Use of Anti-Inflammatory Drugs interventions for the treatment of Muscle Soreness: a Systematic Review and Meta-analysis.

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Systematic Review

**Keywords:** Pharmacology, Pain, Sports Medicine, Evidence-Based Medicine, non-steroidal anti-inflammatory drug, Delayed Onset Muscle Soreness (DOMS)

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Abstract

**Objective:** To investigate the effects of pharmacological interventions in the treatment of Delayed Onset Muscle Soreness (DOMS).

**Design:** Systematic review and meta-analysis of randomised controlled clinical trials (RCTs).

**Data sources:** The PubMed / MEDLINE, EMBASE, SPORTDiscus, Scielo and CENTRAL (Cochrane Central Register of Controlled Trials) databases were searched from the oldest records to August 3, 2020.

**Eligibility criteria:** 1) Used a RCTs design; 2) Evaluate the effects of Steroidal or Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) for treatment DOMS; and 3) Therapeutically used drugs, after exercise.

**Results:** In total, 26 studies (patients = 934) were eligible for qualitative analysis on the treatment of DOMS. The results of the meta-analysis showed no superiority between the use or not of NSAIDs, in the improvement of late muscle pain, since statistically significant differences were not verified (21 studies, n=955; SMD= 0.02; 95% CI -0.58, 0.63; p=0.94; I²=93%). The quality of the synthesized evidence was very low according to the criteria of Evaluation, Development and Evaluation of the Classification of Recommendations, associated with the significant heterogeneity among the included studies.

**Conclusion:** The results demonstrate that the use of NSAIDs is not a superior treatment to the control / placebo on DOMS improvement. The variation between dose-response and exercise protocol used in the studies may have influenced the results. In addition, the high risk of identified bias characterizes limitation to be considered in profound interpretations.

Introduction

The excess of exercise for a given physical conditioning can cause inflammation. Strenuous and unusual exercises can cause sub-macroscopic tissue damage, which is associated with symptoms such as stiffness, impairment of range of motion and discomfort. These events normally result in a late-onset muscle pain, known as Delayed Onset Muscle Soreness (DOMS) and are responsible for impairing sports performance [1]. Pain is not perceived either during or right after exercise, but generally happens in a 24 - 48 hours period [2, 3]. The inflammatory response developed after exercise characterizes a process for tissue recovery and is related to muscle recovery and adaptation essential for the functional gain [3]. Pain constitutes an unpleasant experience, which limits daily activities. And its treatment is the aim of both the prescriber and the patient. Thus, the use of non-steroidal anti-inflammatory drugs (NSAIDs) are commonly suggested to contain pain and improve the recovery process.

NSAIDs act by inhibiting cyclooxygenase family (EC 1.14.99.1) enzymes. Leading to the decrease of prostaglandins, prostacyclins and thromboxane synthesis. The decrease of prostaglandins concentration reduces acute inflammation, lowering pain neural pathways and inhibiting installation of edema [4]. It is well known that NSAIDs blocks mTOR signaling [5]. Consequently, the use of NSAIDs may suppress myofibril regeneration as well as cell proliferation or differentiation and hypertrophy [4, 6].

Previous studies have shown ambiguous data on the use of NSAIDs in DOMS. Ibuprofen decreases macrophage infiltration in the damaged tissue within 24 hours after exercise [7]. On the other hand, the use of naproxen did not alter tissue infiltration of inflammatory cells after experimental muscle damage protocol [8].

Vella et al. (2016) propose that NSAIDs decreases the intensity of the inflammatory response and leukocyte infiltration in skeletal muscle. Their hypothesis reinforces that the intensity of exercise and tissue responses influence the clinical and side effects of anti-inflammatory drugs used to treat DOMS [9].

About the pain, one classical sign of inflammation, clinical trials using NSAIDs showed effect decreasing pain related to exercise when the use of diclofenac [10] and, also, with ibuprofen [11].

There are conflicting data about the use of NSAIDs for the treatment of DOMS. Some reports show decrease of pain and others report the impairment in the process of adaptation or function and the lack of effect in pain [12, 13]. Thus, more studies need to be done to enlighten this apparent contradiction. The consideration of the dose-response, population profile and type of exercise must be associated with therapy. And more the use of personalized medicine can be a way to help the understanding of the different responses to NSAIDs in different exercise protocols [14].

