J Rehabil Med 2014; 46: 294–306

**REVIEW ARTICLE**

# THE EFFICACY OF ORAL NON-STEROIDAL ANTI-INFLAMMATORY DRUGS FOR ROTATOR CUFF TENDINOPATHY: A SYSTEMATIC REVIEW AND META-ANALYSIS

Jennifer Boudreault, OT, MSc[1], François Desmeules, PT, PhD[1,2], Jean-Sébastien Roy, PT, PhD[3,4], Clermont Dionne, OT, PhD[3,5], Pierre Frémont, MD, PhD[3,6] and Joy C. MacDermid, PT, PhD[7]

*From the [1]Orthopaedic Clinical Research Unit, Maisonneuve-Rosemont Hospital Research Center, University of Montreal Affiliated Research Center, [2]School of Rehabilitation, Faculty of Medicine, University of Montreal, Montreal, [3]Department of Rehabilitation, Faculty of Medicine, Laval University, [4]Center for Interdisciplinary Research in Rehabilitation and Social Integration, [5]Population Health research unit (URESP), Laval University Affiliated Hospital (CHA) Research Center, [6]Laval University Hospital (CHU) Research Center, Quebec City, Quebec and [7]School of Rehabilitation Science, McMaster University, Hamilton, Ontario, Canada*

***Objective:*** **To conduct a systematic review and meta-analysis on the efficacy of oral non-steroidal anti-inflammatory drugs for rotator cuff tendinopathy.**

***Design:*** **Systematic review.**

***Method:*** **A literature search was conducted in 4 databases for randomized controlled trials published until 05/2013, comparing the efficacy of oral anti-inflammatory drugs to any other intervention. Studies characteristics were extracted using a standardized form and the methodological quality was evaluated. Results were summarized qualitatively or quantitatively.**

***Results:*** **The mean methodological score of the 12 included studies was 53.6±8.8%. The majority of studies included acute cases and were underpowered to detect differences in adverse events. Compared to a placebo, oral non-steroidal anti-inflammatory drugs were found to provide short-term pain relief (pooled mean difference: –2.69; 95% confidence interval: –1.96 to –3.41) but not function. Oral anti-inflammatory drugs and corticosteroids injections have similar short-term efficacy in terms of pain reduction as well as in function (pooled standardized mean difference: 0.09; 95% confidence interval: –0.25 to 0.44).**

***Conclusion:*** **Low to moderate grade evidence exists regarding the efficacy of non-steroidal anti-inflammatory drugs for rotator cuff tendinopathy. Oral anti-inflammatory drugs are effective in reducing short-term pain but not function. In terms of pain and function, oral anti-inflammatory drugs in the short term are as effective as corticosteroid injections.**

*Key words:* anti-inflammatory agents; rotator cuff; shoulder; tendinopathy.

J Rehabil Med 2014; 46: 294–306

*Correspondence address: François Desmeules, Orthopaedic clinical research unit, Centre de recherche de l'Hôpital Maisonneuve-Rosemont (CRHMR), 5415 Blvd L'Assomption, Pav. Rachel Tourigny, office 4163, Montréal, QC H1T 2M4, Canada. E-mail: f.desmeules@umontreal.ca*

Accepted Jan 14, 2014; Epub ahead of print Mar 13, 2014

## INTRODUCTION

Disorders of the rotator cuff (RC) tendons are the most common pathology of the shoulder, with RC tendinopathy accounting for 35% to 50% of rendered diagnoses (1). RC tendinopathy is a generic term used to describe a pathology in a RC tendon (2) and includes other diagnosis such as impingement syndrome, subacromial bursitis, partial thickness tear and long head of the biceps tendinopathy (3). The theories of the pathogenesis of RC tendinopathy may be divided into extrinsic and intrinsic causes, or combination of both. Extrinsic causes often relate to an irritation from the anteroinferior aspect of the acromion onto the superior aspect of the RC often associated with alterations in scapular and glenohumeral kinematics (4, 5). As for intrinsic causes, factors within the tendon itself such as alterations in tendon vascularity, physiology or mechanical properties have been proposed (4).

Studies have suggested that oral non-steroidal anti-inflammatory drugs (NSAIDs) may allow a reduction in symptoms in patients suffering from various types of tendinopathies (6–8) but evidence also cautions that oral NSAIDs may be associated with important risks of gastrointestinal and cardio-vascular adverse effects, especially when taken for longer periods (9–11). It also remains unclear if the pathophysiology of tendinopathy is inflammatory and if either non-selective cyclo-oxygenase (NS COX) inhibitors or COX-2 selective inhibitors, will adequately address the pathophysiology, especially for chronic patients (6, 8, 12). Evidence suggests that what has been called tendinitis is not exactly an inflammatory process, but the result of overuse of the tendon, and the term tendinopathy or tendinosis may be more appropriate, in particular in patients with chronic symptoms (13–16). For patients presenting with acute tendinopathy, some authors still recommend NSAIDs use (12, 17) as more classic signs of inflammation have been observed from RC biopsies confirming the presence of inflammatory cells and mediators (18).

Previous reviews on populations suffering from non-specific shoulder disorders have concluded that a short duration treat-

ment of oral NSAIDs appears to be an effective therapeutic modality for the reduction of pain and disabilities and to increase shoulder range of motion (6, 19, 20). A recent systematic review focusing on the effectiveness of pharmaceutical interventions including oral NSAIDs, corticosteroids and other type of injections for RC tendinopathy concluded that a laser intervention was more effective than oral NSAIDs in short term pain relief and that oral NSAIDs were as effective as corticosteroids injections to reduce pain in the short term. The authors did not, however, perform a meta-analysis and several relevant RCTs were excluded from their analyses, therefore limiting their conclusions (21). The aim of this review was to perform a systematic review and pooled results into a meta-analysis on the efficacy of oral NSAIDs to treat adults suffering from RC tendinopathy.

## METHODS

*Literature search and study identification*

A search in 4 bibliographical databases, Pubmed, CINAHL, Embase, and PEDro, was performed using a combination of keywords and MESH terms. All databases were searched from their date of inception to May 2013. Manual searches of previous published reviews and retrieved study reference lists were also conducted.

*Study selection*

Two authors reviewed the title and abstract of each article to determine eligibility. Pairs of raters then independently reviewed each article to determine whether it met the following inclusion criteria: *i*) participants suffered from RC tendinopathy or other related diagnostics such as impingement syndrome, subacromial bursitis, partial tear (non-full thickness tear) and long head of the biceps tendinopathy; *ii*) adult population (≥18 years old); *iii*) at least one of the interventions under study included oral NSAIDs compared to any other type of intervention; *iv*) study design was a randomized controlled trial (RCT); *v*) The language of articles was either English or French. All outcomes measures were considered. Studies with inclusion criteria that incorporated shoulder pain patients were also eligible as long as it could be determined that the majority of the study participants were suffering from RC tendinopathy. Trials evaluating NSAIDs withdrawn from market because of unwanted side effects were excluded.

*Data extraction*

Characteristics of the included studies were extracted with a standardized form and included: cohort characteristic, interventions and co-interventions, outcome measures, follow-up period, main results and type and incidence of adverse events.

*Risk of bias/Methodological quality appraisal tool*

The risk of bias and the methodological quality of the included studies were assessed with the Cochrane risk of bias tool (22). This tool includes 6 methodological domains: sequence generation, allocation concealment, blinding (participants, provider and assessor), incomplete outcome data, selective outcome data reporting, and other sources of bias. Each item is appraised regarding its risk of potential bias: 'yes' indicates low risk of bias, 'no' indicates high risk of bias, and 'unclear' indicates an unclear or unknown risk of bias with the information presented in the study (22). For each methodological item, a score of 2 was given if a low risk of bias was present, a score of 1 if the risk of bias was unclear or unknown and a score of 0 if a high risk of bias was found to be present. This allowed us to calculate a total score (out of 16) to give an overview of the methodological quality of the included RCTs (22).

*Data analyses*

After the independent evaluation of each study by two independent evaluators, the pair of raters met to compare ratings and resolve differences. Weighted kappa was used to calculate preconsensus inter-rater agreement on individual methodological items and an intraclass correlation coefficient (ICC) was calculated to evaluate inter-rater reliability of the total methodological scores. There was no formal mechanism to exclude studies on the basis of quality. The studies that used similar outcome measures were identified, and results were pooled into a meta-analysis when possible. Analyses were conducted using Review Manager (version 5.2) of the Cochrane Collaboration (23). Treatment effect size and variance of individual studies were used to obtain an overall summary effect. Mean differences (MD) and standardized mean differences (SMD) with 95% confidence intervals (95% CIs) were calculated. To determine the degree of heterogeneity, testing was conducted using the $I^2$ measure. $I^2 < 60\%$ was considered to be acceptable for pooling the data (23). Because the overall number of studies included in the meta-analysis was small and true effect sizes varied between studies, a random effects model was used. Funnel plots were not generated because of the small number of trials included for each analysis. The statistical significance was considered at $p < 0.05$ (23).

