from electronic literature search and screened

9 citations excluded

29 potentially relevant articles retrieved for scrutiny (full text, if available)

1 potentially relevant report retrieved from other sources (grey literature, hand search)

30 potentially relevant reports

23 reports excluded:
- irrelevant intervention (1)
- irrelevant comparator (5)
- irrelevant outcomes (4)
- already included in at least one of the selected systematic reviews (6)
- other (review articles, editorials) (7)

7 reports included in this review
(1 cost-effectiveness analysis was included in 1 HTA)
## APPENDIX 2: Characteristics of Included HTAs, SRs and MAs

<table>
<thead>
<tr>
<th>First Author, Publication Year, Country</th>
<th>Study Design</th>
<th>Patient Characteristics</th>
<th>Intervention</th>
<th>Comparator(s)</th>
<th>Main Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trelle, 2011, Switzerland(^3)</td>
<td>SR and MA (included large scale RCTs)</td>
<td>Patients with OA or RA</td>
<td>Celecoxib</td>
<td>nsNSAIDs, other COX-2 selective inhibitors, and placebo</td>
<td>Fatal/non-fatal MI, fatal/non-fatal stroke, CV death, all-cause death, and composite outcome</td>
</tr>
<tr>
<td>AHRQ, 2011, US(^1)</td>
<td>SR (included SRs, RCTs, cohort studies, case-control studies)</td>
<td>Adults with OA. Studies that reported safety in patients with RA or who were taking drug for cancer or Alzheimer’s prevention were included also.</td>
<td>Celecoxib</td>
<td>Another oral and topical analgesics or placebo</td>
<td>Improvements in OA symptoms, AEs (for use of drugs in OA, RA or cancer treatment)</td>
</tr>
<tr>
<td>Peterson, 2010, US(^1)</td>
<td>SR (included good-quality SRs and controlled trials; observational studies were included for safety assessment)</td>
<td>Patients with OA, RA, soft tissue pain, back pain and AS</td>
<td>Celecoxib</td>
<td>Other NSAIDs</td>
<td>Pain, functional status, discontinuation due to lack of effectiveness, AEs (GI, CV etc.)</td>
</tr>
<tr>
<td>Gotzsche, 2009, Denmark(^3)</td>
<td>SR (included SRs of RCTs)</td>
<td>Patients with symptomatic musculoskeletal disorders</td>
<td>NSAIDs including celecoxib</td>
<td>Other oral NSAIDs</td>
<td>Pain intensity, Personal preference for one drug over another, Clinically significant GI complications</td>
</tr>
<tr>
<td>Chen, 2008, UK(^1)</td>
<td>HTA (included RCTs)</td>
<td>Patients with OA and RA</td>
<td>COX-2 selective NSAIDs</td>
<td>Other COX-2 selective NSAIDs, nsNSAIDs, placebo</td>
<td>Clinical effectiveness (pain intensity, AEs) Cost-effectiveness (incremental cost per QALY)</td>
</tr>
<tr>
<td>Chen, 2007, UK(^2)</td>
<td>SR and MA (included double-blind RCTs)</td>
<td>OA, RA, AS, chronic low back pain; colorectal adenomas and mild cognitive impairment or early Alzheimer’s disease</td>
<td>COX-2 selective inhibitors</td>
<td>Placebo, nsNSAIDs, or another COX-2 selective NSAID</td>
<td>MI</td>
</tr>
</tbody>
</table>

\( AHRQ = \) 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; \( RA = \) rheumatoid arthritis; \( OA = \) osteoarthritis; \( QALY = \) quality-adjusted life-year; \( RCT = \) randomized controlled trial; \( SR = \) systematic review
# APPENDIX 3: Characteristics of Included Economic Evaluations

<table>
<thead>
<tr>
<th>First Author, Publication Year, Country</th>
<th>Type of Economic Evaluation, Study Perspective</th>
<th>Patient Population</th>
<th>Intervention (n)</th>
<th>Comparators (n)</th>
<th>Assumptions</th>
</tr>
</thead>
</table>
| Chen, 2008<sup>15</sup> UK             | CEA in an HTA report, an NHS perspective      | Patients with OA or RA | COX-2 selective inhibitors with or without aspirin | nsNSAIDs with or without gastroprotective agents, COX-2 selective inhibitors with or without gastroprotective agents | • Only 1 new event (GI or MI) can occur in any 3-month cycle  
• Second MIs are fatal  
• nsNSAIDs do not protect against the risk of MI |
| Contreras-Hernandez, 2008<sup>16</sup> Mexico | CEA, a Mexican institutional perspective       | Patients with OA    | Celecoxib 200mg BID | Naproxen 500mg BID, Diclofenac 100mg BID, Piroxicam 20mg/day | • Once the AEs occurred, the actions taken were to administer concomitant treatment or drug discontinuation; in this way, none of the AEs should occur again in the same subject.  
• In the decision tree model, 3 decision nodes represented the 3 alternatives (acetaminophen, nsNSAIDs or celecoxib). Once "no pain improvement" occurred, the prescription of 1 of the 2 remaining alternatives available is mandatory |