The clinical management of DOMS involves the attenuation of the inflammatory process, reducing both function and performance. Despite the various NSAIDs options used for the treatment of DOMS, little is known about the magnitude of their clinical effects, mostly due to the use of different protocols. An
additional concern is the high frequency of adverse reactions resulting from the use of these drugs. These collateral effects are worsened by the indiscriminate use without a medical recommendation [15].

Due to the many pharmacological options and the complexity to the management of DOMS, a review may be useful to assist in understanding the clinical control of DOMS. Therefore, the objective of the present review and meta-analysis study was to investigate the effects of NSAID-type pharmacological interventions in the treatment of DOMS.

**Methods**

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was used as a guideline [16, 17]. This review was registered in the International Prospective Register of Systematic Reviews (PROSPERO). We analyzed a total of 13,497 studies retrieved from different databases and one from the references on that studies [18].

**Study search and selection strategy**

We performed a broad search of keywords and terms related to DOMS, late muscle pain and anti-inflammatory drugs were combined to search in major databases. We used PubMed/MEDLINE, EMBASE, SPORTDiscus, Scielo and CENTRAL (Cochrane Central Register of Controlled Trials) to review all the manuscripts until August 03, 2020. In addition, a manual search in the references of all included studies was performed in order to add the electronic searches. A summarized description of this process is showed in Figure 1.

**Inclusion and exclusion criteria**

The next processes took place in stages (title, abstract and full text). We included studies that: 1) used a randomized controlled clinical trials (RCTs) design; 2) evaluated the effects of NSAIDs for treatment DOMS; and 3) analyzed therapeutic drugs after exercise. Case reports, case series, comments, editorials, letters to the editor and literature reviews were excluded. There were no restrictions regarding: age, gender, clinical condition, level of activity, date of publication or language. Both pathological and healthy clinical conditions were considered for selection. We only included studies with healthy participants, free of acute or chronic diseases. Both the detailed search strategy used can be found in supplemental material. For the purpose of this review and meta-analysis we did not seek studies related to steroidal anti-inflammatory drugs.

**Figure 1. Description of excluded studies according to the established criteria.**

**Data extraction**

We collected the following information after selecting the eligible studies: (1) general characterization of the study (authors; year of publication and design), (2) data of the studied population (sample size; gender distribution and age), (3) information related to late muscle pain (the protocol used for inducing muscle damage; type of intervention; dose-response; the method for assessing pain intensity; evaluations timeframe) and (4) outcomes of clinical pain improvement. The corresponding author of the studies was contacted to provide clarification in the case of lack of information.

**Risk of bias assessment**

The risk of bias was investigated for each analyzed study. The following items were considered and reported: potential selection bias (regarding sequence and concealment of allocation), performance bias (blinding of subjects and researches), detection bias (blinding evaluation of results), friction bias (incomplete result data), report bias (selective result report), and other bias. Thus, for each item described, the studies received possible ratings: low, high or unclear risk (when the information presented in the study was not sufficient to assess a particular area) [19].

Inclusion and exclusion criteria; data extraction and Risk of bias assessment were simultaneously analyzed by two independent authors using the Cochrane Collaboration Risk of Bias Tool [17, 20]. The data were analyzed using Review Manager (RevMan, 5.3.5).
Statistical analysis

The data were grouped in meta-analysis and reported as standardized mean difference (SMD) with 95% confidence interval (CI). The random-effect model was adopted due to the heterogeneity of the studies ($I^2=93\%$) and reported as the value of $I^2$. We included 19 studies for meta-analysis. Seven studies were excluded because of the use of visual analogue scale and three that presented incomplete data (the authors did not provide the requested information).

Results

Due to the different denominations of DOMS in this review we treated late-onset muscle pain and Delayed Onset Muscle Soreness (DOMS) as synonyms for both analyzes and discussion. A broad selection of papers retrieved 13,497 studies. A total of 127 investigations were considered eligible after applying the criteria (Fig 1). Of these, 23 studies were excluded for not using NSAIDs-type pharmacological interventions; 36 were excluded for not using the intervention after the effort and 42 studies were excluded because of the use of supplements, hormones or homoeopathy. We did not seek studies related to steroidal anti-inflammatory drugs. At the end we included 26 studies that met the proposed criteria (Table 1).