## RESULTS

*Description and findings of included studies*

The literature search resulted in the initial identification of 25 RCTs (Fig. 1). Eight RCTs were excluded because participants suffered from other shoulder pathologies; one RCT was excluded because the participants suffered from elbow tendinopathy (24); two RCTs were excluded because the medications under study (phenylbutazone and rofecoxib) have been withdrawn from the market (25, 26); one study was excluded because both groups received NSAIDs and the objective was to evaluate the effect of a medication used to reduce the gastrointestinal adverse events associated with NSAIDs (27). Twelve publications met the inclusion criteria and were analysed in this review (Table I). Two studies were from the same cohort of participants and were analysed together (28, 29).

All included studies compared the effectiveness of oral NSAIDs to other interventions such as other types of NSAIDs, corticosteroid injections, laser or a placebo (Table I). One study compared two NS COX inhibitors (30); one study compared a NS COX inhibitor to a placebo (31); 4 studies compared NS COX inhibitors to COX-2 inhibitors (28, 29, 32, 33); 3 studies compared NS COX inhibitors to a corticosteroid injection (34–36); and, two studies compared NSAIDs at different dosages (37, 38). One study compared laser therapy to either a placebo laser or a NS COX inhibitor (39).

*NS COX inhibitors vs. placebo.* The study by Mena et al. (31) compared the efficacy of flurbiprofen (a NS COX inhibitor, 3 × 25 mg 4×/day (QID)) to a placebo (3 tablets QID), in terms of pain and shoulder range of motion in 69 patients suffering from acute (< 3 weeks) RC tendinopathy. After two weeks, a greater proportion of participants receiving flurbiprofen reported feeling better (30%) compared to the placebo group (19%). The proportion of patients showing reduction in pain at rest and during movement, in tenderness on pressure, and increase shoulder range of motion was also greater in the

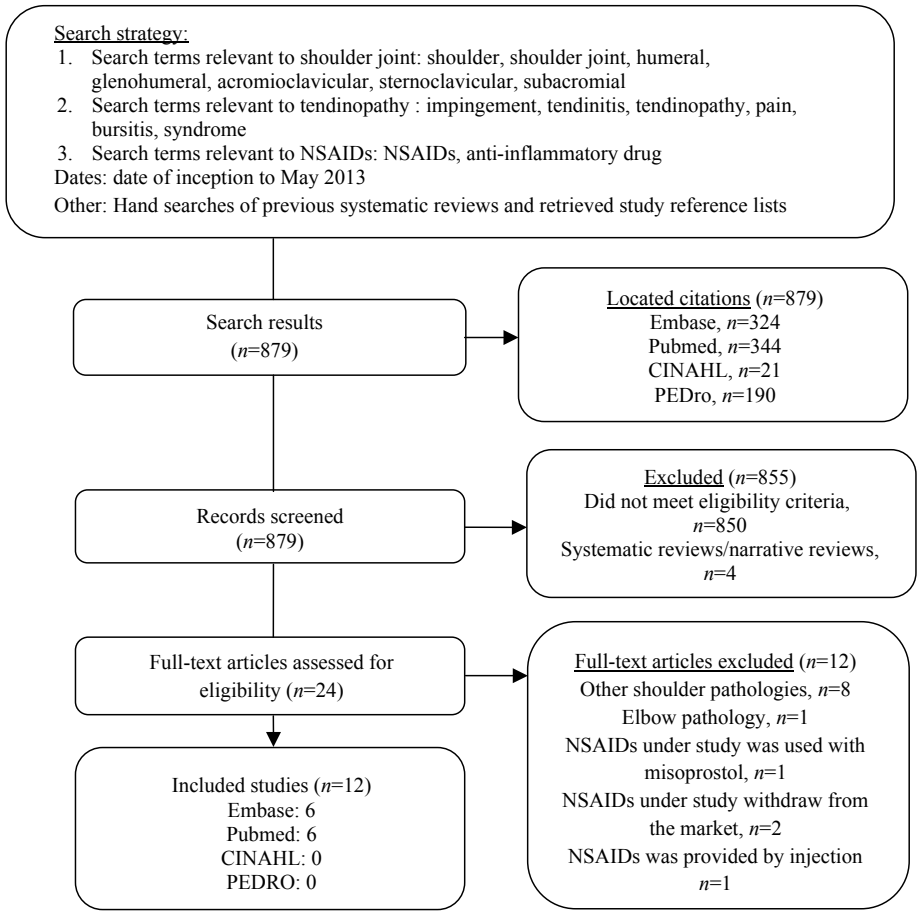


*Fig. 1.* Literature search results.

intervention group. However, no statistical testing was done to confirm between group differences for all these variables. Overall, only one severe adverse event was reported in the placebo group. Eight participants in the flurbiprofen group and 3 in the placebo group suffered from minor side-effects of the upper or lower gastrointestinal tract (31). England et al. (39) compared the efficacy of naproxen (500 mg 2×/day (BID)) for two weeks to a dummy laser in 30 patients suffering from shoulder tendonitis. A trend was shown in favour of the NSAIDs group in terms of movement restriction (point estimate of drug effect on a 10 cm visual analogue scale (VAS): –1.25 cm, 95% CI 0 to –2; $p = 0.05$) and function (point estimate on a 10 cm VAS: –1 cm, 95% CI 0 to –2; $p = 0.05$) but this was not statistically significant (39).

Two studies ($n = 160$) provided data on the effectiveness of NS COX inhibitors compared to a placebo on overall pain at similar time points and were pooled together into a meta-analysis (34, 35). Fig. 2 demonstrates that there was a significant effect of NS COX inhibitors on overall pain reduction compared to a placebo at 4 weeks (SMD 2.69; 95% CI 1.96 to 3.41; $p < 0.00001$). These two studies also presented results on the efficacy of NS COX inhibitors compared to a placebo on shoulder range of motion in abduction. However, they were not pooled together given the significant heterogeneity for that outcome ($Tau^2 = 195.69$, $\chi^2 = 27.02$, degrees of freedom (df) = 1 ($p < 0.00001$); $I^2 = 96\%$) (34, 35). The NSAIDs group showed significantly better shoulder range of motion and self-reported function than the placebo group (inter-group comparison: $p < 0.05$ for both outcomes) in the study by Adebajo et al. (34). However, in the study by Petri et al. (35), no significant differences were found between the NS COX inhibitor compared to the placebo group in terms of shoulder abduction and self-reported function. In terms of function, the two studies presented results on the efficacy of NS COX inhibitor compared to a placebo. However, they were not pooled together for that outcome given the significant heterogeneity ($Tau^2 = 4.60$, $\chi^2 = 16.79$, df = 1 ($p < 0.0001$); $I^2 = 94\%$).

*Oral NS COX inhibitors vs. subacromial corticosteroids injection.* Three studies compared the efficacy of oral NS COX inhibitors to subacromial corticosteroid injections (34–36). The three studies used pain as an outcome measure. However, significant heterogeneity was found for this outcome and the results were not pooled ($Tau^2 = 0.52$, $\chi^2 = 20.76$, df = 2 ($p < 0.0001$), $I^2 = 90\%$). Both interventions were equally effective in reducing night pain and pain during activities. In the

