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Impact of drugs with anti-inflammatory effects on skeletal muscle and inflammation: A systematic literature review

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Abstract

Background:

Ageing-related low-grade inflammation is suggested to aggravate sarcopenia and frailty. This systematic review investigates the influence that drugs with anti-inflammatory effects (AIDs) have on inflammation and skeletal muscle.

Methods:

PubMed and Web of Science were systematically screened for articles reporting the effects of AIDs on inflammation on one hand and on muscle mass and/or performance on the other.

Results:

Twenty-eight articles were included. These articles were heterogeneous in terms of the subjects studied, intervention components, setting, and outcome measures. Articles on older humans with acute inflammation showed evidence that celecoxib and piroxicam could reduce inflammation and improve performance and that ibuprofen improves exercise-induced muscle hypertrophy and gains in strength. In younger humans, only the effects of AIDs combined with exercise were investigated; no significant benefits of non-selective COX-inhibitors were reported, but improved strength gains with etanercept and reduced muscle soreness with celecoxib were noted. Indomethacin increased acute exercise-induced inflammation and reduced satellite cell differentiation in exercising muscle. Most articles did not systematically report occurrences of side effects.

Conclusions:

Although AIDs showed significant reduction in inflammation-induced muscle weakness in older hospitalised patients with acute inflammation, robust evidence is still lacking. When combined with exercise, AIDs presented a protective effect against age-related loss of muscle mass, thus enhancing muscle mass and performance. The mechanism regulating muscle strength and its mass seems to differ between individuals of old and young age. However, the effects seem drug-specific and dose-dependent and appear to be influenced by subjects' trainability and the clinical context. In addition, the balance between benefits and harm remains unclear.

Keywords

inflammation, exercise, muscle mass, physical performance, elderly

Key points:

- AIDs reduce acute inflammation and improve muscle performance in hospitalised geriatric patients.
- NSAIDs or TNF-α inhibitors enhance positive effect of resistance-training.
- Adverse events were not systematically reported in most of the articles.

1. INTRODUCTION

Ageing is accompanied by a chronic low-grade inflammatory profile (CLIP) characterised by elevations in circulating pro-inflammatory markers (Krabbe et al., 2004). Several intrinsic phenomena related to the ageing process contribute to CLIP, including disturbances in immune functions (Kuek et al., 2007), an increase in adipose mass (Wellen and Hotamisligil, 2005), and an accumulation of Advanced Glycation End (AGE) products (Puyvelde et al., 2014). Moreover, common chronic, ageing-related illnesses can contribute to inflammatory processes; these illnesses include ischemic cardiovascular disease (Hansson, 2005), type 2 diabetes (Pradhan et al., 2001), chronic obstructive pulmonary disease (Gan, 2004), Alzheimer's disease (Akiyama et al., 2000), and osteoarthritis (Robinson et al., 2016). In addition, pathological situations such as trauma, infections, stroke (Hallenbeck, 2002), or cancer (Landi et al., 2003) can exacerbate the inflammatory burden. Recent evidence suggests that CLIP and exacerbations of inflammation are involved in the onset and/or progression of sarcopenia and to accelerate the evolution towards frailty, disability, morbidity, and mortality (Visser and Schaap, 2011). Therefore, CLIP could be considered one of the major challenges associated with ageing.

Sarcopenia is an intrinsic ageing-related process characterised by the gradual loss of skeletal muscle mass and function. It can manifest in different degrees of severity. It is considered a significant problem today, at both the individual and population levels (Sayer, 2010). The costs of sarcopenia among non-institutionalized older adults in the United States have been estimated at $12–26 billion annually, corresponding to about 1.5% of direct total health care expenditures (Janssen et al., 2004). In a recent study from The Netherlands, sarcopenic subjects showed annual health care spending of €11,168 (about $14,840) above that of non-sarcopenic subjects (Mijnarends et al., 2016). Therefore, preventing and reversing sarcopenia is of great importance.

Recent research has shown a strong link between CLIP and sarcopenia, with elevated levels of tumour necrosis factors α (TNF-α) and interleukin 6 (IL-6) the most frequently reported inflammatory mediators (Beyer et al., 2012a). With the goal of limiting sarcopenia and regulating muscle protein metabolism to decrease the risk of muscle strength loss, researchers have studied several pharmacological and non-pharmacological strategies to reduce CLIP and restore muscle anabolism. However, treatment and management approaches are still unsatisfactory and the subject of debate. Management

recommendations have emphasised the need for changes in lifestyle and diet (Waters et al., 2010). The most commonly recommended non-pharmacological approach, considered first-line therapy, is regular resistance exercise training and/or protein supplements.

Many studies within the literature with high-quality scientific evidence (meta-analysis of high-quality RCTs) have applied non-pharmacological approaches, these studies have shown improvements in muscle protein synthesis, muscle mass, and muscle performance in elderly men and women (Doherty, 2003; Fiatarone et al., 1990; Frontera et al., 1988; Yarasheski et al., 1999). Furthermore, physical exercise has an anti-inflammatory effect which has been shown to reduce CLIP (Cruz-Jentoft et al., 2014; Peterson et al., 2010; Stewart et al., 2014).

Several studies have proposed a number of pharmacological approaches towards slowing down or treating sarcopenia (Brass and Sietsema, 2011). One of these approaches is to attenuate CLIP through the use of drugs with anti-inflammatory effects (AIDs) (Mets et al., 2004). These drugs include not only non-steroidal AIDs (NSAIDs) but also drugs with important anti-inflammatory properties, including some lipid-lowering agents (Albert et al., 2001; Belfort et al., 2010; Horiuchi et al., 2010), angiotensin-converting enzyme (ACE)-inhibitors, angiotensin receptor blockers (ARBs) (Corsonello et al., 2010), and nitric oxide (NO) donors (Miller and Megson, 2007).

While high-intensity exercise is recommended as the best form of exercise in terms of changes in concentrations of circulating cytokines and of restoring the strength deficit in older adults (Fiatarone, 1990; Singh et al., 2012), not every older person is able to perform this exercise. Recent studies showed that a tailored resistance exercise accompanied by the use of AIDs may positively interfere with training effects on muscle mass and strength in older adults (Buford et al., 2012; Trappe et al., 2011). One study showed that the use of a cyclooxygenase (COX) inhibitor during resistance training produced favourable effects, with a 25–50% greater increase in muscle mass and strength compared to the results of a placebo-consuming group of older men and women who had completed the same 12-week resistance training program (Trappe et al., 2011). On the other hand, animal studies had shown controversial results. In treated elderly rats, AIDs prevented the development of inflammation by reducing the low-grade inflammation associated with ageing and maintained the anabolic response to food intake showing improvements in muscle mass (Rieu et al., 2009); however, when AIDs were administered in

combination with exercise, skeletal muscle regeneration was hindered (Machida and Takemasa, 2010), and the inflammatory process in the skeletal muscle and brain worsened (Enos et al., 2013).

Here, we aim to systematically review the existing evidence regarding the influence of AIDs on skeletal muscle and inflammation, with or without an exercise intervention. Our secondary aim is to report adverse events if the included articles mention them.

2. METHODS

2.1. Literature search

A literature search was performed in PubMed and Web of Science. (The last search was performed on April 22, 2018.) An extensive search key action including all relevant synonyms was specifically adopted in order to avoid the risk of missing relevant articles; we chose the following search terms combined (see supplementary table S1): anti-inflammatory drugs, anti-inflammatory agents, non-steroidal, statins, hydroxymethylglutaryl-CoA reductase inhibitors, nitric oxide donors, muscle strength, muscle weakness, muscle fatigue, muscle fibers, skeletal muscle, muscular atrophy, hypertrophy, inflammation, inflammatory, inflammatory profile, chemokines, interleukins, cytokines, acute-phase proteins, and acute-phase reaction. The following study designs were included: randomized controlled trials, nonrandomized controlled trials, non-controlled trials, explorative/cross-sectional studies, and cohort studies, addressing the interactions between AIDs and inflammation on the one hand and between AIDs and muscle mass and/or performance on the other, in either humans or animals; human subjects were adults without an upper-limit age restriction. Given the focus of the available information, we did not restrict our review to studies involving older persons. Rather, we explored whether age influenced the results. We set no limit on the publication date. We excluded studies that were not written in English, that dealt with specific chronic diseases (e.g., cachexia, Duchene muscular dystrophy) or dementia, or in which the intervention included an induction of inflammation by injuring the skeletal muscle. We did not include studies dealing with steroids or corticosteroids in our search because these substances cannot be used for a prolonged time due to the development of severe side effects, which may force the interruption or cessation of treatment. Finally, we screened the reference lists of the included articles and added relevant studies to our review.

The screening process was independently performed by two reviewers who were blind to each other's results. First, articles were screened based on title and abstract. Subsequently, full texts were screened. In the event of disagreement over the inclusion of an article, a consensus was achieved by involving a third reviewer. If insufficient information was available to include or exclude a study, the corresponding author was contacted.

2.2. Quality assessment

Randomized controlled trials were assessed using the National Institute for Health and Clinical Excellence (NICE) guidelines for randomised controlled trials ("NICE. Methodology checklist: randomised controlled trials.," 2012). The non-randomized controlled studies were analysed using the STROBE statement (von Elm et al., 2008).

2.3. Data extraction

For all articles, the main characteristics of the participants and interventions were identified. Next, all outcome parameters regarding the inflammatory profile, the muscle mass, strength, and performance were extracted. Data regarding these outcome parameters were identified, and effect size (ES) was calculated using Cohen's d (small ES (d <0.2), medium ES (d from 0.2 to 0.5) and large ES (d >0.5)) (Lakens, 2013). ES is shown for descriptive purposes only. Due to the heterogeneity of the included studies (e.g., differences in age groups, medication, dose regimens, and exercise intensities), no attempt was made to pool the obtained ES from the included studies. Whenever necessary, authors were contacted so that we could obtain supplementary data allowing us to calculate ES. However, for several studies we had to estimate those values based on the figures presented. If insufficient data were available, the ES was reported as 'no data available' (n.d.a.).

3. RESULTS AND DISCUSSION

We systematically reviewed papers describing AIDs' effect on inflammatory markers and muscle mass and/or muscle performance, with special attention paid to older subjects. The systematic literature search yielded a total of 1065 articles: 486 in PubMed and 579 in Web of Science. After screening the articles based on title and abstract, we kept 210 for further analysis. The full texts were judged based on their content. In total, 185 articles were excluded and 22 were included. Six articles were retrieved from the

reference lists of those 22 identified articles. Finally, 28 articles were included in this systematic review representing 22 studies. Figure 1 shows the flowchart of the literature selection.

3.1. Study and participant characteristics

The 28 articles included in our review comprised 21 articles in human (18 were randomized control trials and three articles were non-randomized controlled trials) and 6 randomized controlled trial articles in animal models, published between 2001 and 2018.

There were 11 publications that were based on the same data but with different aims; – two by (Trappe et al., 2002, 2001 and one by Peterson et al., 2003) – two by (Beyer et al., 2012b, 2011) – two by (Cesari et al., 2010, 2009) – two by (Trappe et al., 2013, 2011) – and two by (Mikkelsen et al., 2011, 2009).

The 21 human studies included 10 articles in elderly subjects; three articles were in hospitalized geriatric patients (Beyer et al., 2012b, 2011) and (Mets et al., 2004), two articles in older adults with high cardiovascular risk (Cesari et al., 2010, 2009), two articles in older adults with knee osteoarthritis (OA) and three articles in healthy untrained older adults (Dideriksen et al., 2016) and (Trappe et al., 2013, 2011). The remaining 11 articles were on recreationally active young adults.

3.2. Methodological quality of the included papers

Tables S2, S3, and S4 provide an overview of the methodological evaluation of the included articles. Generally, the 13 intervention studies on humans were of good quality; however, most of these studies did not provide the information necessary to properly judge their quality and estimate the risk of the existence of different types of bias. In terms of the seven intervention studies on animals, the overall quality was good, with a low risk of bias. However, most of these studies also lacked information about selection bias.

The two NRCTs were generally of low quality. Neither study addressed potential sources of bias or provided sufficient information about the way in which missing data had been addressed, the sampling strategy, and sensitivity analyses. The studies also did not provide information about reasons for nonparticipation at each stage and the number of participants with missing data for each variable of interest.

3.3. Interpretation of studies' results

For our systematic literature review we choose to structure the results and discussion section according to relevant topics that were retrieved from the literature; to avoid redundant repetitions, we merged the results and discussion sections. First, studies in older adults were presented, then those in younger ones and finally we provided evidence supported by animal studies.