We analyzed characteristics of the subjects and studies and summarized them in Table 1. We retrieved three decades of studies starting in 1988. The majority of the studies were performed in parallel groups protocol (65.4%), some with cross-over (30.8%) and a minority of counter-balanced (3.8%). A total of 934 subjects were studied (18-70 years, mean and SD = 35.9± 34.2 yrs), from these 55.0% male. The subjects were described as trained (15.4%) or physically active - healthy (84.6%).

The majority of the studies were carried out in North America (57.7%): United States [7, 10, 21-30]; Canada [8, 31, 32]; Europe (34.6%): United Kingdom [33-35]; Germany [36, 37]; Greece [11]; Denmark [18, 38]; Belgium [39]; Africa (3.8%): South Africa [40] and Oceania (3.8%): Australia [9].

Concerning sample size, 13 articles (51.8%) included surveyed samples up to 20 participants, 12 studies (44.4%) had between 21 and 100 participants, and one study included more than 100 participants (3.8%). The majority of the studies (57.7%) only men, while other studies included both sexes.

The protocols used in the studies for inducing muscle damage varied both on the anatomical region and the type of equipment used for evaluation. Thus, in relation to the anatomical site, the studies varied between systemic protocols (23.1%) [24, 29, 33, 34, 37, 40] or localized, in the latter case 8 studies (30.8%) applied upper limb damage protocol [18, 21, 22, 25, 28, 30, 32, 35]; 11 studies (42.2%) lower limbs [7-11, 23, 26, 27, 31, 37] and one study (3.8%) with exercise in the temporomandibular joint [33]. Regarding the equipment used for comparation of the results, two studies (7.7%) used the isokinetic dynamometer [37, 39], 17 studies (65.4%) used conventional weight machines [7-11, 18, 21-23, 25-28, 31, 32, 35] and 6 studies (23.1%) performed aerobic exercises, lasting more than 30 minutes [24, 29, 33, 34, 37, 40].

NSAIDs are classified according to their selectivity to cyclooxygenase (COX) 2 inhibition. We found that 23 studies that used non-selective inhibitors (88.4%), while two studies investigated selective models, (7.6%). One study [24] did not concern about the type of NSAIDs used, since that the participants were free to use their choice of NSAIDs.

It was observed that the studies varied in the types of non-selective NSAIDs used, with more than half of the studies investigating ibuprofen (56.0%) [7, 9, 11, 18, 22, 23, 25, 28-30, 32, 34, 35, 38]. Other types used were naproxen (12.0%) [8, 26, 31]; diclofenac (8.0%) [10, 33]; ketoprofen (8.0%) [27, 36]; acetaminophen (8%) [7, 21]; aspirin (4.0%) [21] and piroxican (4%) [39].

The major route of administration was oral (77.0%) [6,7,8,10,17,20,21,22,23,25,27,29,28,30-34,36,37,38,39]. Some studies analyzed topical (11.5%) [9,24,26] or both (11.5%) [23,35,37]. Treatment beginning after the effort and remaining for different periods of time, with a maximum duration of seven days.

Thirteen studies (50.0%) did not find significant effects on the oral use of non-selective NSAIDs for the treatment of DOMS, while ten (38.5%) considered positive outcomes. All studies that used topical route had good outcomes on DOMS.
Regarding the two studies investigating selective NSAIDs, one used etoricoxib [37] (90mg/day for 7 days) and the other, rofecoxib [40] (50mg/day for 3 days). In both studies no significant effect was found.

The evaluation of pain was assessed by either visual analogue scale (82.2%) and mechanical pain (17.8%). Different moments of pain were evaluated in the studies. Most commonly, the follow-up started before the effort (baseline). Also, different follow-ups were used ranging from 24 hours to 7 days.

Risk of bias assessment

The bias risk assessment for each study is presented in Figure 2. As observed, the studies were prone to expose the following percentages of low risk of bias random sequence generation (80.9%), allocation concealment (4.7%), blinding of participants and personnel (71.4%), blinding of outcome assessment (14.2%), incomplete outcome data (33.3%), selective reporting (0%) and other bias (42.8%).