Table I. *Description of included studies*

| Study | Participants | Medications and posology | Partici-pants, *n* | Follow-up period, days | Outcome measures | Main results | Proportion of participants with adverse reactions | Methodo-logical score (0–16) |
|---|---|---|---|---|---|---|---|---|
| *Non-selective COX inhibitors vs placebo* | | | | | | | | |
| Mena et al., 1986 (31) | Acute shoulder, bursitis/tendinitis with pain episode ≤4 days<br>Mean age: 48.7 years<br>Gender: proportion not specified | Flurbiprofen (F) 3 × 25 mg QID<br>Placebo (P) 3 tablets, QID | 35<br>34 | 14 | Proportion of participants showing improvement (%) at day 14 in:<br>1. Pain at rest<br>2. Pain on motion<br>3. Tenderness on pressure<br>4. Abduction<br>5. External rotation<br>6. Swelling<br>No statistical analysis reported<br>At day 14, proportion (%) of participants feeling:<br>1. Better<br>2. Same<br>No statistical analysis reported | <br>1. F: 90.6%, P: 71%<br>2. F: 85.7%, P: 71.9%<br>3. F: 90.9%, P: 75%<br>4. F: 91.2%, P: 50.%<br>5. F: 80%, P: 57.1%<br>6. F: 92.3%, P: 93.8%<br><br><br>1. F: 30%, P: 19%<br>2. F: 2%, P: 11% | F: 22%<br>P: 8% | 10 |
| England et al., 1989 (39) | Adults with either supraspinatus or bicipital tendonitis lasting for at least 4 weeks<br>Mean age: 48 years<br>Gender: male: 15, female: 15 | Active laser therapy for 5 min duration (904 nm, 3 mW, 4000 Hz), 3×/week for 2 weeks (La)<br>Dummy laser therapy (Du)<br>Naproxen sodium 550 md BID for 2 weeks (Na) | 10<br>10<br>10 | 14 | Differences between medians for active range of motion between La and Na:<br>1. Extension<br>2. Flexion<br>3. Abduction<br>Difference between medians for VAS (0–10) for pain between La and Na<br>Difference of medians for VAS score (0–10) for subjective impression of benefit between Du and Na, for:<br>1. Movement<br>2. Function | <br>1. 10° (95% CI 0 to 20)<br>2. 15° (95% CI 5 to 30)<br>3. 20° (95% CI 10 to 40)<br>2 cm (95% CI 1 to 3.5)<br><br>1. –1.25 cm (95% CI 0 to –2)<br>2. –1 cm (95% CI 0 to –2) | 0% drop-out<br>No adverse events reported | 9 |
| *Non-selective COX inhibitors – piroxicam vs naproxen* | | | | | | | | |
| Smith et al., 1986 (30) | Shoulder pain for one month (on movement, at night), reduction of range of motion of the shoulder, likely to have RC tendinopathy<br>Mean age: 63.9 years<br>Gender: male: 28, female: 12 | Piroxicam (P) 20 mg DIE<br>Naproxen (N) 250 mg DIE | 20<br>20 | 21 | Pain assessed with VAS (cm) at baseline, and at day 21:<br>1. On movement<br>2. At night<br>Mobility (°) at baseline, and at day 21:<br>1. Abduction<br>2. External rotation | <br>1. P: 1.2±0.6 and 4.0±0.6, N: 4.8±0.6 and 4.4±0.6 $p \geq 0.05$[a]<br>2. P: 5.8±0.7 and 4.1±0.5, N: 4.2±0.7 and 3.7±0.6, $p = 0.022$[b]<br>No inter-group comparison<br><br>1. P: 78.2±3.2 and 95.3±5.6, N: 75.6±3.6 and 94.2±5.5, $p < 0.001$[a]<br>2. P: 39.7±3.5 and 42.6±3.7, N: 39.7±3.3 and 45±3, $p = 0.048$[b]<br>No inter-group comparison | P: 35%<br>N: 40% | 11 |

Table I. *Contd.*

| Study | Participants | Medications and posology | Partici-pants, *n* | Follow-up period, days | Outcome measures | Main results | Proportion of participants with adverse reactions | Methodo-logical score (0–16) |
|---|---|---|---|---|---|---|---|---|
| *Non-selective COX inhibitors vs corticosteroid injections* | | | | | | | | |
| White et al., 1986 (36) | Adults who had signs and symptoms of RC tendinitis experiencing pain for less than 12 weeks<br>Mean age: 54.5 years<br>Gender: male: 15, female: 25 | Indomethacin 25 mg mg QID and placebo injection (In)<br>Placebo capsules and subacromical bursa injection of 1 mL of 40 mg/ml triamcinalone acetonide (Pl)<br>Some participants were reinjected | 20<br>20 | 42 | Mean change in shoulder abduction (°) at 3 weeks<br>Mean change in patient total pain score (2 VAS of 9 cm each for day and night pain, 0–18 cm)<br>Mean change in overall severity self-assessment score (0–3 point, lower is better) | In: 16±45, $p \geq 0.05$[b]<br>Pl: 30±37, $p \leq 0.001$[b]<br>Between groups: $p \geq 0.05$[c]<br>In: –5.5±8.3, $p \leq 0.025$[b]<br>Pl: –4.3±5.2, $p \leq 0.005$[b]<br>Between groups: $p \geq 0.05$[c]<br>In: –2.8±3.4, $p \leq 0.025$[b]<br>Pl: –2.9±2.7, $p \leq 0.005$[b]<br>Between groups: $p \geq 0.05$[c] | In: 10%<br>Pl: 5% | 8 |
| Petri et al., 1987 (33) | Participants with painful abduction, painful arc of movement from 45 to 120° or tenderness over the insertion of the supraspinatus tendon, likely to have RC tendinopathy<br>Gender: male: 69, female: 31 | 1. Subacromical bursa injection with 4cc of 1% lidocaine and naproxen 500 mg BID (Na)<br>2. Subacromial bursa injection with 3 cc of 1% lidocaine and 1 cc of 40 mg/ml triamcinolone, and naproxen BID (Tn)<br>3. Subacromial bursa injection with 3 cc of 1% lidocaine and 1 cc of 40 mg/ml triamcinolone, and placebo pill BID (Tr)<br>4. Subacromial bursa injection with 4cc of 1% lidocaine and placebo pill BID (Pl) | 25<br>25<br>25<br>25 | 30 | Mean change at 4 weeks in:<br>1. Active abduction<br>2. Pain (0–5 scale, 0 = worst pain and 5 = no pain)<br>3. Overall function (0–5, 0 = severe disabilities and 5 = normal function)<br>4. Clinical index (composite score of outcomes 1 to 3) | 1. Na: 1.39±0.31, Tn: 1.95±0.23, Tr: 1.56±0.24, Pl: 0.77±0.24<br>Tr: $p = 0.002$ vs placebo, Na: $p \geq 0.05$ vs placebo<br>2. Na: 1.76±0.31, Tn: 1.95±0.35, Tr: 2.04±0.31, Pl: 1.00±0.32<br>Tr: $p = 0.01$ vs placebo, Na: $p \geq 0.05$ vs placebo<br>3. Na: 1.71±0.34, Tn: 1.61±0.28, Tr:1.64±0.26, Pl: 1.02±0.35<br>Tr: $p \geq 0.05$ vs placebo<br>Na: $p \geq 0.05$ vs placebo<br>4. Na: 4.86±0.85, Tn: 5.51± 0.74, Tr: 5.24±0.74, Pl: 2.80±0.77<br>Tr: $p = 0.004$ vs placebo<br>Na: $p \geq 0.05$ vs placebo | Na: 8%<br>Tn: 16%<br>Tr: 12%<br>Pl: 12%<br>Total frequency of complications was 6%<br>$p > 0.05$ for number of adverse events between groups | 10 |
| Adebajo et al., 1990 (34) | Adults with shoulder pain exacerbated by resisted movement on abduction, or internal rotation present for less than 3 months<br>Mean age: 53.3 years<br>Gender: male: 32, female: 28 | Diclofenac 50 mg TID and subacromial injection of 3 ml of 5% lignocaine (Di)<br>Placebo tablets TID and a subacromial injection of 3 ml of 5% lignocaine and 1 ml of 80 mg/ml of triamcinolone hexacetonide (LT)<br>Placebo tablets TID and a subacromial injection of 3 ml of 0.5% lignocaine (Li) (placebo group) | 20<br>20<br>20 | 28 | Mean change in overall pain assessed with a 10 cm VAS<br>Mean change in active abduction (°)<br>Mean change in limitation of function (scale: 0–3, lower is better) | Di: 3.6±0.67, $p < 0.05$ vs Li<br>Lt: 4.95±0.74, $p < 0.001$ vs Li<br>Li: 1.35±0.74<br>Di: 46.8±5.64, $p < 0.05$ vs Li<br>Lt: 50.4±8.05, $p < 0.01$ vs Li<br>Li: 5.4±10.47<br>Di: 0.85±0.11, $p < 0.05$ vs placebo<br>Lt: 0.85±0.15, $p < 0.01$ vs placebo<br>Li: 0.3±0.10 | Di: 10%<br>Li: 5%<br>$p \geq 0.05$ in number of adverse events between groups | 11 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| *Non-selective COX inhibitors vs selective COX inhibitors* | | | | | | | | |
| Wober et al., 1998 (29) Wober, 1999 (28) | Adults 18–70 years suffering from acute shoulder biccipital tendinitis and/or subdeltoid bursitis (≤7 days) with limitation of motion, pain and tenderness over the involved area Gender (% of female): Ni: 58.1%, Di: 65.0% | Nimesulide (Ni): 100 mg BID<br>Diclofenac (Di): 75 mg BID | 62<br>60 | 14 | Mean combined score of 7 symptoms (0–28, lower is better):<br>1. Baseline<br>2. Day 14<br>Proportion (%) of participants with positive outcome as rated by:<br>1. Investigators<br>2. Patients | <br>1. Ni: 15.4±3.13 (CI: 14.6–16.2) Di: 15.5±2.99 (CI : 14.8–16.3)<br>2. Ni :4.2±3.07 (CI: 3.4 – 5) Di : 5.4±4.4 (CI 4.1–6.6)<br><br>1. Ni: 79, Di: 78<br>2. Ni: 82.3, Di: 78 | Ni :14.5% Di: 26.7% $p=0.0749$ between groups | 8 |
| Bertin et al., 2003 (32) | Adults 18–65 years with acute shoulder pain Maximum VAS ≥40 mm and with onset ≤14 days. Mean age: 46.7 years Gender (% of female): Ce: 56.6%, Na: 58.3% | Celecoxib (Ce): 400 mg DIE<br>Naproxen (Na) 1g DIE | 91<br>89 | 14 | Mean change in maximum pain at rest on the VAS (mm)<br>Mean change in functional score (ASES 0–30 0=complete disability, 30=no disability)<br>Mean improvement (%) in mobility:<br>1. Passive anterior elevation<br>2. Active anterior elevation<br>3. Passive internal rotation<br>4. Active internal rotation<br>Proportion (%) of patient with overall assessment of treatment outcome as good or excellent as rated:<br>1. By patient<br>2. By physician | Ce: –47.9±2.5, Na: -42.3±2.5, $p=0.163$<br>Ce: 10.1±7.3, Na: 8.5±6.4<br><br>1. Ce: 68.7, Na: 67, $p=0.77$<br>2. Ce:77.8, Na:66, $p=0.16$<br>3. Ce:68.7, Na: 62.1, $p=0.58$<br>4. Ce: 72.7, Na: 66, $p=0.44$<br><br>1. Ce: 73.2, Na: 63.4<br>2. Ce: 76.3, Na: 67.3 | Ce: 40.4% Na: 44.7% | 6 |
| Petri et al., 2004 (33) | Adults ≥18 years with acute episode of tendinitis and/or subacromial bursitis of <7 days Mean age: 48.8 years Gender: male: 197, female: 109 | Celecoxib (Ce): 400 mg followed by 200 mg 8 h later on day 1, then 200 mg BID<br>Naproxen (Na): 500 mg BID<br>Placebo (Pl) BID | 98<br>100<br>108 | 14 | Mean reduction in maximum pain at rest on 10 cm VAS (mm) at day 14<br>Mean change on a 5 point scale, lower is better) at day 14:<br>1. Patient's global assessment<br>2. Physician's global assessment<br>Mean change in active abduction (°)<br>Patient overall satisfaction on a scale 0–10 (0=very dissatisfied and 10=very satisfied) at day 14 | Ce: –35±3.06, $p<0.05$ vs placebo Na at day 7 : –26.4±2.70 Pl: –25±3.05, $p<0.05$ vs placebo<br>1. Ce: –1.02±0.11, $p\geq0.05$ vs placebo Na: –0.9±0.1, $p\geq0.05$ vs placebo Pl: –0.76±0.1<br>2. Ce: –1.18±0.11, $p<0.05$ vs placebo Na: –1.17±0.12, $p\geq0.05$ vs placebo Pl: –0.87±0.1<br>Ce: 27.29±2.88, $p\geq0.05$ vs placebo Na: 29.49±3.41, $p<0.05$ vs placebo Pl: 19.75±2.85<br>Ce: 6.1±0.35, $p\geq0.05$ vs placebo Na: 6±0.33, $p\geq0.05$ vs placebo Pl: 5±0.34 | Ce: 36.7% Na: 36% Pl: 29.6% | 6 |