Tables 1 through 4 summarise the included studies by category. In order to provide a clear, comprehensive and concise overview of the robustness of the evidence we provided a summary of the evidence available for each class of drug under investigation for human and animals (tables 5 and 6), then provided more detailed information about the particularities of each study. As each included study had its own outcome for muscle and performance measures, more details on these measures and the way they were measured are provided in table S5.

3.4. Use of AIDs without exercise interventions (see Figure 2 and Tables 1 and 2)

Six articles, representing four studies, examined the effects of AIDs on different anti-inflammatory pathways in elderly subjects.

3.4.1. Findings in human studies.

Three studies of older people were retrieved, two of which were on hospitalised geriatric patients. In those two studies, piroxicam and celecoxib were used to counter inflammation induced by acute infection, showing beneficial changes in inflammation and physical performance. The use of piroxicam had a positive impact on patients with respect to grip work (GW), fatigue resistance (FR), and elderly mobility scale (EMS), while celecoxib enhanced FR. One study showed that the use of fosinopril did not have advantageous effects on inflammation or physical performance in older adults presenting with high cardiovascular risk.

3.4.1.1. Non-selective COX inhibitor Beyer et al. (Beyer et al., 2012b, 2011) studied the effect of 10mg/day piroxicam, a nonselective COX inhibitor, for 10 days in a randomized double-blinded, placebo-controlled clinical trial to investigate its effect on the evolution of muscle performance and mobility in 30 hospitalized geriatric Caucasian patients median age 84.0 years (range 70 – 94 years) and BMI 23.7 (20.1–26.7) kg/m² with acute infection, adequately treated with antibiotic therapy. In this setting, no significant difference between the piroxicam and placebo groups was found. The piroxicam group showed a significant decrease in baseline values in IL-6 (ES at the second week 0.90 and at the

third week 0.92) and IP-10/CXCL10 (ES at the first week 0.36 and at the third week 0.55). In both groups, CRP levels were significantly attenuated throughout the study period. Piroxicam did not significantly decrease most of the studied inflammatory markers. For muscle performance, the piroxicam group showed a significant improvement in EMS from the baseline to two weeks of treatment (ES: 1.21), as well as an improvement in GW at weeks 2 and 3 compared to the baseline (ES: 0.48 and 0.72, respectively), and in FR at week 3 (ES 0.69), which were not observed with the placebo. The study showed that the early decrease in IL-6 serum levels correlated with increased GW in the second week, thus illustrating that a decrease in cytokine levels was related to an improvement in muscle performance. The authors mentioned that one participant in the intervention group dropped out from the study due to GI bleeding, a possible side effect of piroxicam use.

3.4.1.2. Selective COX-2 inhibitors One study by Mets et al. (Mets et al., 2004) was identified. In this randomised, single-blind, controlled study, celecoxib, a COX-2 inhibitor, was examined alongside acetaminophen, an antipyretic and analgesic drug, and a group of controls who did not receive any medication, for their effects on muscle performance in hospitalised geriatrics (31 were women mean age, 85±6 years and 12 were men mean age, 82±6 years) with acute infection adequately treated with antibiotic therapy. The drugs were administered for 14 consecutive days (celecoxib 200mg/day; acetaminophen 1000mg/ 3 times/day). While a significant decrease from the baseline was noted in all groups for CRP and IL-6 values, the trial demonstrated significant differences in changes in the anti-inflammatory cytokine IL-10 serum concentration; the celecoxib group showed a significant decrease in IL-10 values compared to the acetaminophen group (ES: 0.48) and controls (ES: 0.49). The authors indicated that the changes in IL-10 might have been due to early decreases in the inflammatory cytokines during the first days of treatment. At the end of the study, muscle performance in the celecoxib group had improved significantly with respect to FR as compared to the acetaminophen group (ES: 0.48) and controls (ES: 0.53).

For the two previous studies, it is necessary to mention that hospitalised geriatric patients are potentially more fragile and more prone to sarcopenia. Consequently, the high levels of inflammation can be another threatening risk to their muscle function in comparison to older adults with lower inflammatory status. (Bautmans et al., 2005; Norheim et al., 2017b, 2017a). Although AIDs may present an attractive

194 therapeutic approach in countering acute inflammation and improving muscle recovery in these patients,
195 the potential side effects and associated risks make implementing AIDs as standard care in clinical
196 practice questionable (table S6). In addition, the authors of these studies also do not recommend using
197 NSAID as a part of the standard care of the hospitalized geriatric patients.
198 Because both studies were performed under an acute high-grade inflammation, this state of
199 inflammation may have a restricted potential effect as compared to the CLIP associated with ageing.
200 3.4.1.3. ACE inhibitors ACE inhibitors are known to lower blood pressure and protect renal function;
201 it has also been suggested that they have anti-inflammatory effects because they decrease NF-κB
202 activation, which in turn blocks angiotensin II-inducible IL-6 and subsequent CRP (Han et al., 1999;
203 Kranzhöfer et al., 1999; Morrissey and Klahr, 1997).
204 Cesari et al. (Cesari et al., 2010, 2009) examined the effects of fosinopril 20mg/day for one week,
205 followed by 40mg/day for six months in a randomised (n=290, women 43.4%, mean age 66.0±7.4
206 years), double-blind, cross-over, placebo-controlled trial involving adults presenting with a high
207 cardiovascular risk profile. After six months of follow-up, the researchers failed to detect any significant
208 differences in inflammatory markers (CRP, IL-6, and PAI-1) between fosinopril and placebo users
209 (Cesari et al., 2009). Furthermore, fosinopril did not result in any significant improvement in physical
210 performance namely grip strength, the 4-meter walking speed test, the chair-stand test and the balance
211 tests (Cesari et al., 2010).
212 Although ACE-inhibitors have been proposed to have favourable effects on elderly person's physical
213 performance (Sumukadas et al., 2008, 2007), fosinopril did not show any positive effects in humans in
214 comparison to previous studies with other ACE-inhibitors or to studies that used COX inhibitors
215 (selective COX-2/non-selective COX). This could be due to the fact that the drugs were tested in
216 different populations and under different situations. Possibly, fosinopril treatment was not sufficient to
217 further reduce plasma inflammatory markers in subjects who showed already relatively lower circulating
218 levels. Interestingly, two studies showed that ACE inhibitors can attenuate the increase in postoperative
219 inflammation after a coronary artery bypass graft surgery (Brull et al., 2002; Radaelli et al., 2007).
220 However, it is not clear to which extent ACE inhibitors can have positive effects on skeletal muscle
221 outcomes in patients with higher levels of inflammation.

3.4.2. Findings in animal studies.

While there was no study conducted in humans on the effect of ibuprofen on chronic inflammation and muscle outcomes without exercise intervention, a study of good quality was performed on old rats treated with ibuprofen without exercise to prevent low-grade inflammation observed a decrease in the low-grade inflammation and an increase in muscle protein synthesis and, consequently, muscle mass (hind limb muscle mass) by restored protein anabolism at a post-prandial state. This study would support an interesting approach for future studies of good quality in older human with CLIP.

3.4.2.1. Non-selective COX inhibitors In a study by Rieu et al. (Rieu et al., 2009), ibuprofen, a nonselective COX inhibitor, was administered for five months to a group of old Wistar rats (20 months old) to examine its effect on the long-term prevention of low-grade inflammation. After five months of treatment with a dose of 30mg/kg/day, this study showed a significant improvement in plasma concentration of three inflammatory markers: IL-6, IL1β, and fibrinogen (ibuprofen group vs controls: ES: 0.47, 0.45, and 0.89, respectively). That effect was associated with a significantly lower loss of muscle mass in the treated group. The hind limb muscle mass (gastrocnemius, extensor digitorum longus, and tibialis anterior muscles) in the treated group was significantly higher (ES: 3.17, 3.33, and 3.22, respectively). The higher ES values for muscle markers as compared to inflammation markers might point to a mechanism independent of the specific makers determined in this study. (Rieu et al., 2009) have studied the regulation of muscle protein synthesis and proteolysis by food intake, showing that in the treated rats, muscle protein synthesis significantly increased and proteolysis significantly decreased (ES: 0.83 and 0.94, respectively).

Overall, only a few articles – and only those about older subjects – have been retrieved and examined for the relationship between AIDs use without exercise intervention and its effects on inflammation, muscle mass, and performance. Three articles using NSAIDs showed evidence for a reduction in the number of inflammatory markers; in addition, an improvement in some muscle performance parameters was observed (EMS, GW and FR), and, in animals, protection from muscle mass loss. However, the use of fosinopril could not confirm a beneficial effect on inflammation and physical performance that earlier observations had suggested (Bauer et al., 2008; Brull et al., 2002; Carter et al., 2004; Cohn et al., 2007; Onder et al., 2002; Sumukadas et al., 2008, 2007, 2006; Witham et al., 2008). Future specially designed

intervention trials are needed to evaluate other drugs for long-term treatment with anti-inflammatory effects for their action on muscle mass and performance.

3.5. Use of AIDs with short-term exercise interventions (see Figure 3 and Tables 3 and 4)

Twenty-two articles representing 18 studies examined the effects of drugs influencing several anti-inflammatory pathways with exercise interventions.

Overall, these studies have classified the exercise interventions as either "short-term" which is accompanying with the acute effects (i.e., occurring immediately after exercise) or "long-term" which is in turn referring to the repeatedly exercise performance for more than seven days and find to be accompanying with basal levels (i.e., occurring when the acute effects were washed out).

Noteworthy the "short-term" with its acute effects was found to lead to some cytokines elevations, however, this increase does not really reflect an ongoing inflammatory process but in fact, could indicate that myokines are being produced by the triggered muscles as adaptations to the exercise.

On the other hand, the "long-term" was found to decrease basal levels of multiple pro-inflammatory markers through the stimulation of anti-inflammatory cytokines release (Forti et al., 2017).

Hence, the aforementioned mechanisms can guide to hypothesise that AIDs usage might blunt the acute response of exercise and accentuate the long-term effect on inflammation.

3.5.1. Findings in human studies.

This category included eight studies that observed the influence of AIDs with short-term exercise and on inflammation and muscle mass and/or performance.

Two studies were mainly focused on the use of ibuprofen in older adults with either a slight increased systemic inflammation or knee OA. Based on this, there was no influence on muscle mass parameters in both groups despite the positive inflammatory influence of ibuprofen on $PGF_{2\alpha}$ plasma levels in knee OA patients in comparison with the second group. On the other hand, three more studies in healthy young adults using ibuprofen in two studies and indomethacin in another one, have encountered a negative impact on inflammation. In line with these three trials, celecoxib (Cox-2 inhibitor) has failed to show any significant positive influence on inflammation in the healthy young adults despite its association with muscle soreness attenuation.

277 In contrast to the general negative impact of NSAIDs on inflammation as shown in the aforementioned
278 studies, the TNF-α inhibitor represented in etanercept was assessed in healthy young adults and found
279 to lead to favourable changes in muscle strength of the quadriceps muscle with a significant decrease in
280 inflammation.
281 Hence, TNF-α inhibitor might contribute to tissue repair and, therefore, functional recovery whereas
282 NSAIDs can yield negative outcomes through the lack of a capability to reduce inflammatory cytokines
283 and the lack of a beneficial effect on muscle mass, strength, or performance after acute bouts of exercise.
284 3.5.1.1. Non-selective COX inhibitor In a randomised, double-blind, placebo-controlled study,
285 Petersen et al. (S. Petersen et al., 2011) evaluated the effect of ibuprofen on post-exercise muscle protein
286 synthesis in older patients with knee OA (mean age 60±2 years). Patients were randomly assigned to
287 receive 1200 mg/day of ibuprofen or placebo, three days before exercise and on the day of exercise. The
288 exercise consisted of 60 minutes of one-legged kicking at 55% of the maximal workload; the other leg
289 did not engage in any exercise. The authors reported a significant decrease in $PGF_{2\alpha}$ plasma levels 24
290 hours post-exercise in the ibuprofen group as compared to the placebo group (ES: 1.78); however, no
291 difference was found between groups in terms of myofibrillar fractional synthetic rate.
292 Dideriksen et al. (Dideriksen et al., 2016) studied ibuprofen's effects on post-exercise protein synthesis
293 in a group of older participants (mean age 67±1 years) with or without a slightly increased systemic
294 inflammation (CRP > 2mg/l). The study was a randomised, cross-sectional, double-blinded (medication
295 within the inflamed groups) and placebo-controlled design. Each participant performed 10 sets of eight
296 repetitions at 70% 1-RM of a unilateral knee extension exercise. Participants with higher CRP levels
297 were randomly chosen to receive either 1800 mg/day ibuprofen or placebo for seven days, starting the
298 day before the experiment. Individuals with low CRP levels did not receive any medication and served
299 as healthy controls. After the exercise session, samples taken on the experiment day revealed no
300 significant difference in CRP levels or myofibrillar fractional synthetic rate in participants receiving
301 ibuprofen as compared to the placebo group.
302 In a non-randomized controlled trial, Nieman et al. (Nieman et al., 2006) reported an increase in
303 inflammatory cytokines in ibuprofen users compared to non-users after a 160-km endurance race (mean
304 age 47.9±1.4 years). Ibuprofen users received 600 mg the afternoon before the race and 1200 mg on the

race day. In the intervention group, at the end of the race, plasma CRP (ES: 0.59), IL-1ra (ES: 0.76), IL-6 (ES: 0.59), IL-8 (ES: 1.01), IL-10 (ES: 0.59), G-CSF (ES: 0.98), MCP-1 (ES: 0.65), and MIP-1β (ES: 0.65) were significantly higher. TNF-α showed no significant difference between the two groups. Following the race, no significant difference was found between ibuprofen users and non-users in terms of delayed onset of muscle soreness (DOMS). The ultra-distance race induced muscle inflammation due to muscle damage, oxidative stress, increased metabolic demands, and stress hormone release, as well as increased gastrointestinal permeability and endotoxemia (Lambert, 2009; Nieman et al., 2005). However, two doses of ibuprofen seem unable to induce any beneficial effect in this setting.