Figure 2. Bias risk evaluation of the selected studies examining the efficacy of NSAIDs for muscle soreness. Low risk (+), unclear risk (blank) and high risk (-) for different features of the Cochrane Risk of Bias Tool.
<table>
<thead>
<tr>
<th>Year</th>
<th>Design</th>
<th>Subjects</th>
<th>Exercise Protocol*</th>
<th>Drugs and route of administration</th>
<th>Dose</th>
<th>Assessment</th>
<th>Assessment protocol</th>
<th>Results Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arendt et al., 2007</td>
<td>Parallel groups</td>
<td>n=60</td>
<td>Intensive eccentric exercise of the first dorsal interosseous muscle of the left hand on a standardized hand exerciser for two minutes</td>
<td>Oral ibuprofen, glucosamine sulphate or placebo</td>
<td>1,200mg/d 22d VAS (0-9 cm) BEx; AEx (15, 16 and 22 days)</td>
<td>Not significant</td>
<td>&quot;Ibuprofen is not capable of inhibiting experimentally induced muscle tenderness/soreness&quot;</td>
<td></td>
</tr>
<tr>
<td>Bourgeois et al., 1999</td>
<td>Cross-over</td>
<td>n=8</td>
<td>Unilateral knee concentric/ eccentric weightlifting with 6 sets x 10 repetitions at 80-85% of the 1 RM contraction</td>
<td>Oral naproxen or placebo</td>
<td>1,000mg/d 2d VAS (0-10 cm)</td>
<td>BEx; AEx (0, 24 and 48 h)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cannavino et al., 2003</td>
<td>Parallel groups</td>
<td>n=32</td>
<td>Leg extension and flexion exercise program designed to create DOMS in quadriceps muscles</td>
<td>Topic ketoprofen or placebo</td>
<td>cream 10% 8/8h VAS (0-10 cm)</td>
<td>BEx; AEx (24 and 48 h)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Croisier et al., 1996</td>
<td>Cross-over</td>
<td>n=10</td>
<td>Eight stages of five maximal contractions of the knee extensor and flexor muscle groups of both legs separated by 1 min rest phases, on a KinTrex device at 60°/s angular velocity</td>
<td>Oral piroxicam or placebo</td>
<td>20mg/d 6d VAS (0-10 cm)</td>
<td>BEx; AEx (0, 24 and 48 h)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donnelly et al., 1988</td>
<td>Cross-over</td>
<td>n= 20</td>
<td>Running (heart rate equivalent to 75% of age adjusted maximum 220-age) for 45 minutes.</td>
<td>Oral diclofenac or placebo</td>
<td>150md/d (50mg 8/8h;72h) VAS (1-10 cm) and pain tolerance threshold</td>
<td>BEx and AEx (6, 24,48 and 72 h)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donnelly et al., 1990</td>
<td>Cross-over</td>
<td>n=32</td>
<td>Running (heart rate equivalent to 75% of age adjusted maximum 220-age) for 45 minutes.</td>
<td>Oral ibuprofen or placebo</td>
<td>2,400mg/d (600mg 6/6h;72h) VAS (1-10 cm) and pain tolerance threshold</td>
<td>BEx and AEx (6, 24, 48 and 72 h)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dudley et al., 1997</td>
<td>Cross-over</td>
<td>n=8</td>
<td>Ten sets of seven to 10 eccentric actions with each quadriceps femoris with a load equal to 85% of the eccentric one repetition</td>
<td>Oral Naproxen or placebo</td>
<td>600mg/d (200mg 8/8h;4d) VAS (1-100 mm)</td>
<td>BEx and AEx (24, 96 and 240 h)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* "NSAID administration did not cause muscle soreness"
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
<th>Age</th>
<th>Exercise</th>
<th>Intervention</th>
<th>Outcome Measure</th>