Table I. *Contd*

| Study | Participants | Medications and posology | Participants, *n* | Follow-up period, days | Outcome measures | Main results | Proportion of participants with adverse reactions | Methodological score (0–16) |
|---|---|---|---|---|---|---|---|---|
| *Different dosages of non-selective COX inhibitors* | | | | | | | | |
| Ginsberg & Famaey, 1985 (38) | Study A<br>Adults with tendinitis or bursitis of the shoulder<br>Mean age: 41.5 years<br>Gender: male: 13, female:17 | Fentiazac (slow-release formulation) 300 mg DIE + 3 placebo (Sr)<br>Fentiazac 100 mg QID (Fe) | 17<br><br>15 | 14 | Mean change at final visit on symptoms severity (scale 1–4. 1=none, 2=mild, 3=moderate, 4=severe) rated by investigator:<br>1. Tenderness<br>2. Swelling<br>3. Redness<br>4. Pain on motion<br><br>Mean change at final visit on symptoms severity (scale 0–10, lower is better) as rated by participants:<br>1. Overall pain<br>2. Swelling<br>3. Tenderness<br>4. Range of motion<br>Investigators/participants evaluations of overall symptoms at day 7<br>Proportion of participants:<br>1. Improved<br>2. Unchanged<br>3. Worse | <br>1. Sr:–2.2, Fe: –2.2, $p<0.001$[a]<br>2. Sr: –0.2, Fe: –0.2, $p\geq0.05$[a]<br>3.Sr: –0.1, Fe: –0.1, $p>0.05$[a]<br>4. Sr: –2.2, Fe: –2.1, $p<0.001$[a]<br>Between groups: $p\geq0.05$[d]<br><br>1. Sr: –2.1, Fe: –2.0, $p<0.001$[a]<br>2. Sr: –0.1, Fe: –0.5, $p<0.05$[a]<br>3. Sr: –7.2, Fe:–7.2, $p<0.001$[a]<br>4. Sr: +3.4, Fe: +3.6, $p<0.01$[a]<br>Between groups: $p\geq0.05$[d]<br><br>1. Sr: 13/13, Fe: 13/14<br>2. Sr: 2/1, Fe: 2/1<br>3. Sr: 0/1, Fe: 0/0 | Sr: 13.3%<br>Fe: 26.7% | 6 |
| | Study B<br>Mean age: 43 years<br>Gender: male: 13, female: 17 | Fentiazac 300 mg slow-release DIE (Sr) + 1 placebo<br>Fentiazac 200 mg BID (Fe) | 15<br><br>15 | 14 | Mean change at final visit on symptoms severity (4 level scale: 1=none, 2=mild, 3=moderate, 4=severe) rated by investigator:<br>1. Tenderness<br>2. Swelling<br>3. Redness<br>4. Pain on motion<br>Mean change at final visit on symptom severity (scale 0–10) by participant on:<br>1. Overall pain<br>2. Swelling<br>3. Tenderness<br>4. Range of motion<br><br>Investigators/participants evaluations of overall symptoms at day 7<br>Proportion of participants:<br>1. Improved<br>2. Unchanged<br>3. Worse | 1. Sr: –1.9, Fe: –1.9, $p<0.001$[a]<br>2. Sr: –0.1, Fe: –0.3, $p\geq0.05$[a]<br>3. Sr: 0.0, Fe: –0.1, $p\geq0.05$[a]<br>4. Sr:–1.8, Fe: –1.9, $p\geq0.05$[a]<br>Between groups: $p\geq0.05$[d]<br><br>1. Sr: –2.1, Fe: –1.9, $p<0.001$[a]<br>2. Sr: –0.5, Fe: –1.0, $p\geq0.05$[a]<br>3. Sr: –6.1, Fe: –5.8, $p<0.001$[a]<br>4. Sr: +3.1, $p<0.05$[b]<br>Fe: +2.9, Pre-post treatment comparison $p<0.001$<br>*p*-values inter-group for the 4 elements: ≥0.05<br>Between groups: $p\geq0.05$[d]<br><br>1. Sr: 14/14, Fe: 14/13<br>2. Sr: 1/0, Fe: 1/1<br>3. Sr: 0/1, Fe: 0/1 | Sr: 20%<br>Fe: 33.3% | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Friis, et al., 1992 (37) | Nontraumatic shoulder pain in participants >18 years, suggestive of tendonitis<br>Mean age: 51.1 years<br>Gender: male: 61, female: 86 | Ibuprofen (CI) 600 mg QID + 2 placebo tablets BID<br>Ibuprofen (SRI) 600 mg QID<br>All participants received a corticosteroid injection at day 0 | 74<br>73 | 21 | Proportion of participants with complete pain relief<br>Proportion of participants who improved following treatment (better or complete relief) | CI: 21%, SRI: 7%<br>Significant difference between groups $p = 0.02$<br>CI: 77% (95% CI : 65 to 86)<br>SRI: 68% (95% CI: 55 to 77) | Proportions not reported | 9 |