In a randomised, double-blind, placebo-controlled study, Vella et al. (Vella et al., 2016) investigated whether 1200 mg/day of ibuprofen influenced leucocyte recruitment and infiltration following an acute bout of resistance exercise in healthy young adults (mean age 23±1.3 years). The exercise session consisted of 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. After exercise, ibuprofen did not have any effect on blood inflammatory cells' MPO^+, $CD66b^+$, and $CD68^+$ or subjective muscle soreness. Vella et al. failed to demonstrate that NSAIDs had any effect on the restoration of immune function after exercise. Trappe et al. in a double-blind placebo-controlled trial in healthy adults (mean age 25±3 years), investigated the effect of NSAIDs on inflammatory markers and muscle mass and performance 24 hours post-exercise (Trappe et al., 2002, 2001), using 1200 mg/day ibuprofen as compared to 4000 mg/day acetaminophen (initial doses at the onset of the injury protocol, with additional doses given at 6 hours intervals and a fourth dose was administered the following morning before the second biopsy), following a bout of supramaximal eccentric exercise. Prostaglandin F2alpha ($PGF_{2\alpha}$) and Prostaglandin E2 (PGE_2) had profound effects on skeletal muscle protein synthesis and degradation, respectively; both treatment groups experienced a significant reduction in the exercise-induced increase of $PGF_{2\alpha}$ levels compared to the placebo group (ES: 1.66 and 0.89, respectively). However, only the acetaminophen group significantly dulled the PGE_2 response to exercise as compared to controls (ES: 1.18). The researchers also noted that the placebo group had a significantly higher skeletal fractional synthetic rate as compared to ibuprofen and acetaminophen users. This could mean that ibuprofen and acetaminophen blunted the protein synthesis response and had a negative effect on muscle protein synthesis 24 hours after a single

bout of heavy exercise. As compared to the placebo, both drugs induced no significant change in muscle soreness and had no influence on muscle inflammatory cell concentrations (Peterson et al., 2003). From these values, the authors concluded that NSAIDs reduced post-exercise mixed protein synthesis by suppressing $PGF_{2\alpha}$ production through the COX enzyme pathway. Thus, NSAIDs may negatively regulate muscle growth after supramaximal eccentric exercise in young adults by inhibiting protein synthesis.

In a non-randomized trial, Mikkelsen et al. (Mikkelsen et al., 2011, 2009) investigated the effect of indomethacin, evaluating eight healthy male volunteers (mean age 23±3 years). On the day of the exercise, indomethacin 45mg was infused locally via a catheter into the vastus lateralis muscle of one leg before, during, and after exercise, while the control leg was infused with placebo. The participants were asked to perform 200 unilateral maximal eccentric knee extensor contractions. No significant changes between the two legs were seen in inflammatory cells ($CD16^+$ and $CD68^+$), muscle performance (total work performed and maximal isometric muscle strength), or myofibrillar fractional synthetic rate. Five hours after exercise, the muscle tissue analysis of the indomethacin perfused legs showed a significant increase in IL-6, IL-1β, and TNF-α. After eight days, levels of TNF-α significantly decreased in the indomethacin-perfused legs (ES: n.d.a), possibly due to a reduction in PGE_2 signalling. However, the treated leg had significantly lower satellite cell proliferation eight days after the exercise compared to the control leg: $Pax7^+$ cells (ES: 1.38), $NCAM^+$cells/ fibre (ES: 0.40), and $NCAM^+$cells/myonuclei (ES: 1.81). This study points to NSAIDs single infusion attenuates satellite cell proliferation pathways during the early post-exercise phase.

3.5.1.2. Selective COX-2 inhibitor In a randomised, double-blind, placebo-controlled trial, Paulsen et al. (Paulsen et al., 2010) investigated the effect that administration of 400mg/day celecoxib for nine days had on recovery after maximal eccentric exercise in young, healthy participants (mean age 28±5 years). Volunteers were asked to perform (with one arm per session and the other arm serving as a non-exercised control) two bouts of 70 maximal unilateral eccentric actions of the elbow flexors (bouts 1 and 2) separated by three weeks. The number of satellite cells/myoblasts did not differ significantly between groups after exercise. This result contrasted with what Mikkelsen et al. reported using indomethacin (Mikkelsen et al., 2009). In terms of muscle function, the treated group showed no significant difference

compared to the placebo group, indicating that celecoxib had no effect on muscle recovery. However, the DOMS was reduced significantly in bout 1 for participants using celecoxib as compared to those in the placebo group (ES: 0.75). A possible explanation for the results is the analgesic effect that celecoxib has on muscle tissue and the central nervous system. The authors stated that three participants experienced slight nausea, but one of these subjects was in the placebo group. One subject from the celecoxib group experienced an unexpected swelling of the forearm of the exercised arm, which was shown to be from excess fluid in the participant's subcutaneous tissue.

3.5.1.3. TNF-α inhibitors Rice et al. (Rice et al., 2008) conducted a randomised, double-blind, placebo-controlled crossover study to identify the effect of injecting 25mg of etanercept one hour before exercise in the attenuation of DOMS after exercise. The trial included 12 healthy young men (mean age 24±3 years) who, on two separate occasions, performed four sets of 15 repetitions of leg presses at 80% 1-RM. Two hours after the exercise, no TNF-α could be detected in the muscle of the etanercept group (ES: n.a.d.). After the exercise session, muscle strength of the quadriceps muscle was significantly reduced in both groups compared to before exercise. However, after 48 hours, the etanercept group showed significant improvement compared to the placebo group (ES: 0.39), returning to pre-exercise values and continuing to improve at 72 hours post-exercise (ES: 0.60). Etanercept and placebo subjects experienced similar DOMS at 24, 48, and 72 hours after exercise, showing that etanercept did not reduce muscle soreness.

3.5.2. Findings in animal studies.

In one study in a mice model, indomethacin use with short-term exercise was associated with worse performance (run time to fatigue) and a significant increase in inflammatory markers. Similar evidence was confirmed in a human study showing that indomethacin did not have beneficial effects on inflammation or performance after an acute session of exercise (Mikkelsen et al., 2011, 2009).

3.5.2.1. Non-selective COX inhibitor To evaluate the combined effect of indomethacin and exercise, Enos et al. (Enos et al., 2013) gave 2.5mg/kg of indomethacin to C57BL/6 mice one hour before a 90-minute bout of treadmill running at 25m/min and an 8% grade for five consecutive days; serving as controls were mice that performed the same exercise but without taking the drug. In contrast to Mikkelsen et al. (Mikkelsen et al., 2009), significant differences in inflammatory parameters between

groups were found after the exercise. In the gastrocnemius muscle, the intervention group had significantly higher mRNA expression for IL-1β (ES: 1.62), MCP-1 (ES: 0.52), and TNF-α (ES: 1.06) compared to the control group. No significant differences were found in IL-6 among the two groups. Indomethacin showed an effect on run times, which were significantly reduced in the intervention group at day 4 and day 5 compared to the controls (ES: 2.04 and 1.14, respectively). These results are similar to those of (Nieman et al., 2006), who also reported significant elevations in inflammatory markers after short-term ibuprofen treatment combined with exercise.

3.6. Use of AIDs with long-term exercise interventions (see Figure 3 and Tables 3 and 4)

3.6.1. Findings in human studies.

This category included four studies observing the influence of non-selective Cox inhibitors and long-term exercise on inflammation and muscle mass and/or performance.

Two studies focused on the usage of ibuprofen in older adults either in healthy individuals or knee OA patients, both studies revealed decreases in inflammation from baseline levels to the end of the exercise sessions as well as increases in muscle strength parameters (quadriceps muscle strength, maximal isometric strength, maximal eccentric muscle strength and maximal eccentric work).

The two other studies were conducted in healthy young adults, in which the first one has showed that naproxen decreased the $PGF_{2\alpha}$ levels without any influence on muscle mass (skeletal muscle tissue lean body mass). In the second study, the influence of high dose ibuprofen compared to low dose of acetylsalicylic acid was assessed and showed an attenuation in the muscle strength (maximal isometric and isokinetic muscle strength and training specific strength) and muscle mass (quadriceps muscle volume and muscle quadriceps means cross-sectional area (CSA)) with ibuprofen compared to acetylsalicylic acid after long-term exercise.

Overall, the decrease in inflammatory markers after long-term resistance training programs with continued use of NSAIDs showed mainly positive results in muscle mass, strength, and performance, (except for Brewer et al. and Lilja et al. in younger adults) highlighting the possibility that the inflammatory process has a different role in young and old adults.

3.6.1.1. Non-selective COX inhibitor During 12 weeks of knee extensor progressive resistance exercise training, Trappe et al. (Trappe et al., 2013, 2011), conducted a double-blind placebo-controlled

study of an elderly population (mean age 64±1 years) to investigate the effects of the use of 1200mg/day ibuprofen or 4000mg/day acetaminophen or a placebo on muscle mass and strength. Participants executed progressive resistance exercises for knee extensor three days a week. At the end of the study, several components of the COX pathway ($cPLA_2$, $PGF_{2\alpha}$ synthase, PGE_2 to $PGF_{2\alpha}$ reductase), as well as the PGE_2 receptor-4, increased from pre- to post-training in all groups. Only in the ibuprofen and acetaminophen treatment groups was the $PGF_{2\alpha}$ receptor up-regulated, thus stimulating muscle cell growth by enhancing skeletal muscle sensitivity to exercise. However, IL-6 and IL-10 were suppressed in both treatment groups, while, though not statistically significant, the inflammatory cytokines TNF-α and IL-1β were suppressed exclusively by ibuprofen. Both treatment groups showed an enhancement in muscle hypertrophy and strength gains compared to subjects taking a placebo. Quadriceps muscle volume in both the ibuprofen and acetaminophen groups significantly increased compared to the control group (ES: 0.38 and 0.91, respectively). Also, Muscle RING-finger protein-1 (MuRF-1), a promoter of muscle degradation acting via the suppression of PGE_2, was significantly reduced (ES: 1.2 and 0.98, respectively), while quadriceps muscle strength significantly increased in the ibuprofen and acetaminophen groups (ES: 0.56 and 0.59, respectively).

For a period of 12 weeks, and with an older population with a history of bilateral tibio-femoral knee osteoarthritis (mean age 61.7±5.2 years), Petersen et al. (S. G. Petersen et al., 2011) explored, in a randomised, double-blind, placebo-controlled trial, the effect of 1200mg/day ibuprofen on muscle hypertrophy. Participants underwent a training program consisting of unilateral knee extensions and leg presses for both legs with intensity increasing from four sets of 15-RM in the first week to four sets of 8-RM by week 7 until the end of week 12. At the end of the 12 weeks, ibuprofen group showed a significant within-group change from baseline for CRP levels, however, no significant difference was observed between ibuprofen and placebo groups for CRP and $CD56^+$ levels. Moreover, no significant muscle mass gain (quadriceps muscle cross-sectional area) was reported. However, a significant difference was reported between the placebo group and the ibuprofen group, with greater gains in maximal isometric strength (ES: 0.39), maximal eccentric strength (ES: 0.98), and maximal eccentric work (ES: 0.97); however, ibuprofen's pain-relieving effect cannot be neglected in such patients.