<th>Results/Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grossman et al., 1995</td>
<td>Parallel groups</td>
<td>n=30</td>
<td>20 men 10 women</td>
<td>Training level: &quot;healthy subjects&quot; 22.1 ± 6.9 yrs</td>
<td>Oral ibuprofen or placebo, 2,400mg/d</td>
<td>VAS (0-10 cm)</td>
<td>Oral ibuprofen and intense exercise more effective than a placebo in treating the effects</td>
</tr>
<tr>
<td>Hasson et al., 1993</td>
<td>Parallel groups</td>
<td>n=20</td>
<td>20 men 10 women</td>
<td>Training level: DNR 23.8±4.3 yrs</td>
<td>Oral ibuprofen, placebo or control, 1,200mg/d</td>
<td>Pressure pain threshold (level of soreness after the application of 50N)</td>
<td>At 48 h prophyl. therapy ibuprofen significantly reduced muscle sorenes (p &lt; 0.001)</td>
</tr>
<tr>
<td>Hyldahl et al., 2010</td>
<td>Parallel groups</td>
<td>n=106</td>
<td>41 men 65 women</td>
<td>Training level: DNR 18 - 65 yrs</td>
<td>Topical ibuprofen or placebo, gel 125mg/d, VAS (0-100 mm)</td>
<td>BEx and AEx (0, 36, 60, 84 and 108 h)</td>
<td>We found significant differences between active ibuprofen gel and placebo</td>
</tr>
<tr>
<td>Krentz, et al., 2008</td>
<td>Counter-balanced</td>
<td>n=18</td>
<td>12 men 6 women</td>
<td>Training level: DNR 24.1 ± 0.6 yrs</td>
<td>Oral ibuprofen or placebo, 400mg/d</td>
<td>VAS (0-9 cm)</td>
<td>No effect on muscle soreness daily per 6 weeks</td>
</tr>
<tr>
<td>Lecomte et al., 1998</td>
<td>Cross-over</td>
<td>n=20</td>
<td>20 men 6 women</td>
<td>Training level: DNR 24.0 ± 3.5 yrs</td>
<td>Oral naproxen or placebo, 1g/d</td>
<td>VAS (0-10cm)</td>
<td>Naproxen reduced perception of muscle sorenes 3 when sorenes highest (p=0.04)</td>
</tr>
<tr>
<td>Loram et al., 2005</td>
<td>Cross-over</td>
<td>n=15</td>
<td>10 men 5 women</td>
<td>Training level: &quot;physically active but not competitive&quot; 24.0 ± 4.5 yrs</td>
<td>Oral rofecoxib; tramadol or placebo, 50mg/d</td>
<td>VAS (0-100 mm)</td>
<td>Use of during exercise not relieving muscle or DOM</td>
</tr>
<tr>
<td>McAnulty et al., 2007</td>
<td>Parallel groups</td>
<td>n=60</td>
<td>45 men 15 women</td>
<td>Training level: &quot;experienced ultramarathoners&quot; 160 km following the Western States Endurance Run</td>
<td>Oral or topical route not clear in methodology &quot;Categorized as NSAID users if reported use during running and non-users reported to avoid NSAIDs&quot;</td>
<td>VAS (0-10 cm)</td>
<td>Use of during exercise not relieving muscle or DOM</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>n</td>
<td>Gender</td>
<td>Age</td>
<td>Exercise Protocol</td>
<td>Intervention</td>
<td>Outcome Measures</td>
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<td>-----------------------------------------------------------------------------------</td>
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<tr>
<td>Nieman et al., 2006</td>
<td>Parallel</td>
<td>29</td>
<td>Men</td>
<td>47.9 ± 1.4 yrs</td>
<td>Competing in a 160-km race</td>
<td>Oral ibuprofen or control (no intervention)</td>
<td>VAS (1-10 cm)</td>
</tr>
<tr>
<td></td>
<td>Parallel</td>
<td>29</td>
<td>Men</td>
<td>47.9 ± 1.4 yrs</td>
<td>Training level: ultramarathoners</td>
<td>Oral ibuprofen or control (no intervention)</td>
<td>VAS (1-10 cm)</td>
</tr>
<tr>
<td>Rahnama et al., 2005</td>
<td>Parallel</td>
<td>44</td>
<td>Men</td>
<td>24.3 ± 2.4 yrs</td>