[a]Pre-post treatment comparisons for both groups; [b]Pre-post treatment comparison; [c]No significant difference; [d] No significant differences in mean change for outcomes 1 to 4.
Home physical therapy program for all patients recommended. 1: Range of motion was multiplied by 36.
ASES: American Shoulder and Elbow Surgeons questionnaire; cc: cubic centimeter; DIE: 1×/day, BID: 2×/day, QID: 4×/day; VAS: visual analogue scale; RC: rotator cuff; COX: cyclo-oxygenase.

study by White et al. (36), no significant differences were found between the two types of interventions in terms of total pain (day and night); the oral NSAIDs group showed a mean change on a 18 cm VAS of 5.5 cm ± 8.3 compared to 4.3 cm ± 5.2 for the injection group ($p \geq 0.05$). In the two other studies, the authors did not perform direct statistical comparisons between oral NS COX inhibitor and subacromial corticosteroid injections. However, each group was compared to a placebo (34, 35). In the study by Adebajo et al. (34), the oral NSAIDs and the corticosteroids injections showed a significant reduction of pain compared to the placebo group ($p < 0.05$ and $p < 0.001$, respectively). In contrast, in the study by Petri et al. (35) only the injection group showed a significant reduction in pain compared to the placebo group ($p < 0.01$). The oral NSAIDs group showed a trend toward a reduction in pain compared to the placebo group, but the difference was not statistically significant (1.76 ± 0.31 for naproxen and 1.00 ± 0.32 for placebo group on a 5 point scale $p \geq 0.05$).

Pooling of the results of these 3 studies was possible on the following outcomes: shoulder range of motion in abduction and self-reported function (34–36). Therefore, a meta-analysis was performed for these two outcomes. These 3 studies ($n = 130$) measured active shoulder range of motion in abduction at similar time points (between 21 to 28 days). Pooling of results revealed a significant overall effect in favour of corticosteroids injections over oral NS COX inhibitor (MD = –4.73°; 95% CI –8.10 to –1.36; $p = 0.006$; Fig. 3) (34–36). For self-reported function, no significant differences were found at the same time points between the two types of intervention (SMD = 0.09; 95% CI –0.25 to 0.44; $p = 0.59$; Fig. 3).

In the RCT of Petri et al. (35), the combined effect of NS COX inhibitors with a corticosteroids injection was also evaluated. The combined group showed greater results in terms of shoulder active abduction (mean change: 1.95 ± 0.23, compared to the corticosteroid injection group (1.56 ± 0.24), to the naproxen group (1.39 ± 0.31), or to the placebo (0.77 ± 0.24)), but no statistical testing was done to confirm those results. In terms of pain and overall function, the corticosteroids injections group showed better results than the combined intervention group (35). But again no statistical testing was done to confirm those results.

Adverse events were reported as mild to moderate dyspepsia events in these 3 studies. In two studies, no statistical difference was showed for the incidence of adverse events between the two types of care (34, 35). In the RCT of White et al. (36), more adverse events were reported in the injection group compared to the oral NSAIDs group (10% vs 5%), but no statistical testing was done to confirm that trend.

*NS COX inhibitors – piroxicam vs. naproxen.* One study assessed the efficacy of two different NS COX inhibitors (piroxicam and naproxen) in participants with acute RC tendinopathy ($n = 40$) (30). Results showed that the group using piroxicam improved pain at night significantly compared to the group using naproxen at the 21 day follow-up (mean difference between groups was –1.7 ± 0.86 on a 10 cm VAS, $p = 0.022$). As for range of motion in abduction, both groups improved (mean improvement: 17.1° ± 6.4 for piroxicam, 18.6° ± 6.6 for naproxen) (30). No between-group comparison was performed by the authors on this outcome. Minor

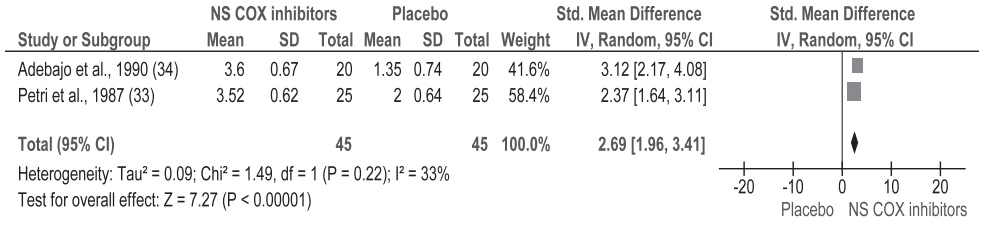


*Fig. 2.* Forest plot of pooled studies comparing non-selective COX (NS COX) inhibitors to a placebo intervention for change in overall pain at 4 weeks. SD: standard deviation; SM: standardized mean; CI: confidence interval.

adverse events were reported (35% for the piroxicam group and 40% for the naproxen group) and were mainly dyspepsia (no statistical analysis was performed to measure difference in incidences of adverse events between groups).

*NS COX inhibitors vs. COX-2 inhibitors.* Three RCTs compared NS COX inhibitors to COX-2 inhibitors (28, 32, 33). In terms of pain at rest, two studies presented results on the efficacy of NS COX inhibitors compared to COX-2 inhibitors. However, they were not pooled together for that outcome given the significant heterogeneity ($Tau^2 = 4.35$, $\chi^2 = 29.28$, df = 1 ($p < 0.00001$); $I^2 = 97\%$). For these 3 RCTs, in terms of reduction of pain at rest, pain during movement and shoulder range of motion after a 14-day treatment, there was no significant difference between the two types of oral NSAID (28, 32, 33). In terms of tolerability, in the study of Wober et al. (28) ($n = 122$), COX-2 inhibitors did not present a significantly better tolerability compared to NS COX inhibitors (14.5% and 26.7%, respectively, $p = 0.07$). In the two other studies, a similar trend was seen although no statistical testing was presented (proportions of adverse events were respectively 40.4 and 36.7% for COX-2 inhibitors, and 44.7 and 36.0% for NS COX inhibitors). The gastro-intestinal events were the most common adverse events. However, the severity of adverse events was generally not reported.

*NS COX inhibitors vs. laser therapy.* One study compared oral NS COX inhibitor (naproxen 550 mg BID) to laser therapy (5 min, 3 times/week, 3 mW, 904 nm wavelength, 4,000 Hz, 10 W peak output) for 2 weeks in 30 participants. The laser therapy showed greater results in terms of pain on 10 cm VAS (2 cm, 95% CI 1 to 3) as well as for shoulder active range of motion ($p < 0.05$) compared to the oral NSAIDs group (40).

*Different dosages of NS COX inhibitors.* Two studies compared two different dosages of NS COX inhibitors: Fentiazac (slow-release tablet of 300 mg once daily vs one regular tablet of 100 mg 4 times daily) and Ibuprofen (two slow-release tablets of 600 mg twice daily vs a regular tablet of 600 mg 4 times a day) (37, 38). In Ginsberg & Famaey (38), no significant between-groups differences were observed for the Fentiazac. On overall pain, mean changes were –2.1 for slow-release dose of fentiazac and –2.0 for regular dose on a 10 point scale ($p < 0.001$ pre-post treatment comparison), and for range of motion (movement not specified) mean changes were 3.4

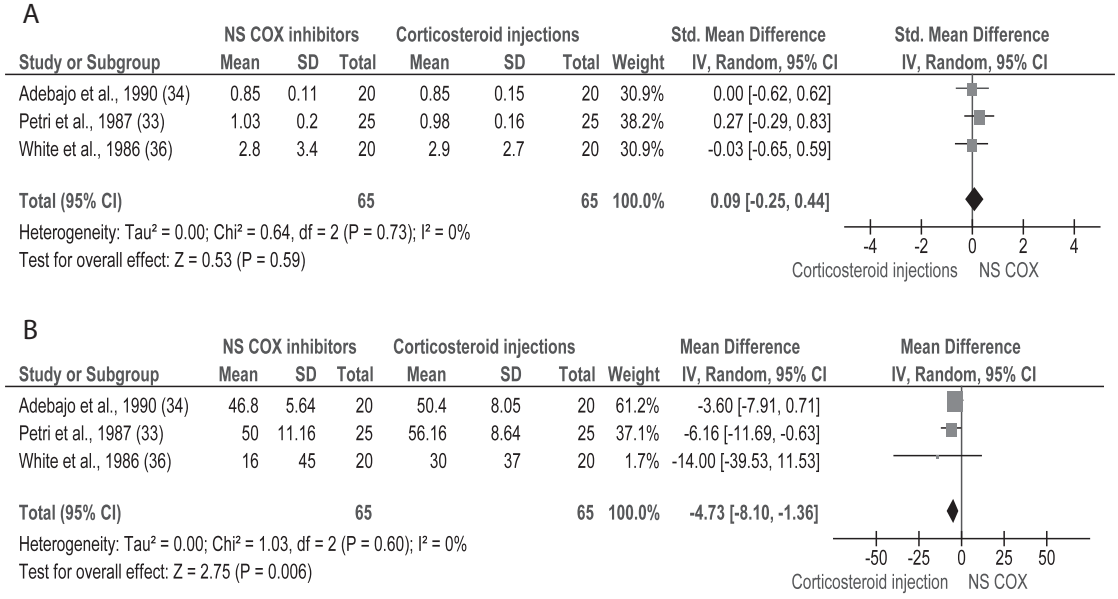


*Fig. 3.* Forest plots of pooled studies comparing non-selective COX (NS COX) inhibitors to corticosteroids injections for change in limitation of function (A) and for change in shoulder mobility in abduction (B) at 3 to 4 weeks. SD: standard deviation; SM: standardized mean; CI: confidence interval.