AE=adverse event; BID=twice daily; CEA=cost-effectiveness analysis; GI=gastrointestinal; HTA=health technology assessment; MI=myocardial infarction; NHS=National Health Service; NSAID=non-steroidal anti-inflammatory drug; nsNSAID=non-COX-2 selective NSAID; OA=osteoarthritis; RA=rheumatoid arthritis.
### APPENDIX 4: Critical Appraisal of Included Studies

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<th>First Author, Publication Year</th>
<th>Strengths</th>
<th>Limitations</th>
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<tr>
<td><strong>Health Technology Assessments, Systematic Reviews and Meta-analyses</strong></td>
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</table>
| Trelle, 2011<sup>11</sup> | ● Research questions and selection criteria were defined and presented  
● Comprehensive literature search based on pre-defined criteria  
● 2 independent investigators performed study selection, and data extraction  
● List of included studies  
● Appropriate methods for data synthesis  
● Conflict of interests declared | ● Unclear if there was a limit on language in literature search  
● Lack of list of excluded studies  
● Quality assessment of the included studies was not described  
● Results were not reported in sufficient details |
| AHRQ, 2011<sup>1</sup> | ● 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 | ● Most of the RCTs in SRs evaluated short-term use of celecoxib  
● Non-English language studies were excluded |
| Peterson, 2010<sup>14</sup> | ● 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  
● Conflict of interest declared | ● Non-English language studies were excluded  
● No description for trial characteristics  
● Results were not reported in sufficient details |
| Gotzsche, 2009<sup>3</sup> | ● Research questions and selection criteria were defined and presented  
● Comprehensive literature search based on pre-defined criteria  
● Quality assessment on the included studies  
● Results reported in sufficient details | ● Lack of description of study characteristics and excluded studies  
● Unclear if there was a limit on language in literature search  
● Unclear whether two independent reviewers conducted the review  
● Included primary RCTs were old  
● Conflict of interests was not declared |
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| **Chen, 2008** | ● Research questions and selection criteria were defined and presented  
● Comprehensive literature search based on pre-defined criteria; no limit on language  
● Quality assessment on the included studies  
● In the clinical review section, 2 reviewers conducted the study selection; data extraction and quality assessment were carried out by 1 reviewer and verified by another  
● Conflict of interests declared | ● The last search date was 2004 which was relatively old  
● Some trial data that were commercial-in-confidence were removed; therefore not all the data were available for review |
| **Chen, 2007** | ● Research questions and selection criteria were defined and presented  
● Comprehensive literature search based on pre-defined criteria  
● Quality assessment on the included studies  
● Appropriate methods for data synthesis | ● Conflict of interests was not declared  
● Lack of list of excluded studies |

**Economic Evaluations**

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| **Chen, 2008** | ● Research questions and selection criteria were defined and presented  
● Sources of effectiveness estimates used were stated  
● Choice of model used and the key parameters on which it was based were justified  
● Conflict of interests declared | ● In the economic evaluation section, study selection and data extraction were performed by 1 reviewer  
● No details were reported for price adjustments for inflation and discount rates  
● The answer to the study question was not clear |
| **Contreras-Hernandez, 2008** | ● Research questions and selection criteria were defined and presented  
● Sources of effectiveness estimates used were stated  
● Choice of model used and the key parameters on which it was based were justified  
● Conflict of interests declared | ● The literature search was restricted to English and Spanish publications  
● No details were reported for price adjustments for inflation and discount rates  
● The results were not reported in sufficient details |
## APPENDIX 5: Main Study Findings and Authors’ Conclusions – Clinical Effectiveness