<td>70 eccentric contractions of the biceps muscle of the non-dominant. Set of 10 contractions, with load was 80% of the maximal voluntary contraction.</td>
<td>Oral ibuprofen or control (no intervention)</td>
<td>VAS (1-30 cm)</td>
</tr>
<tr>
<td></td>
<td>Parallel</td>
<td>44</td>
<td>Men</td>
<td>24.3 ± 2.4 yrs</td>
<td>Training level: &quot;non-athletic&quot;</td>
<td>Oral ibuprofen or control (no intervention)</td>
<td>VAS (1-30 cm)</td>
</tr>
<tr>
<td>Rother et al., 2014</td>
<td>Cross-over</td>
<td>48</td>
<td>25 Men</td>
<td>23 Women</td>
<td>Eccentric exercise at 45 % of peak torque until volitional fatigue</td>
<td>Oral etoricoxib or placebo</td>
<td>VAS (0-10 cm)</td>
</tr>
<tr>
<td></td>
<td>Parallel</td>
<td>48</td>
<td>25 Men</td>
<td>23 Women</td>
<td>Training level: &quot;healthy and had an BMI &gt; 20 and &lt; 30&quot;</td>
<td>Oral etoricoxib or placebo</td>
<td>VAS (0-10 cm)</td>
</tr>
<tr>
<td>Seidel et al., 2016</td>
<td>Parallel</td>
<td>168</td>
<td>86 Men</td>
<td>82 Women</td>
<td>Walked for approximately 40 min downstairs with a total altitude of 300-400 m</td>
<td>Topical ketoprofen + oral placebo (two groups); Oral ketoprofen or oral placebo (two groups)</td>
<td>VAS (0-9 cm)</td>
</tr>
<tr>
<td></td>
<td>Parallel</td>
<td>168</td>
<td>86 Men</td>
<td>82 Women</td>
<td>Training level: &quot;Healthy&quot;</td>
<td>Oral ketoprofen + topical placebo</td>
<td>VAS (0-9 cm)</td>
</tr>
<tr>
<td>Simmons et al., 2018</td>
<td>Parallel</td>
<td>37</td>
<td>DNR</td>
<td>DNR</td>
<td>Exercise regimen and utilizing a customized, non-invasive armband (Band O°)</td>
<td>Oral ibuprofen or placebo</td>
<td>VAS (0-10 cm); sum of Pain Intensity Differences (SPID); and sum of DOMS</td>
</tr>
<tr>
<td></td>
<td>Parallel</td>
<td>37</td>
<td>DNR</td>
<td>DNR</td>
<td>Training level: DNR</td>
<td>Oral ibuprofen or placebo</td>
<td>VAS (0-10 cm); sum of Pain Intensity Differences (SPID); and sum of DOMS</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>n</td>
<td>Gender</td>
<td>Age</td>
<td>Intervention Details</td>
<td>Outcome Measures</td>
<td>SSMD</td>
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<tr>
<td>Singla et al., 2015</td>
<td>Parallel groups</td>
<td>24</td>
<td>15 men</td>
<td>28.3 yrs</td>
<td>Diclofenac or placebo</td>
<td>VAS (0-10 cm)</td>
<td>SSMD</td>
</tr>
<tr>
<td>Smith et al., 1995</td>
<td>Parallel groups</td>
<td>36</td>
<td>36 men</td>
<td>24.4 yrs</td>
<td>Aspirin, acetaminophen</td>
<td>VAS (1-10 cm)</td>
<td>SSMD</td>
</tr>
<tr>
<td>Stone et al., 2002</td>
<td>Parallel groups</td>
<td>40</td>
<td>20 men</td>
<td>23 yrs</td>
<td>Bromelain, ibuprofen or placebo</td>
<td>VAS (1-10 cm)</td>
<td>SSMD</td>
</tr>
<tr>
<td>Svensson et al., 1997</td>
<td>Parallel groups</td>
<td>10</td>
<td>10 men</td>
<td>24.6 yrs</td>
<td>Oral ibuprofen, placebo</td>
<td>VAS (1-10 cm)</td>
<td>SSMD</td>
</tr>
<tr>
<td>Tokmakidis et al., 2003</td>
<td>Parallel groups</td>
<td>19</td>
<td>14 men</td>
<td>24.6 yrs</td>
<td>Oral ibuprofen or placebo</td>
<td>VAS (1-10 cm)</td>
<td>SSMD</td>
</tr>
<tr>
<td>Trappe et al., 2002</td>
<td>Parallel groups</td>
<td>24</td>
<td>24 men</td>
<td>24 yrs</td>
<td>Oral ibuprofen, placebo</td>
<td>VAS (1-10 cm)</td>
<td>SSMD</td>
</tr>
</tbody>
</table>
25 ± 3 yrs the knee extensors 1d application of 40N