for slow-release dose and 3.6 for regular dose, on a 10 point scale with a pre-post treatment statistical significant difference ($p < 0.01$). The studies did not find any difference in the tolerability or frequency of adverse events between groups during their 14-day follow-up period. In Friis et al. (37), proportion of participants with complete pain relief was 21% in conventional formulations and 7% in sustained-release formulations with a statistical significant difference between group ($p = 0.02$).The proportion of participants who improved following treatment reached 77% (95% CI: 65 to 86) for conventional formulations and 68% (95% CI: 55 to 77) for sustained-release formulations.

*Methodological quality of included studies*

Mean score for the methodological quality of the included studies was 53.6 % (SD 8.8%) and no trials received a methodological score exceeding 70%, indicating low to moderate methodological quality of the included studies studies (Table I). In terms of reviewers agreement on the methodological quality of included studies, the intraclass correlation coefficient for overall methodological score between reviewers was 0.46 (95% CI –0.13 to 0.81) and the inter-rater agreement on specific items of the methodological appraisal scale ranged from poor to perfect agreement: $\kappa = 0.03$ for incomplete outcome data, $\kappa = 0.07$ for blinding of assessor, $\kappa = 0.3$ for selective outcome reporting, $\kappa = 0.37$ for other source of bias, $\kappa = 0.43$ for sequence generation, $\kappa = 0.63$ for allocation concealment, $\kappa = 0.67$ for blinding of participants and $\kappa = 1$ for blinding of provider/personnel. Nonetheless after discussion between reviewers consensus was always achieved.

All of the studies lack some relevant information on the appraised methodological criteria, particularly on the sequence generation, allocation concealment and blinding of the participants, providers, or assessors (Table II). All the studies had a short-term follow-up of less than one month, except for one RCT, that followed the participants for 42 days (36).

Only two of the included studies reported adequately their allocation sequence generation (34, 35) and only one study reported the procedure for allocation concealment (31). The blinding procedures were adequately presented in 6 studies (31, 34–38). Incomplete outcome data reporting was scored at high risk of bias in 4 studies (28, 29, 33, 38). Selective outcome reporting was scored as unknown/unclear or present in all studies, and was mainly associated with the fact that the research protocol was unavailable, and that important relevant outcome measures were not used (22, 29, 30, 32–39). Other sources of bias were identified in 8 studies, because of the lack of description about the compliance to main treatment, of high proportions of participants lost to follow-up and because non-standardized co-interventions such as injections and rehabilitation were provided to participants as an adjunct to oral NSAIDs (31–38). Seven studies did not monitor the compliance to medication use (22, 29, 33, 35–37, 39).

The identification of the population under study varied depending on the studies. Although all studies included participants with RC tendinopathy, some studies included participants on the only basis that they experienced shoulder pain, leading to the possibility that participants with other pathologies may have been included (30, 32, 37). Moreover, when RC tendinopathy was the population of interest, the diagnostic criteria were often not well-described leading to the possibility that participants with other pathologies may have been included and the majority of studies only included patients with acute symptoms (28, 29, 31, 33–36, 38).

The most common outcome measure used in the included studies was pain measured with a VAS. However, 6 out of 12 studies used non-standardized, non validated assessment tools to evaluate treatment effect (28, 31, 35, 37, 38). Functional or health related quality of life outcome measures were only used in 4 studies (22, 33, 35, 36). Four studies reported an affiliation with a pharmaceutical enterprise and this enterprise was the manufacturer of the medication used in the study (30, 32–34).

Table II. *Detailed methodological assessment of included studies using the Cochrane Risk of Bias Tool*

| | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants | Blinding of personnel/provider | Blinding of outcome assessment (detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) | Other bias |
|---|---|---|---|---|---|---|---|---|
| Adebajo et al., 1990 (34) | + | ? | + | + | + | + | – | – |
| Bertin et al., 2003 (32) | ? | ? | ? | ? | ? | + | – | – |
| England et al., 1989 (39) | ? | ? | ? | – | + | + | ? | ? |
| Friis et al., 1992 (37) | ? | ? | + | ? | + | ? | ? | + |
| Ginsberg & Famaey, 1985 (38) | ? | ? | + | ? | ? | – | – | – |
| Mena et al., 1986 (31) | ? | + | + | ? | + | ? | ? | – |
| Petri et al., 1987 (35) | + | ? | + | + | + | ? | – | – |
| Petri et al., 2004 (33) | ? | ? | ? | ? | ? | – | ? | – |
| Smith et al., 1986 (30) | ? | ? | ? | ? | ? | + | + | + |
| White et al, 1986 (36) | ? | ? | + | ? | ? | + | – | – |
| Wober et al., 1998, 1999 (29, 28) | ? | ? | ? | ? | ? | – | ? | + |

+: low risk of bias, –: high risk of bias, ?: unclear or unknown risk of bias.

## DISCUSSION

The aim of our study was to evaluate the scientific literature in regards to the efficacy of oral NSAIDs for adults with RC tendinopathy. Twelve RCT were included and the methodological quality of the majority of trials was low to moderate (53.6 %; SD 8.8%). No studies received a score exceeding 70% in terms of their methodological quality and risk of bias.

*Main findings*

From this review we are able to conclude from 4 RCTs of moderate quality that there is low to moderate evidence that,

Table III. *Summary table of the evidence for the efficacy of oral non-steroidal anti-inflammatory drugs (NSAIDs) for rotator cuff tendinopathy*

| Treatment | Studies *n* | Participants (follow-up periods, days) *n* | Pooled effects | Conclusions | Quality of evidence |
|---|---|---|---|---|---|
| NS COX inhibitors vs placebo | 4 | 120 (14) | Pain (10 cm VAS): MD: 2.69 (95% CI: 1.96 to 3.41) in favour of NS COX inhibitors<br>Function and shoulder ROM: pooling of results was not possible | NS COX inhibitors provide short term pain relief<br>No evidence of short term benefits in self-reported function and in shoulder range of motion | Low to moderate evidence |
| NS COX inhibitors vs COX 2 inhibitors | 3 | 608 (14) | Pooling of results was not possible | Both type of NSAIDs present similar short term efficacy in terms of pain reduction and gain in shoulder ROM<br>Short term tolerability and incidence of adverse events appear to be similar between the two categories of NSAIDs | Low to moderate evidence |
| Oral NS COX inhibitors vs Corticosteroids injections | 3 | 200 (33) | Pain: pooling of results was not possible<br>Self-reported function: SMD: 0.09 (95% CI: –0.25 to 0.44)<br>Shoulder ROM in abduction: MD:– 4.73° (95% CI: –8.10 to –1.36) in favour of corticosteroids injections | No differences in short term efficacy between the two types of treatment in terms of pain and self-reported function<br>Corticosteroids injections provide greater short term gain in ROM in abduction but difference is not clinically important compared to Oral NS COX inhibitors | Low to moderate evidence |

NS COX: non-selective cyclo-oxygenase inhibitors; COX-2: cyclo-oxygenase selective inhibitors; MD: mean difference; 95% CI: 95% confidence interval; ROM: range of motion; SMD: standard mean difference.

in the short term, oral NSAIDs lead to a reduction in pain in individuals with RC tendinopathy compared to a placebo intervention (Table III) (31, 34, 35). Only one study of moderate methodological quality concluded that oral NSAIDs were not effective in reducing pain compared to a placebo and that laser therapy was superior (39). The fact that no effect on functional improvement was observed in the included studies may be due to the short follow-up (less than 30 days). It may also be related to the use of non-validated functional outcomes such as in-home assessment tool (34, 38, 39). These 3 studies presented results on the efficacy of NS COX inhibitors compared to a placebo. However, they were not pooled together for that outcome given the significant heterogeneity. For these reasons, further studies are needed to draw conclusion on the effect of oral NSAIDs on function in individuals with RC tendinopathy.