444 In general, continued use of NSAIDs (ibuprofen) and resistance training programs on CLIP in older
445 adults may explain the possible beneficial effects on muscle protein synthesis, muscle mass, and muscle
446 performance.
447 Lilja et al. (Lilja et al., 2018) in a randomised single-blind trial, testing high doses of ibuprofen
448 1200mg/day in comparison to low doses of acetylsalicylic acid 75mg/day in young adults (mean age
449 27±5 years) performing knee-extensor resistance training in which one leg was subjected to training
450 with maximal volitional effort in each repetition using a flywheel ergometer (FW), while the other leg
451 performed conventional (work-matched across groups) weight-stack training (WS) for eight weeks,
452 observed that participants who received lower doses of acetylsalicylic acid showed a significantly
453 greater increase in quadriceps muscle volume (ES: 0.84) and maximal isometric and isokinetic muscle
454 strength in FW leg (ES: 0.4-1.0) as compared to those in the ibuprofen group. They noted a significant
455 group x time interaction of the inflammatory marker IL-6 mRNA, where the acetylsalicylic acid group
456 showed increased expression levels while the ibuprofen group showed decreased expression levels (ES:
457 1.01). The authors mentioned that during the study period, 15 adverse events – moderate to mild in their
458 severity – were reported and resolved before the end of the study. However, no participant was excluded
459 for any medical reason.
460 Unfortunately, in this study the authors did not include a control group, thus making it difficult to
461 appraise the net effect of AIDs treatment.
462 In a randomised, double-blind, placebo-controlled trial, Brewer et al. (Brewer et al., 2015) examined the
463 effect of naproxen 440mg, twice weekly for six weeks, in healthy young adults (mean age 20.5±1.3
464 years). Both groups were assigned to perform bilateral resistance training of the upper back and M.
465 biceps brachii musculature (three sets of 6-10 repetitions at 66-86% 1RM, two sessions per week). After
466 exercise, naproxen had significantly attenuated the elevation of $PGF_{2\alpha}$ (ES at the first week 1.32 and at
467 the fourth week 0.62). In both groups, a significant increase from the baseline values was observed in
468 the dominant arm's skeletal muscle tissue; however, no significant differences between groups were
469 reported. Thus, in younger individuals, this decrease in inflammation did not translate into gains in
470 muscle mass and strength as it did in older individuals (previously described by Trappe et al. (Trappe et
471 al., 2013)) or in muscle volume (Trappe et al., 2011). A possible reason is that Trappe et al. maintained

a longer period of treatment and studied a large number of elderly subjects. Brewer et al. concluded that regular use of non-prescription doses of the non-selective COX-inhibitor naproxen did not hinder the development of skeletal muscle tissue with exercise (Brewer et al., 2015).

3.6.2. Findings in animal studies.

Although there is no robust evidence yet in young humans on the effects of ibuprofen on muscle performance in combination with long-term exercise, three studies of good quality in animal models showed beneficial effects on inflammation and physical performance (GS, reach force, duration of task participation and exhaustion time). Additionally, two other retrieved studies found that the use of TNF-α inhibitors with long-term exercise reduced inflammation and prevented performance declines (GS) while one study also observed enhancements in muscle mass (muscle regeneration markers; M-cadherin and myf-6 mRNA). These results were similar to what has been found using etanercept with short-term exercise in young adults.

3.6.2.1. Non-selective COX inhibitor Kietrys et al. (Kietrys et al., 2011) elucidated the exposure-response relationships between voluntary high-force repetitive tasks for upper limb, inflammation, and motor changes with work-related musculoskeletal disorders in young adult female Sprague-Dawley rats (14 weeks of age). At the end of the fourth week of a total of 12 weeks of task performance, 22 rats were administered ibuprofen (45mg/kg/day) for eight weeks. In the ibuprofen group, the central nervous inflammatory response measured in the cervical spinal cord segments for IL-1β was not lowered. In both groups, GS declined at weeks 9 and 12; however, a significantly lesser decline was observed in the treated group at week 12 (ES: 1.98). Also, the ibuprofen group showed a significant improvement in reach force at week 9 (ES: 3.01), duration of task participation at weeks 9 and 12 (ES: 5.88 and 7.49, respectively), and the percentage of successful reaches at week 12 (ES: 3.68). These findings support the notion that NSAIDs favourably influence muscular function.

Lima et al. (Lima et al., 2016) focused on the role of NSAIDs in the prevention of exercise-induced fatigue. They examined the effect of 15mg/kg/day of ibuprofen in 48 male Wister rats undergoing six weeks of swimming training. No significant changes were observed between the groups for TNF-α and IL-1β levels in the gastrocnemius muscle. Trained rats receiving ibuprofen treatment showed a significantly increased exercise time before exhaustion compared to trained but untreated rats (ES: 1.65).

The same observation (ES: 1.53) was made during a comparison of two groups of sedentary rats – an untreated group with an ibuprofen-treated one.

3.6.2.2. TNF-α inhibitors In rodent models, Domínguez-Álvarez et al. (Domínguez-Álvarez et al., 2014) used young male rats (eight weeks old) to study the effect of infliximab on respiratory muscle function, inflammatory and regeneration markers, and muscle structure. Rats had to perform 70% high intensities of the maximal inspiratory pressure of their baseline resting values. After treatment with infliximab 0.01mg/g body weight, every seven days for 14 days, plasma levels of TNF-α (ES: 1.54), IL-6 (ES: 1.68), and IFN-γ (ES: 1.91) were significantly lower compared to the controls. On the other hand, in the diaphragm muscle, infliximab showed higher protein levels of TNF-α (ES: 0.99), IL-1β (ES: 2.22), and IL-6 (ES: 1.09), but not for IFN-γ compared to the control group. No significant difference in the gastrocnemius TNF-α, IL-1β, IL-6, or IFN-γ protein levels between groups was seen. The diaphragm levels of inflammatory cells decreased significantly in the treated rodents (ES: 2.06). The different effects on both muscles and blood can be explained by two distinct sources of TNF-α. The muscle regeneration markers M-cadherin and myf-6 mRNA both showed significantly greater levels (ES: 3.38 and 3.43, respectively) in the diaphragms of the treated group, but did not differ in the gastrocnemius. In the respiratory muscles of treated rats, a significant increase in total muscle abnormalities was seen, while the number of internal nuclei in the diaphragm was significantly higher than the controls (ES: 1.88). Treated rodents also showed an improvement in type-II muscle fibre size and proportions within the diaphragms (ES: 1.05). At the end of the study, rodents in the control group exhibited a significant decrease in maximal inspiratory pressure from baseline values, while this was attenuated significantly in the infliximab group (ES: 1.87).

Abdelmagid et al. (Abdelmagid et al., 2012) used a rodent model to explore the efficacy of ibuprofen and anti-TNF treatments in terms of grip strength. Young Sprague-Dawley female rats (aged 3.5-4 months) had to perform a high-repetition, negligible force handle-pulling task for six weeks. At the beginning of the fourth week of the exercise, rats received either ibuprofen 45mg/kg daily or anti-TNFα 15mg/kg for two weeks. With ibuprofen, but not with anti-TNFα, a significant decrease in TGF-β1 levels in the flexor digitorum muscle was documented compared to the non-treated group (ES: 1.31). Both drugs significantly decreased the quantification of the percent area with connective tissue growth

528 factor (CTGF) immunostaining in the flexor digitorum muscle (ES: for ibuprofen 1.26, for anti-TNFα
529 0.85) and significantly attenuated the declines in GS following the exercise tasks (ES: for ibuprofen
530 1.53, for anti-TNFα n.d.a), compared to the non-treated group.
531 Rani et al. (Rani et al., 2010) used the same rodent model but explored only the anti-TNFα treatment.
532 They found a significant decrease in serum inflammatory cytokines TNFα, IL-1α, and MIP2 as
533 compared to the non-treated controls (ES: 1.29, 1.22, and 1.68, respectively) and a significant
534 improvement in GS in treated rodents compared to non-treated controls (ES: 4.35). Those articles
535 showed that the TNF-α inhibitors reduced inflammatory cytokines and favourably influenced muscle
536 performance in acute as well as long-term exercise situations.
537 In contrast to the NSAIDs studies, TNF-α inhibitors showed mainly a reduction in inflammatory
538 cytokines and favourably influenced markers of muscle mass, muscle strength, and performance in
539 short-term acute as well as long-term repeated exercise situations. These observations did not change
540 with respect to the exercise duration.
541 **4. LIMITATIONS**
542 Due to the limited number of the related studies in the literature, some considerations should be
543 encountered when it comes to data interpretation of this systematic review. Based on this, we kept our
544 scope very open in which we included all known drugs with (high or low) anti-inflammatory effects and
545 considered the inflammatory status in both human or animal studies. Despite the limited number of
546 medications included in this work, we have applied many different parameters including: inflammatory
547 markers, age groups, sample sizes, health statuses, and types of exercise interventions, as well as both
548 human and animal studies. Other issues presented themselves when calculating ES; for four studies,
549 authors did not communicate the pre- and post-intervention measures (three authors did not reply to our
550 request, and one author refused to share the requested data). The heterogeneity of the included studies
551 made it impossible to perform a meta-analysis. In the context of these drugs' potential clinical
552 applicability, the balance between benefits and risks of possible side-effects should be considered. In
553 fact, for most of the AIDs that the included articles investigated, significant side effects – such as
554 gastrointestinal complications – could be expected; table S6 provides an overview of the major possible
555 side effects. Surprisingly, most of the included studies reported no side effects; it remains unclear

whether this is because no side effects occurred in these studies or because side effects were not systematically screened for/recorded.

5. FUTURE RESEARCH

Future studies should include other drugs with anti-inflammatory effects and consider potential drug-drug interactions or side effects, in addition, it should include some standard tests, such as the 6-minute walk test that records walking speed and distance, which will make it simpler to be replicated in clinical practice for health investigators and care providers. In this context, Reginster et al. have recently proposed recommendations for the conduct of clinical trials for drugs to treat or prevent sarcopenia (Reginster et al., 2016). To create beneficial effects for older individuals with CLIP, it is recommended that this population receive more attention.

6. CONCLUSION

Overall, although robust evidence is lacking, we found good quality scientific evidence in the literature pointing towards the potential beneficial impact of AIDs (non-selective Cox and selective Cox-2 inhibitors) on performance and muscle weakness in a specific population of elderly patients with an acute inflammatory condition. This might be related to their direct impact on acute inflammation, thus enhancing recovery. On the other hand, long-term exercise combined with non-selective Cox inhibitors have shown evidence for improvements in muscle strength, especially in the elderly population. These results could relate to the reduction in low-grade inflammation that often occurs with ageing, suggesting the influence of age and the usefulness of AIDs with exercise in reducing CLIP and restoring anabolic response to prevent sarcopenia. Animal studies illustrated the positive impact of TNF-α inhibitors and long-term exercise on inflammation as well as muscle performance. Based on the data from these studies and their favourable outcomes with respect to inflammation, muscle mass, and performance, additional well-designed studies including those three elements are needed to better understand this finding.

The results reveal a gap in our knowledge regarding the best approaches to provide efficacy, effectiveness, and safety in the use of such drugs. In fact, we cannot draw conclusions with respect to the balance between harms and benefits because most of the included papers did not systematically report the occurrence of side effects. Presently, study results are not sufficiently robust to support any recommendation regarding the most appropriate way to use AIDs, or whether to combine it with exercise

584 intervention. Further large-scale longitudinal studies are necessary to fully evaluate the role of drugs
585 with anti-inflammatory effects in CLIP and in restoring muscle mass, strength and performance in older
586 adults who present with sarcopenia.

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Figure 1. Flowchart article selection.