Acetaminophen
4000mg/d
8/8h
1st. dose one 1,500 2nd. dose 1,500 mg, 3rd. dose 1,000mg 1d

| Vella et al., 2016 | Parallel groups | n=16 | three sets of 8–10 repetitions performed on a Smith machine assisted squat, a 45° leg press and a leg extension at 80% of a predicted 1 RM | Oral ibuprofen or placebo | 1,200mg/d (400mg three doses) | VAS (1-10 cm) | BEx and AEx (0 and 24 h) | Not sig  
| | | 16 men | | | | | |  
| | | training level: | | | | | | 
| | | "healthy subjects” | | | | | | 
| | | 23.9 ± 1.3 yrs | | | | | |  

**Legend:** yrs=years; n= number of participants; DOMS= Delayed Onset Muscle Soreness; RM= maximum repetition; VAS= Visual analog scale; DNR : u d=days; h=hours; mg=milligrams; BEx = Before exercise; AEx = After exercise; N = newton;  

The characterization of the studies, subjects and protocols exactly using the paper's authors description.* written exactly as stated in the article.

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### Effect of NSAIDs to treat DOMS

In order to assess the significance in the described use of NSAIDs on DOMS we evaluate the studies using the Random-Effect model (I²=93%). Our analyzes showed no difference regarding the attributed use of NSAIDs (21 studies, n= 955; SMD= 0.02; 95% CI -0.58, 0.63; p=0.94; I²=93%) Figure 3.

**Figure 3.** Forest plot showing the effects of NSAIDs (experimental) versus control condition on the management of DOMS. SD: standard deviation; Std: standardized; CI: confidence interval. Program: (RevMan, 5.3.5); heterogeneity: Tau² = 1.59; Ch² = 2269.77, df = 19 (P 0.000001); I² = 93%

### Discussion

Either Inflammation or pain can be limiting factor for training and exercise and the NSAIDs are widely used in the handling of both symptoms. These drugs are broadly spread either following medical prescription or in an over-the-counter use [41]. In this study, we analyzed by the way of meta-analyze studies related to the effectiveness of selective and non-selective NSAIDs in the management of DOMS related to exercise.

We analyzed by not limiting specific characteristics. This method allowed a holistic perception regarding the analyzes, related to different dose responses, NSAIDs and population profiles. The mechanisms and relationship between DOMS and inflammation was previously described [9]. And there is current evidence showing improvement in pain and inflammatory processes in response to the use of these drugs [28, 35, 38, 39]. While, additional studies showed
that the use of NSAIDs is related to the inhibition of satellite cells, negatively influencing the development of healing, adaptation to stress and subsequently muscle regeneration [42, 43].

There is contradiction in the literature about the functional effects of NSAIDs in signaling and muscle regeneration. Mackey et al. (2016) evaluated the effect of ibuprofen on satellite cells activity after eccentric contractions induced by electrical stimulus [44]. Their study showed that ibuprofen-treated subjects had increased levels of cell proliferation and faster repair of myofibrils. It is important to highlight that the use of electrical stimulation to induce muscle damage is a limiting factor of the study. Electrical-induced muscle contractions do not fully reflect physiological conditions of exercise [45]. Thus, it is important to emphasize this limitation. Other studies showed no correlation in the effects of NSAIDs in the outcome, pain or functional limitation, of DOMS [7, 9, 32, 40]. A possible justification is an impairment in muscle regeneration capacity due to decreasing in monocytes differentiation followed by inhibition of the inflammatory process, and the change in cytokine's signaling. These effects together could be responsible for systemic responses of neuro-muscular adaptation and muscle regeneration [4, 12]. In a practical context the weakening of the described functions tends to limit the subsequent performance in either training or competition [46].

NSAIDs are overused in clinical practice for the treatment of various conditions, including DOMS [41]. The studies by Paulsen et al. [12] and Schoenfeld et al. [4] suggest that mild clinical manifestations of DOMS do not require treatment with NSAIDs. Clinical trials using rofecoxib showed an exponential increase in acute myocardial infarction, justified by high levels of toxicity in selective cyclooxygenase inhibitors [15]. Also, NSAIDs inhibits prostanoids synthesis bringing adverse impacts including side effects on the gastrointestinal tract, renal and cardiovascular system [15] [47-50]. Such information is of concern and should be taken into consideration to evaluate the real need of NSAIDs use associated with the specific clinical condition of each patient [51]. Due to the adverse effects and functional impairment, the indiscriminate use of NSAIDs is alarming. This problem is aggravated by the its prolonged use, mostly without a medical prescription [15].

To the best of our knowledge this is the first systematic review and meta-analysis to investigate the effects of the use of NSAIDs in the treatment of DOMS. Our meta-analysis showed that the use of NSAIDs is neither superior nor responsible for significant levels of improvement when compared to the control/placebo situation. The importance of our findings for clinical practice lies in highlight important evidence about the ineffectiveness use of NSAIDs in DOMS and the possible hazards of its indiscriminate use. The current literature provides a variety of therapeutic options for the treatment of muscle pain [52] with reduced adverse effects and can be considered as an alternative resource whenever possible.