There is low to moderate evidence from 3 moderate quality trials that oral NSAIDs are as effective as corticosteroids injections in reducing pain or improving function in the short term. In terms of range of motion in abduction, corticosteroids injections showed a slight significant superiority compared to NS COX inhibitors (MD = 4.73), but that difference was below the minimal clinically important difference of 16° (41). For self-reported function, no significant differences were seen between both types of treatment when results were pooled.

These findings have implications for clinicians and suggest that RC tendinopathy may be treated with a short term bout of oral NSAIDs to relieve pain but other therapeutic options may be warranted to ultimately insure complete functional recovery. Such interventions could include stretching, strengthening or motor control exercises which have been shown to reduce disabilities in patient with RC tendinopathy (3). Our review does not support the use of corticosteroids injections, at least in the short term, as they have not proved to be superior to oral NSAIDs in relieving pain for RC tendinopathy. Other authors have outlined the potential detrimental effect of corticosteroids injections on tendon integrity (15).

When comparing COX-2 inhibitors with NS COX inhibitors, both types of NSAIDs present similar short-term efficacy in terms of pain reduction and gain in shoulder range of motion. But caution is warranted for the long-term use of COX-2 inhibitors as data from the literature suggests that their use is associated with an increased risk of cardio-vascular events compared to NS COX inhibitors (11). It is important to point out that NS COX inhibitors use has also been associated with an increased risks of cardio-vascular events and the use of other types of medication such as acetaminophen, may be an effective option with less risk of adverse events. Acetaminophen has been recommend as the first pharmaceutical option for osteoarthritis (9, 42). However, in our review no studies compared NSAIDs to acetaminophen.

The systematic review by van der Sande et al. (21) concluded, contrary to the present review, that oral NSAIDs were not effective in reducing pain in the short term. The authors, however, based their conclusions on only one RCT (21). When compared to corticosteroids injections our conclusions regarding the efficacy of oral NSAIDS is similar to the conclusion of van der Sande et al. (21) and in two previous reviews, oral NSAIDs were found to be effective in reducing short-term pain in shoulder pain patients (19, 20). These authors were, however, unable to draw any conclusions regarding the long-term efficacy of NSAIDs, or regarding the risks/benefits of this type of treatment as evidence was either lacking or inconclusive (19–21). In another review of van der Windt et al. (20), the authors concluded that NSAIDs could significantly improve function compared to a placebo treatment but their conclusion was again limited to short term outcomes. In the same review, contrary to the present review, corticosteroids

injections were more effective than NSAIDs in reducing pain in the short term for patients with shoulder pain (20). These findings may explained by the fact that other shoulder pathologies such as osteoarthritis and adhesive capsulitis were included in the trials under study. Another SR on conservative and surgical treatments for all types of tendinopathies concluded that for acute shoulder bursitis/tendonitis, oral and topical NSAIDs seemed to be effective options to relieve pain in the short term (7–14 days) (6).

Although we were able to draw some conclusions regarding the efficacy of oral NSAIDs for RC tendinopathy, methodological quality of included studies was low to moderate and reporting of relevant methodological information was often absent. Patient compliance to treatment was often not optimal, or not monitored/reported and the use of co-interventions such as physiotherapy, exercises, corticosteroid injection, and other rescue medication was often allowed and not controlled (22, 35–37). Therefore, the magnitude of the treatment effect of oral NSAIDs observed may be somewhat biased. Patients included were most often suffering from acute symptoms of less than 6 weeks (28–33, 36). Eligibility criteria used might also have lead to the inclusion of participants not necessarily suffering from RC tendinopathy or participants that may have suffered from another shoulder pathology in conjunction with RC tendinopathy (28, 29, 31, 33–35, 38). In terms of outcome measures selection, only 6 studies out of 12 used standardized and valid evaluation tools. Further, in most studies, the main outcome measure was only pain, and relevant outcomes such function or health-related quality of life were not always accounted for (28, 30, 31, 33, 36–38). As previously mentioned, the follow-up period was short and the duration of treatment was also short-term and this may not reflect current clinical practice where patients suffering from RC tendinopathy are often prescribed repeated courses of NSAIDs treatment over longer periods of time, but caution is probably warranted, as there is emerging evidence regarding the potential deleterious effect of long-term use of NSAIDs on the mechanical properties tendons and soft tissue healing (43). Detrimental effect of oral NSAIDs use on the mechanical properties of the tendons has been observed in animal models (44, 45) and selective COX-2 inhibitors' effect may be worse (46). More studies on the long-term use of oral NSAIDs for musculoskeletal disorders in humans are needed to establish whether there is in fact a deleterious effect on tendon integrity and ultimately on patient function. Although many studies showed a significant treatment effect, all of the included studies were likely underpowered to evaluate and compare the incidence of other adverse events such as cardiovascular problems (9, 47). Interestingly the included trials compared NSAIDs interventions to other NSAIDs, injections or a placebo, but no studies used other commonly prescribed interventions for RC tendinopathy such as acetaminophen or exercise, which have been advocated as therapeutic interventions for RC tendinopathy or other types of tendinopathy (6, 48).

### *Strengths and limitations of the review*

One of the strength in our review is the in-depth literature search. It was performed using 4 important databases that contained the bulk of the scientific literature on this topic. We excluded articles that were not representative of the study population. Moreover, the literature search was performed in English and in French. It is important to note that we concentrated our literature search on RCTs, the highest form of evidence and we did not include other research design.

The methodological tool/risk of bias used in this review to appraise the quality of the included studies (Cochrane risk of bias assessment tool) is a well-known, valid tool but the concordance between the reviewers in our review was found only to be moderate. Nonetheless, after discussion, consensus was always achieved and a third reviewer did not have to intervene to resolve differences. Because of the heterogeneity of the trials, we were only able to pool results from subgroups of studies and for some specific outcomes only. Nonetheless, we believe we were able to draw valid conclusions and to provide estimates of treatment effects of oral NSAIDs for RC tendinopathy.

### *Conclusion*

Low to moderate evidence exists for the efficacy of NSAIDs either selective COX-2 or non-selective COX inhibitors in reducing short term pain for participants with RC tendinopathy. Moderate evidence suggest that oral NSAIDs are as effective as corticosteroid injections in reducing short term pain. Use of NSAIDs may reduce pain in the short term but clinicians should be aware that evidence regarding the efficacy of moderate to long-term use of NSAIDs is lacking and its impact on the tendon healing as well as on overall patient function is unknown in RC tendinopathy patients. More methodologically sound studies are therefore needed.

## ACKNOWLEDGEMENT

The authors declare that they have no competing interests. Financial support has been provided by the Réseau Provincial de Recherche en Adaptation-Réadaptation (REPAR), by the Institut de Recherche en Santé et Sécurité au Travail (IRSST) and by Fonds de Recherche du Québec en Santé (FRQS).

## REFERENCES

1. Tekavec E, Joud A, Rittner R, Mikoczy Z, Nordander C, Petersson IF, et al. Population-based consultation patterns in patients with shoulder pain diagnoses. BMC Musculoskelet Disord 2012; 13: 238.
2. Lewis JS. Rotator cuff tendinopathy. Br J Sports Medicine 2009; 43: 236–241.
3. Hanratty CE, McVeigh JG, Kerr DP, Basford JR, Finch MB, Pendleton A, et al. The effectiveness of physiotherapy exercises in subacromial impingement syndrome: a systematic review and meta-analysis. Semin Arthritis Rheum 2012; 42: 297–316.
4. Seitz AL, McClure PW, Finucane S, Boardman ND 3rd, Michener LA. Mechanisms of rotator cuff tendinopathy: intrinsic, extrinsic, or both? Clin Biomech (Bristol, Avon) 2011; 26: 1–12.
5. Neer CS, 2nd. Anterior acromioplasty for the chronic impingement syndrome in the shoulder: a preliminary report. J Bone Joint Surg Am 1972; 54: 41–50.
6. Andres BM, Murrell GA. Treatment of tendinopathy: what works, what does not, and what is on the horizon. Clin Orthop Relat Res 2008; 466: 1539–1554.
7. Orchard J, Kountouris A. The management of tennis elbow. BMJ 2011; 342: d2687.
8. Skjong CC, Meininger AK, Ho SS. Tendinopathy treatment: where