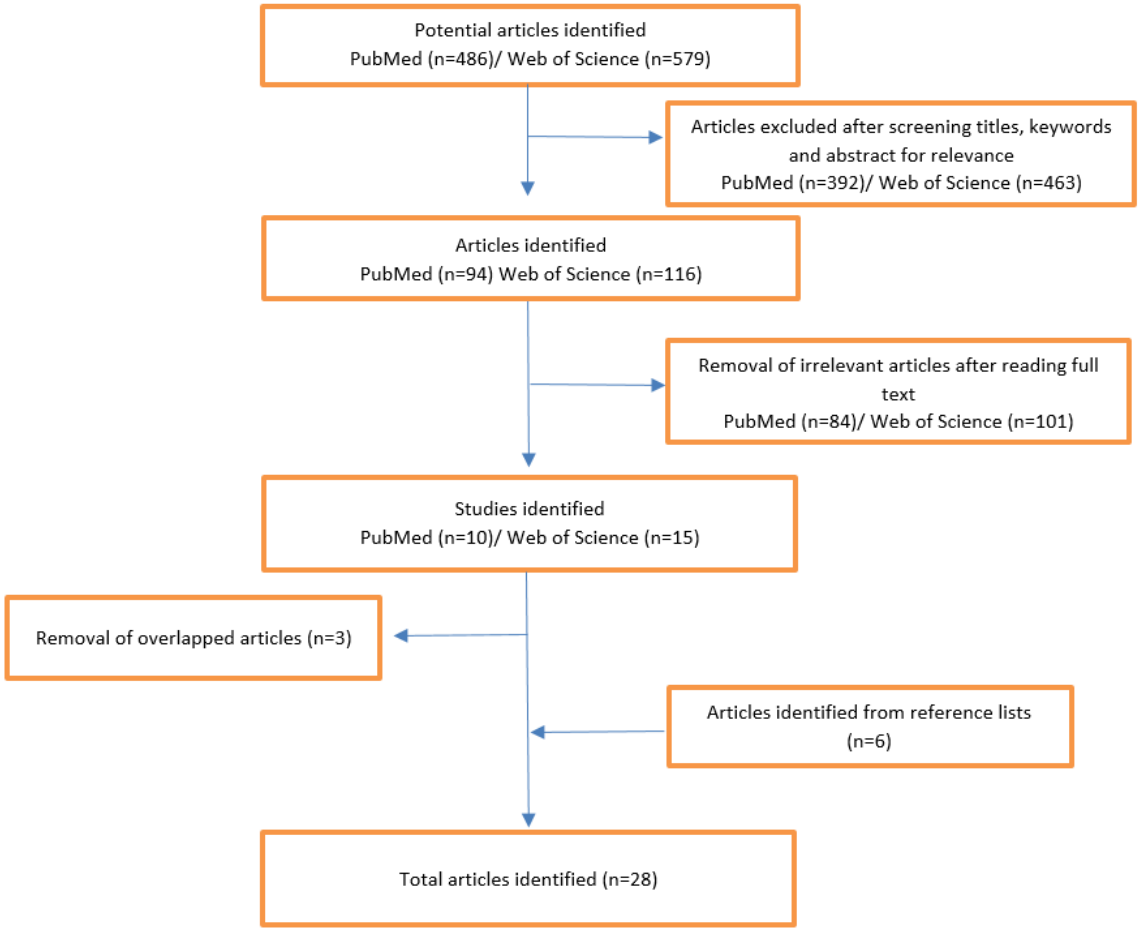
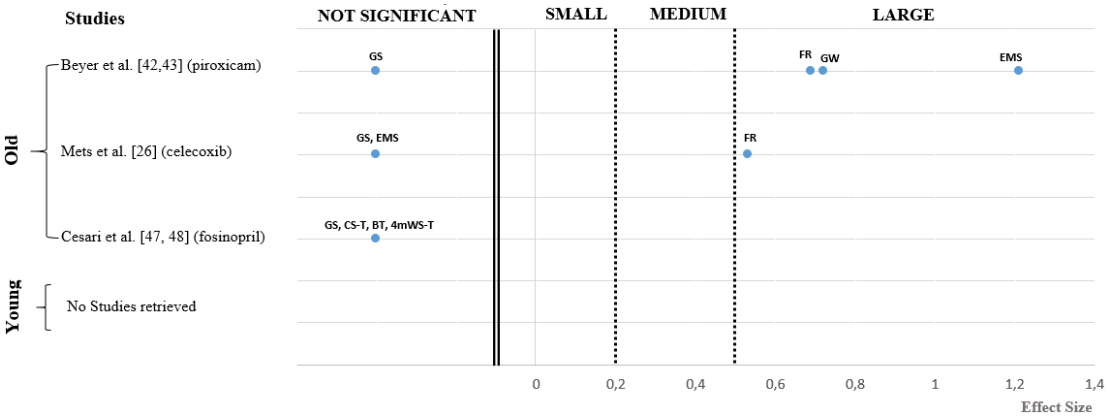
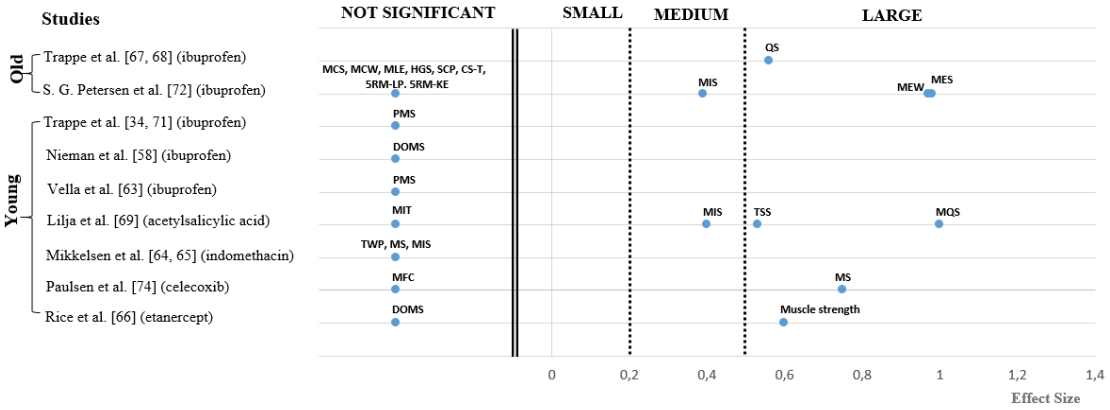


Figure 2. Impact of AIDs on muscle performance without exercise in old and young human studies.



Abbreviation used: GS, Grip strength; FR, Fatigue resistance; GW, Grip work; EMS, Elderly mobility scale; 4m WS-T, 4-meter walking speed test; CS-T, Chair-stand test; BT, Balance test. Effect sizes were shown only when effects were statistically significant. Effect size (ES) was calculated using Cohen's d: small ES (d <0.2), medium ES (d from 0.2 to 0.5) and large ES (d >0.5)

Figure 3. Impact of AIDs on muscle performance with exercise in old and young human studies.



Abbreviation used: PMS, Perceived muscle soreness; DOMS, Delay onset of muscle soreness; QS, Quadriceps muscle strength; MCS, Maximal concentric muscle strength; MCW, Maximal concentric muscle work; MLE, Maximal leg extension power; HGS, habitual gait speed; SCP, Stair-climbing performance; CS-T, Chair stand test; 5RM-LP, 5-RM leg press; 5RM-KE, 5-RM knee extension; MIS, Maximal isometric muscle strength; MQS, Maximal isokinetic muscle strength; MIT, Maximal isometric torque; MEW, Maximal eccentric work; MES, Maximal eccentric strength; TWP, Total work performed; MS, Muscle soreness; MFC, Maximal force-generating capacity; TSS, Training-specific strength. Effect sizes were shown only when effects were statistically significant. Effect size (ES) was calculated using Cohen's d: small ES (d <0.2), medium ES (d from 0.2 to 0.5) and large ES (d >0.5).

Table 1. The impact of using AIDs on inflammation, muscle mass and performance in humans

References	Population	AIDs/dose/ duration	Measurements time points	Effect of AIDs vs control/placebo		
				Inflammation	**Muscle mass**	**Performance**
(Beyer et al., 2012b, 2011)	Geriatric patients with acute infection (70 – 94) yrs n=30	piroxicam 10 mg/day: n=5M/9F CON: Placebo: n=4M/10F [for 10 days]	Baseline, after 1, 2 and 3 days, and after 1, 2 and 3 wk	CRP: piroxicam at wk3 ↓1.47●, placebo at wk3 ↓1.43● IL-6: piroxicam at wk2 ↓0.90● and wk3↓0.92● IP-10/CXCL10: piroxicam at wk1↓0.36● and wk3↓0.55● CCL3/MIP-1α: placebo at wk3↓0.54● CCL4/MIP-1β: placebo at wk3↓0.59● IL-5, IL-13, IL-17 and IFN-g: not detected IL-1b,IL-1RA, IL-2, IL-2R, IL-4, IL-7, IL-10, IL-12, IL- 15, CCL2/MCP-1, CCL5/RANTES, CCL11/Eotaxin, CXCL8/IL-8, CXCL9/ MIG, TNFa, IFN-a, and GM-CSF: n/s	LBM: Total body potassium pool: n/s	EMS: piroxicam at wk2↑1.21●; GS: n/s FR: piroxicam at wk3 ↑0.69● GW: piroxicam at wk2↑0.48● and wk3 ↑0.72●
(Mets et al., 2004)	Geriatric patients (84 ± 6) yrs n=43	celecoxib 200mg/day: n=9F/5M acetaminophen 1000mg/3 times/day: n=11F/3M CON: No medication: N=11F/4M [for 14 days]	Baseline, after 1 and 2 wk	CRP: n/s IL-6: n/s IL-1β: n/s IL-10: celecoxib: at W2 ↓0.49▲, at W2 ↓0.48‡ TNF-α: n/s TGF-β: n/s		EMS: n/s GS: n/s FR: celecoxib: at W2 ↑ 0.53▲, ↑0.48‡
(Cesari et al., 2010, 2009)	Adult patients with high cardiovascular risk profile (65.97 ± 7.41) yrs n=257	fosinopril 20mg/day for 1 wk then 40mg/day for 6 m CON: Placebo for 6 m n= 257 (M/F) [Cross-over study]	Baseline, after 6 and 12 m	CRP: n/s IL-6: n/s PAI-1: n/s		GS: n/s 4-meter walking speed test: n/s Chair-stand test: n/s Balance tests: n/s

Abbreviation used: M, male; F, female; wk, Week; m, Month; yrs, years; CON, controls; EMS, Elderly mobility scale; GS, Grip strength; FR, Fatigue resistance; GW, Grip work; LBM, Lean body mass; n/s, no significant difference between groups; ↑= increase post-intervention ↓= decrease post-intervention; ‡ = significant difference from the other medication; ● = significant from baseline values; ▲= significant difference from controls.

Table 2. The impact of using AIDs on inflammation, muscle mass and performance in animals

References	Population	AIDs/dose/ duration	Measurements time points	Effect of AIDs vs control/placebo		
				Inflammation	Muscle mass	Performance
(Rieu et al., 2009)	Old Wistar rats (20 m) n=70	ibuprofen 30mg/kg body weight: n=23 CON: no medication: n=47 [for 5 m]	Baseline, after 1, 2, 3, 4, 5 m	IL-6: ibuprofen: at m5↓0.47▲ IL-1β: ibuprofen: at m5↓0.45▲ TNF-α: n/s MCP-1: n/s PAI-1: n/s Fibrinogen: ibuprofen: at m5↓0.89▲	(Hind limb muscle mass) Gastrocnemius: ibuprofen: at m5↑3.17▲ EDL: ibuprofen: at m5↑3.33▲ Tibialis anterior: ibuprofen: at m5↑3.22▲ Muscle protein synthesis: ibuprofen: at m5 ↑0.83▲ Muscle proteolysis: ibuprofen: at m5 ↓0.94▲	

Abbreviation used: m, Month; CON, controls; n/s, no significant difference between groups; EDL, Extensor digitorum longus muscle; ↑= increase post-intervention ↓= decrease post-intervention; ▲= significant difference from controls.