Our meta-analysis did not support the use of oral NSAIDs for the treatment of DOMS. Two articles using topical NSAIDs were selected in our meta-analysis, all of them with “good outcomes”. It is difficult in guaranteeing a blind topical study since that some subjects can fell the presence of the active compound (ref). Another possible explanation is that the local drug concentration in topical use can be a reason for the best results comparing with the oral route (ref).

Diclofenac and aspirin are the world most used NSAIDs while ibuprofen or naproxen are far below (ref). During our review we found that ibuprofen was the most examined oral NSAIDs (52.2%), followed by naproxen (13.0%) of the studies. The less investigated drugs were either aspirin or diclofenac (4.3% each). The majority of the studies (96.2%) were conducted in countries with Very High Human Development Index (HDI) according to the United Nations Development Program (ref). We think that researchers and volunteers either propose or engage in studies according with their experiences and resources. This lack of original studies may present a bias in the available published papers leading to a limitation in the results to be analyzed. Our analyzes can be biased by these heterogeneity of original investigations. It is always important to emphasize that correlation it is not necessarily cause and effect. A more comprehensive experimental study in at least most used NSAIDs (in both oral and topical administration) should investigate their mechanisms of action in DOMS.

The majority of the 26 studies selected in this work, (~92%) used a visual analog scale (VAS) as a form of pain assessment to the subjects. VAS is a reliability and efficient tool for clinical research regarding pain [53]. However, VAS is an ordinal scale presented in numbers and should not be confused as a linear numeric scale. This misunderstanding of the scale leads to an essential misconception in data analysis. While found in several scientific papers, it is not wise to convert subjective perceptions in numbers, mathematizing data for further statistical analyzes. Pain is a subjective symptom and its perception includes both psychological inputs and subject behavior [54]. Performing a meta-analysis with subjective data is always a challenge and a method limitation.

Some limitations inherent to the presented outcomes need to be reported. First of all, the majority of the protocols used in the included trials were unsatisfactory, which leads to inadequate evidence. The lack of consistency between the different methodologies of the studies compromised a homogeneous comparison and solid discussions. So, our results and discussion should be interpreted taking into consideration such circumstances. It needs to be emphasized that our findings are related to the use of different drugs and dose-response, as well as protocols for muscle damage, in the original investigations. Such facts should be considered and not extrapolated to different conditions than those reported in this study. Trying to analyze different small clinical studies with broad methodology is always a challenge and our goal was to reunite combined evidences that could enlighten the field.

Conclusions

This study provides evidence that the use of NSAIDs in the management of DOMS does not appear to be superior to the control condition and/or placebo. However, these interpretations should be analyzed with caution, since the types of NSAIDs, dose/response and volume/intensity of the effort made to induce different kind of muscle damage and, then different outputs. As continuous use can trigger several adverse effects in body systems, it is relevant that future studies demonstrate the real improvement prospects on the DOMS.
Declarations

What is already known

Delayed Onset Muscle Soreness is a clinical physiological condition that limits subsequent performance levels. NSAIDs are world used to treat either inflammation or pain mostly without medical prescription.

What are the new findings?

There is no significant improvement in DOMS observed with the use of NSAID; Different NSAIDs do not seem to give different clinical responses.

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CONFLICT OF INTEREST STATEMENT

All authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

RLN designed the study, conducted the analyzes, and wrote the manuscript.

JSSL and ASM assisted in the acquisition, analysis, and interpretation of data, reviewed and edited the article.

LCC made substantial contributions including conception; design of the study; writing and final revision of the manuscript.

All authors read and approved the final manuscript.

References


**Figures**

![Diagram of included and excluded studies](image-url)

**Figure 1**

Description of excluded studies according to the established criteria.
Bias risk evaluation of the selected studies examining the efficacy of NSAIDs for muscle soreness. Low risk (+), unclear risk (blank) and high risk (-) for different features of the Cochrane Risk of Bias Tool.

Figure 2
Figure 3

Forest plot showing the effects of NSAIDs (experimental) versus control condition on the management of DOMS. SD: standard deviation; Std: standardized; CI: confidence interval. Program: (RevMan, 5.3.5); heterogeneity: Tau2 = 1.59; Chi2 = 2269.77, df = 19 (P < 0.00001); I2 = 93%.