is the evidence? Clin Sports Med 2012; 31: 329–350.
9. Antman EM, Bennett JS, Daugherty A, Furberg C, Roberts H, Taubert KA. Use of nonsteroidal antiinflammatory drugs: an update for clinicians: a Scientific statement from the American Heart Association. Circulation 2007; 115: 1634–1642.
10. Hawkey CJ, Langman MJ. Non-steroidal anti-inflammatory drugs: overall risks and management. Complementary roles for COX-2 inhibitors and proton pump inhibitors. Gut 2003; 52: 600–608.
11. Roubille C, Martel-Pelletier J, Davy JM, Haraoui B, Pelletier JP. Cardiovascular adverse effects of anti-inflammatory drugs. Anti-inflamm Antiallergy Agents Med Chem 2013; 12: 55–67.
12. Paoloni JA, Milne C, Orchard J, Hamilton B. Non-steroidal anti-inflammatory drugs in sports medicine: guidelines for practical but sensible use. Br J Sports Med 2009; 43: 863–865.
13. Alfredson H, Lorentzon R. Chronic tendon pain: no signs of chemical inflammation but high concentrations of the neurotransmitter glutamate. Implications for treatment? Current drug targets 2002; 3: 43–54.
14. Fredberg U, Stengaard-Pedersen K. Chronic tendinopathy tissue pathology, pain mechanisms, and etiology with a special focus on inflammation. Scand J Med Sci Sports 2008; 18: 3–15.
15. Khan KM, Cook JL, Bonar F, Harcourt P, Astrom M. Histopathology of common tendinopathies. Update and implications for clinical management. Sports Med 1999; 27: 393–408.
16. Maffulli N, Sharma P, Luscombe KL. Achilles tendinopathy: aetiology and management. J R Soc Med 2004; 97: 472–476.
17. Ziltener JL, Leal S, Fournier PE. Non-steroidal anti-inflammatory drugs for athletes: an update. Ann Phys Rehabil Med 2010; 53: 278–282, 282–288.
18. Millar NL, Hueber AJ, Reilly JH, Xu Y, Fazzi UG, Murrell GA, et al. Inflammation is present in early human tendinopathy. The Am J Sports Med 2010; 38: 2085–2091.
19. Green S, Buchbinder R, Glazier R, Forbes A. Systematic review of randomised controlled trials of interventions for painful shoulder: selection criteria, outcome assessment, and efficacy. BMJ 1998; 316: 354–360.
20. van der Windt DA, van der Heijden GJ, Scholten RJ, Koes BW, Bouter LM. The efficacy of non-steroidal anti-inflammatory drugs (NSAIDS) for shoulder complaints. A systematic review. J Clin Epidemiol 1995; 48: 691–704.
21. van der Sande R, Rinkel WD, Gebremariam L, Hay EM, Koes BW, Huisstede BM. Subacromial impingement syndrome: effectiveness of pharmaceutical interventions-nonsteroidal anti-inflammatory drugs, corticosteroid, or other injections: a systematic review. Arch Phys Med Rehabil 2013; 94: 961–976.
22. Higgins JPT, Altman DG. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Greens S, editors. Cochrane Handbook for Systematic Reviews of Interventions. The Cochrane Collaboration; 2008. Available from: http://www.cochrane.org/sites/default/files/uploads/handbook/Handbook510pdf_Ch08_RiskOfBias.pdf.
23. Higgins JPT, Green S, Collaboration C. Cochrane Handbook for Systematic Reviews of Interventions. Chichester: Wiley-Blackwell; 2008.
24. Lopez JM. Treatment of acute tendinitis and bursitis with fentiazac – a double-blind comparison with placebo. Clin Ther 1982; 5: 79–84.
25. Wielandts L, Dequeker J. Double-blind trial comparing fentiazac with phenylbutazone in patients with tendinitis. Current Medical Research and Opinion 1979; 6: 85–89.
26. Dougados M, Henanff AL, Logeart I, Ravaud P. Short-Term Efficacy of Rofecoxib and diclofenac in acute shoulder pain: A placebo-controlled randomized trial. PLoS Clin Trials 2007; 2: e9.
27. Zuinen C. Diclofenac/misoprostol vs diclofenac/placebo in treating acute episodes of tendinitis/bursitis of the shoulder. Drugs 1993; 45 Suppl 1: 17–23.
28. Wober W. Comparative efficacy and safety of nimesulide and diclofenac in patients with acute shoulder, and a meta-analysis of controlled studies with nimesulide. Rheumatology (Oxford) 1999; 38 Suppl 1: 33–38.
29. Wober W, Rahlfs VW, Buchl N, Grassle A, Macciocchi A. Comparative efficacy and safety of the non-steroidal anti-inflammatory drugs nimesulide and diclofenac in patients with acute subdeltoid bursitis and bicipital tendinitis. Int J Clin Pract 1998; 52: 169–175.
30. Smith MD, Thomas D, McCredie M, Brooks PM. Piroxicam versus naproxen in the treatment of painful shoulder. Pharmatherapeutica 1986; 4: 585–589.
31. Mena HR, Lomen PL, Turner LF, Lamborn KR, Brinn EL. Treatment of acute shoulder syndrome with flurbiprofen. Am J Med 1986; 80: 141–144.
32. Bertin P, Behier JM, Noel E, Leroux JL. Celecoxib is as efficacious as naproxen in the management of acute shoulder pain. J Int Med Res 2003; 31: 102–112.
33. Petri M, Hufman SL, Waser G, Cui H, Snabes MC, Verburg KM. Celecoxib effectively treats patients with acute shoulder tendinitis/bursitis. J Rheumatol 2004; 31: 1614–1620.
34. Adebajo AO, Nash P, Hazleman BL. A prospective double blind dummy placebo controlled study comparing triamcinolone hexacetonide injection with oral diclofenac 50 mg TDS in patients with rotator cuff tendinitis. J Rheumatol 1990; 17: 1207–1210.
35. Petri M, Dobrow R, Neiman R, Whiting-O'Keefe Q, Seaman WE. Randomized, double-blind, placebo-controlled study of the treatment of the painful shoulder. Arthritis Rheum 1987; 30: 1040–1045.
36. White RH, Paull DM, Fleming KW. Rotator cuff tendinitis: comparison of subacromial injection of a long acting corticosteroid versus oral indomethacin therapy. J Rheumatol 1986; 13: 608–613.
37. Friis J, Jarner D, Toft B, Christensen K, Christophersen J, Ibfeldt HH, et al. Comparison of two ibuprofen formulations in the treatment of shoulder tendonitis. Clin Rheumatol 1992; 11: 105–108.
38. Ginsberg F, Famaey JP. A double-blind comparison of slow-release and standard tablet formulations of fentiazac in the treatment of patients with tendinitis and bursitis. Curr Med Res Opin 1985; 9: 442–448.
39. England S, Farrell AJ, Coppock JS, Struthers G, Bacon PA. Low power laser therapy of shoulder tendonitis. Scand J Rheumatol 1989; 18: 427–431.
40. Soubrier M, Rosenbaum D, Tatar Z, Lahaye C, Dubost JJ, Mathieu S. Vascular effects of nonsteroidal antiinflammatory drugs. Joint Bone Spine 2013; 80: 358–362.
41. Muir SW, Corea CL, Beaupre L. Evaluating change in clinical status: reliability and measures of agreement for the assessment of glenohumeral range of motion. NAJSPT 2010; 5: 98–110.
42. Kamath CC, Kremers HM, Vanness DJ, O'Fallon WM, Cabanela RL, Gabriel SE. The cost-effectiveness of acetaminophen, NSAIDs, and selective COX-2 inhibitors in the treatment of symptomatic knee osteoarthritis. Value Health 2003; 6: 144–157.
43. Butterfield TA, Best TM, Merrick MA. The dual roles of neutrophils and macrophages in inflammation: a critical balance between tissue damage and repair. J Athl Train 2006; 41: 457–465.
44. Cohen DB, Kawamura S, Ehteshami JR, Rodeo SA. Indomethacin and celecoxib impair rotator cuff tendon-to-bone healing. Am J Sports Med 2006; 34: 362–369.
45. Ferry ST, Dahners LE, Afshari HM, Weinhold PS. The effects of common anti-inflammatory drugs on the healing rat patellar tendon. Am J Sports Med 2007; 35: 1326–1333.
46. Radi ZA. Pathophysiology of cyclooxygenase inhibition in animal models. Toxicol Pathol 2009; 37: 34–46.
47. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. Ann Intern Med 2001; 134: 657–662.
48. Simpson MR, Howard TM. Tendinopathies of the foot and ankle. Am Fam Physician 2009; 80: 1107–1114.