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<tr>
<th>First Author, Publication Year</th>
<th>Main Study Findings</th>
<th>Authors’ Conclusions</th>
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| AHRQ, 2011³                   | Included SRs showed similar effects on pain control for celecoxib and nsNSAIDs in patients with either OA or RA.  
An SR found celecoxib at doses of 200-400 mg associated with slightly higher rates of withdrawals due to lack of efficacy compared to nsNSAIDs (RR 1.1; 95% CI 1.0; 1.2).  
A large RCT (CLASS): ibuprofen or diclofenac were associated with a higher likelihood of withdrawal due to lack of efficacy compared to celecoxib (15% vs. 13%, p=0.005).  
Another large RCT (SUCCESS-1) found no clinically meaningful (and mostly statistically nonsignificant, actual values NR) differences after 12 weeks in efficacy (pain, global assessment of arthritis, or WOMAC total score) between celecoxib 100 mg or 200 mg BID and diclofenac and naproxen.  
A new trial (n=925, age ≥60 years) found no differences between celecoxib 200 mg QD and diclofenac 50 mg BID in pain scores, global assessment of arthritis, or patient satisfaction through 52 weeks of followup.  
Another new trial (high loss to followup) failed to demonstrate noninferiority of celecoxib 200 mg QD compared to diclofenac 50 mg TID on pain in patients with OA and required joint surgery:  
Diclofenac vs. celecoxib (mean difference between drugs in reduction in pain measured in VAS):  
12.1mm, 95%CI 5.8-18.4 at 6-week;  
10.0mm, 95%CI 2.8-17.3 at 12-week.  
Withdrawals due to lack of efficacy were similar (13% vs. 11%, p value NR). | No clear differences in efficacy for pain relief, or withdrawals due to lack of efficacy when celecoxib compared to nsNSAIDs (strength of evidence: high*). |
| Peterson, 2010¹⁴               | Pain reduction  
Celecoxib 200-800mg/day had similar effect vs. nsNSAIDs in patients with OA, RA, soft tissue pain, and AS, from 11 of 12 RCTs.  
1 RCT reported significantly greater pain reduction on walking in the diclofenac arm in patients with OA and required joint replacement surgery:  
Diclofenac 50mg TID vs. celecoxib 200mg QD (Difference in reduction in pain measured in VAS):  
12.1mm, 95%CI 5.8-18.4 at 6-week;  
10.0mm, 95%CI 2.8-17.3 at 12-week.  
Other SRs found similar pain reduction effects between celecoxib and nsNSAIDs; the SUCCESS-1 trial was included in these SRs. | Celecoxib 200-800mg/day had similar pain reduction effects as nsNSAIDs. |
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<td><strong>Gotzsche, 2009</strong>&lt;sup&gt;3&lt;/sup&gt;</td>
<td><strong>1 SR (included 3 RCTs) was found on celecoxib:</strong>&lt;br&gt;<strong>RCT1:</strong>&lt;br&gt;1149 patients with RA, celecoxib 100/200/400mg BID vs. naproxen 500mg BID&lt;br&gt;At 12 weeks, 21% with naproxen vs. 28% with celecoxib 100mg vs. 21% with celecoxib 200mg vs. 27% with celecoxib 400mg obtained improvement according to ACR 20 criteria. No significant difference between any dose of celecoxib and naproxen for this outcome (p&gt;0.05).&lt;br&gt;<strong>RCT2:</strong>&lt;br&gt;655 patients with RA, celecoxib 200mg BID vs. diclofenac 75mg BID&lt;br&gt;No significant difference between celecoxib and diclofenac in improvement according to ACR 20 criteria, pain, or participant/physician-rated global assessment at 24 weeks. Improvement by ACR 20 response: 25% with celecoxib vs. 22% with diclofenac (p&gt;0.05).&lt;br&gt;<strong>RCT3:</strong>&lt;br&gt;537 patients with OA or RA, celecoxib 200mg BID vs. naproxen 500mg BID&lt;br&gt;No significant difference between celecoxib and naproxen in participant/physician-rated global assessment (both assessments scored from 1=very good to 5=poor) at 12 weeks; Participant assessment: from 2.9 at baseline to 2.5 at 12 weeks for celecoxib and naproxen (p&gt;0.05).&lt;br&gt;Physician assessment: from 2.9 at baseline to 2.4 at 12 weeks for celecoxib and naproxen (p&gt;0.05).</td>
<td>Celecoxib was as effective at reducing pain scores as older NSAIDs in people with RA or OA.</td>
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<td><strong>Chen, 2008</strong>&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Celecoxib vs. nsNSAIDs:&lt;br&gt;VAS pain difference: -0.42, 95%CI -2.4 to 1.6&lt;br&gt;Global efficacy difference: 0, 95%CI -0.05 to 0.03&lt;br&gt;ACR-20: 1.00, 95%CI 0.89 to 1.14&lt;br&gt;Withdrawal due to lack of efficacy: 0.94, 95%CI 0.77 to 1.14</td>
<td>Compared to nsNSAIDs, celecoxib was equally efficacious in pain control.</td>
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*Strength of evidence in the AHRQ review was rated as: high – high confidence that the evidence reflects the true effect and that further research is very unlikely to change the confidence in the estimate of effect; moderate – moderate confidence that the evidence reflects the true effect and further research may change the confidence in the estimate of effect and may change the estimate; low – low confidence that the evidence reflects the true effect and further research is likely to change the confidence in the estimate of effect and is likely to change the estimate; insufficient – indicates evidence either is unavailable or does not permit a conclusion.*