Table 3. The impact of using AIDs with exercise-induced changes in inflammation, muscle mass and performance in humans

Reference	Population	Exercise protocol	AIDs/dose/ duration	Measurements time points	Effect of AIDs vs control/placebo		
					Inflammation	Muscle mass	Performance
(Nieman et al., 2006)	Ultra-marathoners (47.9±1.4) yrs n=54	160-km Endurance Run race in less than 24 hr or a 100-km race in 12-13 hr [depending on age]	ibuprofen: 600mg afternoon prior race and 1200mg on race day: n=29 (M/F) CON: no medication: n=25 (M/F)	Pre-race and 5-15 min post-race	ibuprofen: CRP: ↑0.59▲ IL-6: ↑0.59▲ Il-1ra: ↑0.76▲ IL-8: ↑1.01▲ IL-10: ↑0.59▲ TNF-α: n/s MCP-1: ↑0.65▲ G-CSF: ↑0.98▲ MIP-1β: ↑0.65▲		DOMS: n/s
(S. Petersen et al., 2011)	Sedentary or recreationally active with knee osteoarthritis (50-70) yrs n=20	60 min of one legged kicking at 55% of workload maximum	ibuprofen 1200mg/day n=9 CON: Placebo n=11 (3 days before exercise) [total for 4 days]	Baseline and 24 h post-exercise	$PGF_{2\alpha}$: ibuprofen↓1.78▲ PGE_2,IGF-1, IGF-BP3, and PINP: n/s	myofibrillar FSR: n/s	
(Dideriksen et al., 2016)	Elderly men (>60) yrs n=24	10 sets and 8 repetitions at 70% 1RM of unilateral knee extension exercise	Inflamed group: ibuprofen 1800mg/day: n=7 Placebo: n=7 [for 7 days before Exp. day] Healthy control: no treatment n=10	Blood samples: 4 and 1 wk before Exp. day And at the Exp. day Myofibrillar FSR: At Basal, postprandial and post-exercise	CRP: at Exp. day ibuprofen: ↑0.99# at Exp. day Placebo: ↑1.15# IL-6: n/s	Muscle myofibrillar FSR: n/s	
(Vella et al., 2016)	Healthy untrained (23±1.3) yrs n=16	3 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	ibuprofen 1200mg/day n=8 CON: Placebo: n=8 [throughout the trial day]	Venous blood: Pre-exercise, 5 min, 1, 2, 3 and 24hr post-exercise Muscle biopsy: Pre-exercise, 5min, 3 and 24hr post-exercise	Inflammatory cells: MPO^+: n/s $CD66b^+$: n/s $CD68^+$: n/s		Perceived muscle soreness: n/s

(Mikkelsen et al., 2011, 2009)	Healthy endurance trained (23±3) yrs n=8	200 unilateral maximal eccentric knee extensor contractions	One leg indomethacin 45mg infusion to the vastus lateralis muscle before, during and for 4.5 h after exercise: n=8 M Other leg CON: placebo; Ringer-acetate solution n=8 M	Baseline, 0.5 and 24 h and at 2, 3 and 8 days post-exercise for muscle soreness Baseline and 8 days post-exercise for muscle biopsies	IL-6: in indomethacin at 5h:↑▲n.d.a IL-1β: in indomethacin at 5h:↑▲n.d.a IL1R: n/s TNF-α: in indomethacin at 5h:↑▲n.d.a and at 8 days: ↓▲n.d.a MCP-1: n/s $CD16^+$: n/s $CD68^+$: n/s TGF-β1: n/s	Satellite cells: indomethacin: Pax7 cells per total myonuclei: at D8↓1.38▲ No. of $NCAM^+$ cells/fiber: at D8↓0.40▲ $NCAM^+$ cells/myonuclei, %: at D8↓1.81▲ No. of Myonuclei/fiber: n/s No. of $Ki67^+$-$NCAM^+$ cells/100 fiber: n/s Proportion of active satellite cells, %: n/s Total no. of $Ki67^+$ cells/100 fiber: n/s Central nuclei, %: n/s IGF-IEa: n/s Muscle myofibrillar FSR: n/s	Muscle soreness: n/s Total work performed: n/s Maximal isometric Muscle Strength: n/s
(Trappe et al., 2002, 2001) and (Peterson et al., 2003)	Healthy sedentary or recreationally active (25±3) yrs n=24	10-14 sets of 10 repetitions of unilateral knee extensor exercise at 120% 1-RM separated by 60 s rest intervals	ibuprofen 1200g /day: n=8 M acetaminophen 4000mg/day: n=8 M CON: Placebo: n=8 M [total of four doses]	Baseline and 24 hr post-exercise	$PGF_{2\alpha}$: ibuprofen ↓1.93▲ acetaminophen↓1.80▲ PGE_2: acetaminophen↓2.41▲ $CD15^+$: n/s $CD68^+$: n/s	FSR: ibuprofen: n/s acetaminophen: n/s	Perceived muscle soreness: n/s
(Trappe et al., 2013, 2011)	Healthy untrained (60-85) yrs n=36	2 sets of 5 knee extensions at a light weight, followed by 3 sets of 10 repetitions with 2 min rest interval performed 3 days/wk on nonconsecutive days Total duration: 12 wk	ibuprofen 1200 mg/day: n=9M/4F acetaminophen 4000 mg/day: n=7M/4F CON: Placebo: n=8M/4F [for 12 wk]	Muscle volume: Baseline and at the end of 12 wk Muscle strength: 3x prior training and 2x during the final week of 12wk	IL-1β, IL-8, TNF-α, $cPLA_2$; $sPLA_2$, $PGF_{2\alpha}$ synthase, PGE_2 and $PGF_{2\alpha}$ reductase, PGE_2 synthase-1, PGE_2 synthase-2, PGE_2 synthase-3, PGE_2 receptor-4; n/s	Quadriceps Muscle Volume: ibuprofen↑0.38▲ acetaminophen↑0.91▲ Hamstrings Muscle size: n/s Skeletal muscle water and protein content: n/s Myogenin, MRF4 and myostatin: n/s MuRF-1: ibuprofen ↓1.2▲ acetaminophen↓0.98▲	Quadriceps Muscle Strength: ibuprofen↑0.56▲ acetaminophen↑0.59▲ Quadriceps strength normalized to muscle size: n/s

(S. G. Petersen et al., 2011)	Sedentary or recreationally active with bilateral tibiofemoral knee osteoarthritis (50-70) yrs n=36	4 sets of 15-RM in the first wk progressively increasing to 4 sets of 8RM by wk 7 and onward of the knee extension and leg press performed 3 nonconsecutive days per wk [for 12 wk]	ibuprofen 1200mg/day: n=12 CON: Placebo: n=11 [for 12 wk]	Baseline and at the end of the 12 wk	CRP: n/s $CD56^{+}$: n/s	Quadriceps Muscle Cross-Sectional Area: n/s	Maximal isometric strength: ibuprofen↑0.39▲ Maximal eccentric muscle strength: ibuprofen↑0.98▲ Maximal eccentric work: ibuprofen↑0.97▲ Maximal concentric muscle strength, Maximal concentric muscle work, 5-RM leg press and 5-RM knee extension: n/s Maximal leg extension power, Habitual gait speed, stair-climbing performance and chair stand: n/s
(Lilja et al., 2018)	Healthy recreationally active (18-35) yrs n=31	One leg performed 4 sets of 7 maximal repetitions on FW device and the other leg performed 4 sets of 8-12 repetitions to failure on WS machine of 1-RM (2 and 3 times every other week). [for 8 wk]	ibuprofen 1200mg/day: n=15 acetylsalicylic acid 75mg/day: n=16 [for 8 wk]	Muscle biopsies: Before (pre-) and 48h after the last training session in the 8^{th} wk (post-)	mRNA expression of: IL-6: Ibuprofen ↓ 1.01‡ COX-1, COX-2, PGF2α-receptor, PGE_2-receptor, Atrogin-1, TNF-α: n/s	Quadriceps muscle volume: acetylsalicylic acid ↑0.84 ‡ (average across legs) Muscle quadriceps mean CSA: acetylsalicylic acid ↑ WS0.81 and FW0.82 ‡ Muscle quadriceps signal intensity: n/s Muscle biceps femoris means CSA: n/s MuRF-1: n/s	Maximal isometric and isokinetic muscle strength: acetylsalicylic acid ↑ FW (0.4-1.0) ‡ and WS n/s Training-specific strength: acetylsalicylic acid ↑ FW 0.53 ‡ Maximal isometric torque: n/s
(Brewer et al., 2015)	Healthy recreationally active (20.6±1.3) yrs n= 23	3 sets of 6-10 repetitions for four bilateral resistance training of the upper back and bicep musculature at 66-86% 1RM with 90 s rest in between, two sessions per week separated by 48 hr [for 6 wk]	naproxen 440mg Twice weekly: n=12 CON: Placebo: n=11 [for 6 wk]	(pre- and post-exercise) at 1,4 and 6 wk	$PGF_{2\alpha}$: naproxen: at wk1 ↓1.32▲ and wk4↓0.62▲	Skeletal muscle tissue LBM: n/s	
(Paulsen et al., 2010)	Healthy recreationally active	2 bouts of 70 maximal unilateral eccentric	celecoxib 400mg/day: n=8M/7F	2, 24 and 48 hr after bout 1 for	PGE_2: n/s $CD66b^{+}$: n/s	$CD56^{+}$: n/s	Muscle soreness: celecoxib: ↓0.75▲ and ↓0.86 for bouts 1 and 2

	(~25) yrs n=33	actions of the elbow flexors with 30-35 s rest in-between sets Separated by 3 wk	CON: Placebo: n=14M/4F [for 9 days]	measurement of (PGE2) 1, 48, 96 and 168 hr after bout 1 and 1 and 48 hr after bout 2 for muscle biopsies	$CD68^{+}$: n/s		Maximal force-generating capacity: n/s
(Rice et al., 2008)	Healthy recreationally active (24±3) yrs n=12	On two separate occasions at least 6 weeks apart: 4 sets of 15 repetitions of leg-press at 80% 1-RM	etanercept 25mg SC CON: Vehicle (sterile water): [1 hr before exercise] n=12 M [a crossover conditions]	Muscle biopsies: pre-, 2 and 24 hr post-exercise Blood, strength and pain: pre- and at 24, 48, 72 hr post-exercise	Muscle TNF-α: ↓ n.d.a		DOMS: n/s Muscle strength: etanercept: 48hr: ↑0.39▲, 72hr: ↑0.60▲

Abbreviation used: M, male; F, female; s, seconds; min, minutes; hr, hour; wk, Week; m, Month; yrs, years; CON, controls; LBM, Lean body mass; RM, repetition maximum; FSR, Muscle protein fractional synthesis rate; DOMS, Delay onset of muscle soreness; SC, subcutaneous injection; FW, flywheel ergometer; WS, weight-stack training; n/s, no significant difference between groups; ↑= increase post-intervention; ↓= decrease post-intervention; ‡ = significant difference from the other medication; ▲= significant difference from controls; n.d.a, no data available to calculate effect size; #= Significant difference from healthy group.

Table 4. The impact of using AIDs with exercise-induced changes in inflammation, muscle mass and performance in animals

Reference	Population	Exercise protocol	AIDs/dose/ duration	Measurements time points	Effect of AIDs vs control/placebo		
					Inflammation	Muscle mass	Performance
(Lima et al., 2016)	Male Wister rats (60 -90) days n=48	6- wk swimming training with body weight overload with 5 sessions/wk of 60 min each, then LC test. After 3 days, 3 repeated exhaustive swimming bouts: 72, 144 and 216 h after LC	ibuprofen 15mg/kg/day CON: Saline [for 8 days]	After 1, 2 and 3 bouts of exhaustion and at the end of the study	In gastrocnemius muscle: IL-1β: n/s TNF-α: n/s		Exhaustion time: ibuprofen+trained: ↑1.65∏ ibuprofen+sedentary: ↑1.53† Saline+trained: ↑2.99†
(Kietrys et al., 2011)	Sprague-Dawley young adult female rats (14) wk n=96	Voluntary repetitive upper limb: High repetition with high force task 2 hr/day, 3 days/wk for 12 wk	ibuprofen 45mg/kg n=22 CON: Untreated high n=26 [for 8 wk]	Baseline, 9 and 12 wk	IL-1β in Central nervous system inflammatory response: n/s		GS in contralateral support limb: ↑1.98▲ Reach Force: ibuprofen: at wk9: ↑3.01▲ Duration of task participation: ibuprofen at wk9: ↑5.88▲ and at wk12: ↑7.49▲ Reach rate: n/s %Success Reaches: ibuprofen: at wk12 ↓3.68▲
(Enos et al., 2013)	C57BL/6 mice (8 – 10) wk n= 39	90 min bout of treadmill running for 5 days at 25m/min and 8% grade	indomethacin 2.5mg/kg/ day, 1h before exercise n=10 CON: no treatment n=10 [for 5 days]	Exercise performance: at day 1,2,3,4 and 5 Inflammation: at day 5	IL-6: n/s IL-1β: indomethacin: at day 5 ↑1.62▲ TNF-α: indomethacin: at day 5 ↑1.06▲ MCP-1: indomethacin: at day 5 ↑0.52▲		Run time to fatigue in minutes: indomethacin: at day4 ↓2.03▲ and at day5 ↓1.13▲
(Domínguez-Álvarez et al., 2014)	Pathogen-free Wistar male rats (8) wk n= 48	Maximal inspiratory pressure (MIP) intensities of those resting baseline values: High 70% 2 hr/day for 14 days	infliximab 0.01 mg/g/0.3 mL dose: n=8 CON: No treatment: n=8 [every 7 days for 14 days]	Baseline and at day 14	IL-6: infliximab: in plasma: ↓1.68▲ in diaphragm: ↑1.09▲ IL-1β: n/s TNF-α: infliximab: in plasma: ↓1.54▲ in diaphragm: ↑0.99▲	M-cadherin (in the diaphragm): infliximab ↑3.38▲ myf-6 mRNA (in the diaphragm): infliximab ↑3.43▲ Internal nuclei levels (in the diaphragm): infliximab ↑1.88▲	MIP, % predicted: infliximab: 1.87↑▲

					IFN-γ: infliximab: in plasma↓1.91▲ inflammatory cells: in diaphragm:↓2.06▲	The size of type II fibers (in the diaphragm): infliximab ↑1.05▲	
(Abdelmagid et al., 2012)	Sprague-Dawley female rats (3.5 – 4) m n= 142	High repetition negligible force, handle-pulling task of 4 reaches/ min, 60% max. pulling force for 2h/day, 3days/wk for 6 wk (6HRHF)	ibuprofen 45mg/kg/day [for 2 weeks after 4 weeks of training] Anti-TNF-α 15mg/kg [at beginning of wk 4, at end of wk 4 and end of wk 5]	GS: Baseline, at 1,2,3,4,5 and 6 wk CTGF and TGF-β1: at end of study	TGF-β1 flexor Digitorum Muscle: 6HRHF+ibuprofen↓1.31▲ 6HRHF+Anti-TNF-α n/s	CTGF flexor Digitorum Muscle: 6HRHF+ibuprofen↓1.26▲ 6HRHF+ Anti-TNF-α ↓0.85▲	GS: 6HRHF+ibuprofen at wk 6↑1.53▲ 6HRHF+ Anti-TNF-α: n.d.a
(Rani et al., 2010)	Sprague-Dawley female rats (3) m n=53	High repetition high force task of 12 reaches/min, 60% max. grip force, for 2h/day, 3days/wk for 6 wk (6HRHF)	Anti-TNF-α 15mg/kg [at beginning of wk 4, at end of wk 4 and end of wk 5] CON: without treatment	At the end of the study	In serum: TNFα: 6HRHF+Anti-TNF-α: ↓1.29▲ IL-1α: 6HRHF+Anti-TNF-α: ↓1.22▲ MIP2: 6HRHF+Anti-TNF-α: ↓1.68▲ IL-6, IL-1β, IL-10, MIP3, IL-2, IL-4, GMCSF, MICP1, IFN-β and CINC2a: n/s In Flexor Digitorum Muscle: TNFα: n/s	CTGF: n/s	GS: 6HRHF+ Anti-TNF-α: ↑4.35▲

Abbreviation used: M, male; F, female; s, seconds; min, minutes; hr, hour; wk, Week; m, Month; yrs, years; CON, controls; CTGF, connective tissue growth factor; GS, Grip strength; LC, lactate concentration test; n/s, no significant difference between groups; ↑= increase post-intervention; ↓= decrease post-intervention; ▲= significant difference from controls; n.d.a, no data available to calculate effect size; ∏ = significant difference compared to Saline+trained group; † = significant difference compared to Saline+sedentary group.

Table 5. Summary of evidence on AIDs use in human:

	Population					
	Young Adults			Old Adults		
Medication	**Inflammation**	**Muscle Mass**	**Muscle Performance**	**Inflammation**	**Muscle Mass**	**Muscle Performance**
Ibuprofen	⊖* ? ⊕ ⊕	?	?* ? ? ?	⊕ ⊖* ⊕ ⊕	? ?* ⊕ ?	⊕ ⊕
Indomethacin	⊖* ⊕	⊖	?			
Naproxen	⊕	?				
ASA	?	⊕	⊕			
Piroxicam				+	?	+
Celecoxib	?	?	?	+		+
Fosinopril				?		?
Etanercept	⊕		⊕			

Each symbol represents the outcome of one study (larger symbols are based on high quality RCTs and smaller symbols are based on either low methodological quality RCTs or non-RCTs): ⊕ positive effects with long-term exercise, ⊖ negative effects with long-term exercise, ? no significant change with long-term exercise, + positive effects without exercise, - negative effects without exercise, ? no significant change, ⊕ positive effects with short-term exercise, ⊖ negative effects with short-term exercise, ? no significant change with short-term exercise, ⊖* negative effects with short-term exercise when measured on the same day of exercise, ?* no significant change with short-term exercise when measure on the same day of exercise.

Table 6. Summary of evidence on AIDs use in animals:

	Population					
	Young			Old		
Medication	**Inflammation**	**Muscle Mass**	**Muscle Performance**	**Inflammation**	**Muscle Mass**	**Muscle Performance**
Ibuprofen	? ? ⊕	⊖	⊕ ⊕ ⊕	+	+	
Indomethacin	⊖		⊖			
Infliximab	⊕/⊖	⊕	⊕			
Anti-TNF-α	⊕ ?	? ⊖	⊕			

Each symbol represents the outcome of one study: ⊕ positive effects with long-term exercise, ⊖ negative effects with long-term exercise, ⊕/⊖ positive effects in plasma but negative effects in diaphragm, ? no significant change with long-term exercise, + positive effects without exercise, - negative effects without exercise, ⊖ negative effects with short-term exercise.

Table S1. PubMed and Web of Science search string (April 22, 2018):

KEYWORDS	HITS
(("anti-inflammatory agents"[Pharmacological Action] OR "anti-inflammatory agents"[MeSH Terms] OR "anti-inflammatory drugs"[All Fields] OR "Acetaminophen"[Mesh] OR "Aspirin"[Mesh] OR "Hydroxymethylglutaryl-CoA Reductase Inhibitors"[Mesh] OR "Hydroxymethylglutaryl-CoA Reductase Inhibitors"[Pharmacological Action] OR "statins"[All Fields] OR "Fenofibrate"[Mesh] OR "Fenofibrate"[All Fields] OR "Nitric Oxide Donors"[Pharmacological Action] OR "Nitric Oxide Donors"[Mesh]) AND (("Muscle Strength"[Mesh] OR "Muscle Weakness"[Mesh] OR "Muscle Fatigue"[Mesh] OR "Muscle, Skeletal"[Mesh] OR "Muscular Atrophy"[Mesh]) OR ("Muscle, Skeletal"[Mesh] AND "Hypertrophy"[Mesh]))) AND ("inflammation"[MeSH Terms] OR "Inflammation"[Mesh] OR "Chemokines"[Mesh] OR "interleukins"[MeSH Terms] OR "Cytokines"[Mesh] OR "Receptors, Cytokine"[Mesh] OR "Acute-Phase Proteins"[Mesh] OR "Acute-Phase Reaction"[Mesh])	486
TS=((Anti-Inflammatory Agents, Non-Steroidal) OR (Anti-inflammatory drugs) OR (Acetaminophen) OR (Aspirin) OR (Statins) OR (Hydroxymethylglutaryl-CoA Reductase Inhibitors) OR (Fenofibrate) OR (Nitric Oxide Donors)) AND TS=((Muscle Strength) OR (Muscle Weakness) OR (Muscle Fatigue) OR (Muscle Fibers, Skeletal) OR (Muscle, Skeletal) OR (Muscular Atrophy)) AND TS=((Inflammation) OR (Inflammatory) OR (Inflammatory profile) OR (Chemokines) OR (interleukin) OR (Cytokines) OR (Receptors, Cytokine) OR (Acute-Phase Proteins) OR (Acute-Phase Reaction))	579

Table S2. Quality assessment of the randomized controlled trials included in the present review with the NICE guidelines for human:

References	(A) Selection bias (systematic differences between the comparison groups)				(B) Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)				(C) Attrition bias (systematic differences between the comparison groups with respect to loss of participants)						(D) Detection bias (bias in how outcomes are ascertained, diagnosed or verified)					
	A1	A2	A3	Risk	B1	B2	B3	Risk	C1	C2a	C2b	C3a	C3b	Risk	D1	D2	D3	D4	D5	Risk
Trappe et al. [67, 68] and Peterson et al. [70]	U	U	Y	U	Y	Y	Y	L	Y	U	U	U	U	U	Y	Y	Y	Y	U	L
Mets et al. [26]	U	U	Y	U	Y	U	Y	L	Y	CON: n=3; ACET: n=1; CELE: n=1	Y	n=0	Y	L	Y	Y	Y	N	U	L
Rice et al. [66]	U	U	Y	U	Y	Y	Y	L	Y	n=0	Y	n=0	Y	L	Y	Y	Y	Y	U	L
Cesari et al. [47, 48]	Y	Y	Y	L	Y	Y	U	L	Y	n=37	Y	n=37	Y	L	Y	Y	Y	Y	U	L
Paulsen et al. [74]	U	U	Y	U	Y	Y	U	L	Y	U	U	U	U	U	Y	Y	Y	Y	U	L
S. Petersen et al. [61]	Y	Y	Y	L	Y	Y	Y	L	Y	n=0	Y	n=0	Y	L	Y	Y	Y	Y	Y	L
S. G. Petersen et al. [72]	Y	Y	Y	L	Y	Y	Y	L	Y	IBU: n=1	Y	IBU: n=1	Y	L	Y	Y	Y	Y	Y	L
Beyer et al. [42, 43]	Y	Y	Y	L	Y	Y	Y	L	Y	CON: n=3; PIROX: n=2	Y	CON: n=3; PIROX: n=2	Y	L	Y	Y	Y	Y	U	L
Trappe et al. [34, 71]	U	U	Y	U	Y	Y	Y	L	Y	n=0	Y	n=0	Y	L	Y	Y	Y	Y	U	L
Brewer et al. [73]	U	U	Y	U	Y	Y	U	L	Y	n=0	Y	n=0	Y	L	Y	Y	N	Y	U	L
Dideriksen et al. [62]	Y	U	N	U	Y	U	U	L	Y	n=0	Y	n=0	Y	L	Y	Y	Y	U	U	L
Vella et al. [63]	U	U	Y	U	Y	Y	U	L	Y	n=0	Y	n=0	Y	L	Y	Y	Y	U	U	L
Lilja et al. [69]	U	U	Y	U	Y	N	Y	L	Y	n=0	Y	n=0	Y	L	Y	Y	Y	Y	U	L

A1: adequate method of randomization; A2: adequate concealment of allocation; A3: groups comparable at baseline; B1: groups received same care apart from intervention; B2: participants kept blind; B3: individuals administering care kept blind; C1: groups followed up equal length of time; C2a participants did not complete treatment; C2b: groups comparable for treatment completion; C3a: participants with missing data; C3b: groups comparable for availability in outcome data; D1: appropriate length of follow-up; D2: precise definition of outcome; D3: valid method to determine outcome; D4: investigators blinded to participants' exposure; D5: investigators blind to other important confounding factors**.** ACET, Acetaminophen; CELE, Celecoxib; IBU, Ibuprofen; PIROX, Piroxicam; CON, control; H, high risk; L, low risk; N/A, not applicable; U, unclear; Y, yes; N, no.

Table S3. Quality assessment of the randomized controlled trials included in the present review with the NICE guidelines for animals:

References	(A) Selection bias (systematic differences between the comparison groups)				(B) Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)				(C) Attrition bias (systematic differences between the comparison groups with respect to loss of participants)						(D) Detection bias (bias in how outcomes are ascertained, diagnosed or verified)					
	A1	A2	A3	Risk	B1	B2	B3	Risk	C1	C2a	C2b	C3a	C3b	Risk	D1	D2	D3	D4	D5	Risk
Rieu et al. [36]	U	U	U	U	Y	N/A	U	L	Y	IBU: n=2 CON: n=8	Y	IBU: n=2 CON: n=8	N/A	L	Y	Y	Y	U	U	L
Rani et al. [79]	U	U	U	U	Y	N/A	U	L	Y	n=0	Y	n=0	Y	L	Y	Y	Y	U	U	L
Kietrys et al. [75]	U	U	U	U	Y	N/A	U	L	Y	n=0	Y	n=0	Y	L	Y	Y	Y	U	U	L
Abdelmagid et al. [78]	U	U	U	U	Y	N/A	U	L	Y	n=0	Y	n=0	Y	L	Y	Y	Y	U	U	L
Enos et al. [38]	U	U	U	U	Y	N/A	U	L	Y	n=0	Y	n=0	Y	L	Y	Y	Y	U	U	L
Domínguez-Álvarez et al. [77]	U	U	U	U	Y	N/A	U	L	Y	n=0	Y	n=0	Y	L	Y	Y	Y	U	U	L
Lima et al. [76]	U	U	U	U	Y	N/A	Y	L	Y	n=0	Y	n=0	Y	L	Y	Y	Y	Y	U	L

A1: adequate method of randomization; A2: adequate concealment of allocation; A3: groups comparable at baseline; B1: groups received same care apart from intervention; B2: participants kept blind; B3: individuals administering care kept blind; C1: groups followed up equal length of time; C2a participants did not complete treatment; C2b: groups comparable for treatment completion; C3a: participants with missing data; C3b: groups comparable for availability in outcome data; D1: appropriate length of follow-up; D2: precise definition of outcome; D3: valid method to determine outcome; D4: investigators blinded to participants' exposure; D5: investigators blind to other important confounding factors**.** IBU, Ibuprofen; CON, control; H, high risk; L, low risk; N/A, not applicable; U, unclear; Y, yes; N, no.