**CADTH RAPID RESPONSE SERVICE**

**Celecoxib versus NSAIDS**
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<th>Main Study Findings</th>
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<td>Trelle, 2011&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Results were reported graphically. The figures showed that there were no 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).</td>
<td>No clear associations between celecoxib and CV risk.</td>
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<td>AHRO, 2010&lt;sup&gt;10&lt;/sup&gt;</td>
<td>GI harms: Celecoxib was associated with lower risk of ulcer complications (RR 0.23, 95%CI 0.07-0.76) and ulcer complications or symptomatic ulcers (RR 0.39, 95%CI 0.21-0.73) compared with nsNSAIDs. In CLASS, celecoxib was superior to diclofenac or ibuprofen for ulcer complications or symptomatic ulcers at 6-month follow-up (2.1% vs. 3.5%, p=0.02), but not at 12-month follow-up. The most recent SR of RCTs found celecoxib associated with a lower risk of GI AEs (RR 0.75, 95% CI 0.70 to 0.80) and withdrawals due to GI AEs (RR 0.45, 95% CI 0.33 to 0.56) compared to nsNSAIDs, but the difference in risk of any AE or withdrawal due to any AE did not reach statistical significance). CV harms: No increase in the rate of CV events with celecoxib vs. ibuprofen or diclofenac in CLASS (0.5% vs. 0.3%). A network analysis of RCTs and 3 large observational studies did not find difference in risk of MI compared to naproxen, ibuprofen or diclofenac.</td>
<td>Celecoxib may be associated with decreased risk of serious GI events; its association with CV risks was not clear.</td>
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<td>Peterson, 2010&lt;sup&gt;14&lt;/sup&gt;</td>
<td>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 (CLASS) CV AEs: Celecoxib vs. NSAIDs: 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). Risk of MI in 1 case-control study (n=54,457, age≥65 years): Celecoxib vs. naproxen: OR 0.95, 95%CI 0.74-1.21;</td>
<td>Lower risk of GI harms was observed for celecoxib than nsNSAIDs in the short-term. Celecoxib was not significantly different from nsNSAIDs for rate of MI or other CV events or cerebrovascular events.</td>
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<tr>
<td>Gotzsche, 2009&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Celecoxib vs. ibuprofen: OR 0.98, 95% CI 0.76-1.26</td>
<td>Celecoxib was associated with lower rates of GI ulcers than older nsNSAIDs.</td>
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<td>1 SR (included 3 RCTs) was found on celecoxib:</td>
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<td>RCT1: Celecoxib (all doses) significantly reduced endoscopically diagnosed GI ulcers of at least 3 mm at 12 weeks compared with naproxen; no significant difference between any dose of celecoxib and naproxen in clinical GI AEs or withdrawals due to GI AEs.</td>
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<td>RCT2: 655 patients with RA celecoxib 200 mg BID vs. diclofenac 75 mg BID. Diclofenac significantly increased withdrawals due to GI AEs and increased ulcers of at least 3 mm compared to celecoxib. Ulcers: 16% with diclofenac vs. 4% with celecoxib, p&lt;0.05</td>
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<td>RCT3: 537 patients with OA or RA, celecoxib 200 mg BID vs. naproxen 500 mg BID. Celecoxib significantly reduced GI ulcers at 12 weeks compared with naproxen, 9% vs. 41%, p&lt;0.05. No significant difference between celecoxib and naproxen in withdrawal due to AEs at 12 weeks.</td>
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<td>Chen, 2008&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Celecoxib vs. nsNSAIDs: All AEs: RR 0.90, 95% CI 0.78-1.04. Clinical upper GI events: RR 0.55, 95% CI 0.40-0.76. Complicated upper GI events: RR 0.57, 95% CI 0.35-0.95. Risk of MI: RR 1.77, 95% CI 1.00-3.11.</td>
<td>Celecoxib was associated with superior GI tolerability but higher risk of MI.</td>
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<tr>
<td>Chen, 2007&lt;sup&gt;9&lt;/sup&gt;</td>
<td>The pooled OR for risk of MI associated with celecoxib compared to nsNSAIDs (in 13 RCTs): OR 1.51, 95% CI 0.93-2.45. (these results were also reported in the DERP review)</td>
<td>There were no significant differences of MI risk identified between celecoxib and nsNSAIDs.</td>
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AE = adverse event; CI = confidence interval; CV = cardiovascular; 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.