Table S4. Quality assessment of the non-randomized controlled trials included in the present review with the STROBE checklist for human:

Criteria	Reference	
	Nieman et al. [58]	Mikkelsen et al. [64, 65]
Indicate the study's design with a commonly used term in the title or the abstract	Y	Y
Provide in the abstract an informative and balanced summary of what was done and what was found	Y	Y
Explain the scientific background and rationale for the investigation being reported	Y	Y
State specific objectives, including any prespecified hypotheses	Y	Y
Present key elements of study design early in the paper	Y	Y
Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Y	N
Provides the eligibility criteria as well as the sources and methods of selection of participants	Y	N
Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Y	Y
For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Y	Y
Describe any efforts to address potential sources of bias	N	N
Explains how the study size was determined	N	N
Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Y	Y
Describe all statistical methods, including those used to control for confounding	Y	Y
Describe any methods used to examine subgroups and interactions	N	N
Explain how missing data were addressed	N	N
If applicable, describes analytical methods, taking into account the sampling strategy	U	U
Describes any sensitivity analyses	N	U
Reports numbers of individuals at each stage of study; number potentially eligible, number examined for eligibility, number confirmed eligible, number included in the study, number completing follow-up, and number analyzed	Y	N
Gives reasons for nonparticipation at each stage	N	N
Considers use of a flow diagram	N	N
Gives characteristics of study participants (demographic, clinical, social) and information on exposures and potential confounders	Y	N
Indicates number of participants with missing data for each variable of interest	N	N
Reports numbers of outcome events or summary measures	Y	Y
Gives unadjusted estimates and, if applicable, confounder-adjusted estimates, along with their precision (e.g., 95% confidence interval). Makes clear which confounders were adjusted for and why they were included	N/A	N/A
Reports category boundaries when continuous variables were categorized	N/A	N/A
If relevant, considers translating estimates of relative risk into absolute risk for a meaningful time period	N/A	N/A
Reports results of other analyses, e.g., analyses of subgroups, interactions, and sensitivity analyses	Y	Y
Summarizes key results with reference to study objectives	Y	Y
Discusses limitations of the study, taking into account sources of potential bias or imprecision. Discusses both direction and magnitude of any potential bias	Y	N
Gives a cautious overall interpretation of results, considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Y	Y
Discusses the generalizability (external validity) of the study results	Y	Y
Gives the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Y	Y

N/A, not applicable; U, unclear; Y, yes; N, no.

Table S5. Detailed information over muscle and performance measures for the included human studies

Study	Outcomes	Description	References of the measurement used
Beyer et al., 2011	LBM	Lean body mass: was assessed by measuring naturally occurring isotopic ^{40} K in a whole-body counter.	Delwaide PA. et al., 1970
	EMS	Elderly Mobility Scale: scale of assessment of functional mobility, it is a 20-point validated assessment tool for the assessment of frail elderly subjects.	Smith R., 1994
	GS and FR	Grip strength and fatigue resistance: was measured using a Martin Vigorimeter device.	Bautmans I, Mets T. 2005
	GW	Grip work: was calculated as GW = (GSx0.75)xFR.	Bautmans et al., 2007
Mets et al., 2004	EMS	Elderly Mobility Scale: scale of assessment of functional mobility, it is a 20-point validated assessment tool for the assessment of frail elderly subjects.	Smith R. 1994
	GS and FR	Grip strength and fatigue resistance: was measured using a Martin Vigorimeter device.	Bautmans I, Mets T. 2005
Cesari et al., 2010, 2009	GS	The hand grip strength test: was measured using a hand-held dynamometer (Jamar hydraulic hand dynamometer, Fred Sammons Inc., Burr Ridge, IL).	
	4-meter walking speed, Chair stand and Balance tests	Performance of the lower extremities was assessed using the "Short Physical Performance Battery", composed by three subtests, that are the 4-walking speed, chair-stand, and balance tests.	Onder G. et al., 2002 and Cesari M., et al. 2004
Nieman et al., 2006	DOMS	Delayed onset of muscle soreness: is a 10-point Likert scale to recorded muscle soreness.	Smith et al., 1993
S. Petersen et al., 2011	Myofibrillar FSR	Measurements of Fractional synthesis rates of tendon collagen protein and muscle myofibrillar and sarcoplasmic protein.	Babraj JA. et al., 2005 and Miller BF. Et al., 2005
Dideriksen et al., 2016	Myofibrillar FSR	Fractional synthetic rate of muscle: Muscle myofibrillar and muscle connective tissue protein FSR were calculated according to the precursor-product method: FSR (%/h) = $\Delta E_{product} / (E_{precursor} \times \Delta_{time})$.	Dideriksen et al., 2016
Vella et al., 2016	Perceived muscle soreness	Subjects were asked to rate their subjective muscle soreness on a 0–10 visual analog scale (VAS).	
Mikkelsen et al., 2011, 2009	Satellite cells	In the active phases of the cell cycle were identified by immunofluorescent double staining with antibodies against neural cell adhesion molecule (NCAM), Ki67 and also identified by an antibody against Pax7.	Mackey et al., 2009
	Muscle myofibrillar FSR	Muscle fractional synthesis rates of myofibrillar proteins and muscle collagen protein, calculated based on the incorporation rate of 1,2-$^{13}C_2$ leucine into muscle proteins using a standard precursor– product model.	Holm et al., 2010
	Muscle soreness	Subjects visually recorded their perceived pain on a visual analog scale (VAS).	
	Total work performed	It was calculated by integrating the torque-angle curves of the eccentric phase of each respective contraction.	
	Maximal isometric muscle strength	maximal isokinetic eccentric contractions were performed with the quadriceps femoris muscles of each leg using an isokinetic dynamometer (KinCom KC125AP, Chattanooga Group, Harrison, TN)	Crameri RM. et al. 2007 and Mikkelsen UR. et al. 2008
Trappe et al., 2001, 2002 and Peterson et al., 2003	FSR	Was calculated as the rate of[$^2H_5$] phenyl-alanine tracer incorporation into muscle protein, using the muscle intracellular free phenylalanine enrichment as the precursor.	Phillips SM. et al. 1997
	Perceived muscle soreness	Subjects were asked to rate their subjective muscle soreness on a 1–9 scale.	Newham DJ. et al, 1983

Study	Outcomes	Description	References for more details
Trappe et al, 2013, 2011	Quadriceps muscle volume, Hamstrings muscle size, Skeletal muscle water and protein content	Was measured with MRI in a 1.5T scanner (Genesis Signa, GE Medical Systems, Milwaukee, WI) by using serial inter- leaved images 8-mm thick (TR: 2,000 ms, TE: 9.0 ms, 512 X 512 matrix, field of view: 480 X 480 mm).	Trappe et al., 2007, 2001
	MuRF-1	By the use of the Quantitative PCR (qPCR)	Raue U. et al., 2007, Weinheimer EM. et al. 2007 and Jemiolo B, Trappe S., 2004
	Quadriceps muscle strength and Quadriceps strength normalized	Determined by the maximum amount of weight each subject could lift through a full range of motion one time (i.e., 1 RM) on the resistance exercise training device.	Slivka D. et al. 2008
S.G. Petersen et al. 2011	Quadriceps muscle cross-sectional area	Magnetic resonance imaging scans were conducted on a General Electric MR scanner (Sigma Horizon 1.5T)	
	Maximal isometric strength, Maximal eccentric muscle strength, maximal eccentric work, maximal eccentric muscle Maximal concentric muscle work	Using an isokinetic dynamometer (Kinetics Communicatord [KinCom])	Aagaard P. et al. 2000, 1996
	5-RM leg press and 5-RM knee extension, Maximal leg extension power	Measured using a Nottingham Power Rig.	Bassey EJ. et al., 1992, 1990
	Habitual gait speed,	Measured on a 10-m track, and only 1 trial was carried out.	Bassey EJ. et al., 1992
	stair climbing performance	Measured using a staircase with 13 steps, to walk up the stairs as fast as possible.	Bassey EJ. et al., 1992
	and chair-stand test	In 30 seconds without using their arms	Jones CJ. et al., 1999
Lilja et al., 2018	Quadriceps muscle volume	Cross-sectional images (MRI) were obtained using a 1.5- Tesla Siemens Magnetom Aera unit (Siemens Health- care, Germany).	Berg HE, Tedner B, Tesch PA, 1993
	Muscle quadriceps mean CSA and signal intensity, muscle biceps	Measured using MRI.	Alkner BA, Tesch PA, 2004 and Lundberg TR., et al. 2013

	femoris means CSA MuRF-1	Using Real-time PCR (ABI-PRISMA 7700 Sequence Detector, PerkinEl- mer Applied Biosystems).	Lilja et al., 2018
	Maximal isometric and isokinetic muscle strength, Training specific strength Maximal isometric torque	Maximal isometric strength (0°/s) and isokinetic strength (30°/s, 60°/s, 180°/s and 270°/s) were measured. Averaged across sets and repetitions was assessed using the flywheel device Measured at knee angle 120°.	Lilja et al., 2018 Lilja et al., 2018 Lilja et al., 2018
Brewer et al., 2015	Skeletal muscle tissue LBM	Assessed using dual energy x-ray absorptiometry (DXA) (Hologic Delphi-W; Bedford, MA).	
Paulsen et al, 2010	Muscle soreness Maximal force-generating capacity	Rated on a visual analogue scale where 0 represented ‘‘not sore at all’’ and 100mm ‘‘extremely sore”. Measured as peak torque during two consecutive maximal, isokinetic, concentric elbow flexions at 601/s (ROM: 175–401) and as peak torque during isometric actions at 901 in the elbow joint (5 s actions; two attempts; Technogym, REV 9000).	Paulsen et al, 2010 Paulsen et al, 2010
Rice et al., 2008	DOMS Muscle strength	A 100-mm visual analogue scale (VAS) anchored with ‘‘no pain’’ on the left and ‘‘worst pain ever experienced’’ on the right was used after subjects performed a simple squat. Measured for leg-press 1RM, using a 45u incline leg- press machine (Cardio Genesis Fitness Systems, South Africa).	

Table S6. The possible major side effects of the included AIDs

Drug name	Possible major side effects	Articles reported screening for side effects
Piroxicam	Cardiovascular: Edema Central nervous system: Dizziness, headache Dermatologic: Pruritus, skin rash Gastrointestinal: Abdominal pain, anorexia, constipation, diarrhea, dyspepsia, flatulence, gastrointestinal hemorrhage, gastrointestinal perforation, heartburn, nausea, ulcer (gastric, duodenal), vomiting Hematologic & oncologic: Anemia, prolonged bleeding time Hepatic: Increased liver enzymes Otic: Tinnitus Renal: Renal function abnormality	(Beyer et al. 2012b,2011)
Celecoxib	Cardiovascular: Peripheral edema Gastrointestinal: Diarrhea, dyspepsia, abdominal pain, flatulence, gastroesophageal reflux disease, vomiting Hepatic: Increased liver enzymes Renal: Nephrolithiasis Respiratory: Upper respiratory tract infection, sinusitis, pharyngitis, rhinitis, dyspnea	(Paulsen et al., 2010)
Ibuprofen	Cardiovascular: Edema Central nervous system: Dizziness, headache, nervousness Dermatologic: Skin rash, pruritus Endocrine & metabolic: Fluid retention Gastrointestinal: Epigastric pain, heartburn, nausea, abdominal pain, constipation, decreased appetite, diarrhea, dyspepsia, flatulence, vomiting Otic: Tinnitus	(Lilja et al., 2018) (S. G. Petersen et al. 2011)
Acetylsalicylic acid	Many side effects of aspirin are dose related, and are rare at low dosages: Cardiovascular: Cardiac arrhythmia, edema, hypotension, tachycardia Central nervous system: Agitation, cerebral edema, coma, confusion, dizziness, fatigue, headache, hyperthermia, insomnia, lethargy, nervousness, Reye's syndrome Dermatologic: Skin rash, urticaria Endocrine & metabolic: Acidosis, dehydration, hyperglycemia, hyperkalemia, hypernatremia (buffered forms) Gastrointestinal: Gastrointestinal ulcer, duodenal ulcer, dyspepsia, epigastric distress, gastritis, gastrointestinal erosion, heartburn, nausea, stomach pain, vomiting Genitourinary: Postpartum hemorrhage, prolonged gestation, prolonged labor, proteinuria, stillborn infant Hematologic & oncologic: Anemia, blood coagulation disorder, disseminated intravascular coagulation, hemolytic anemia, hemorrhage, iron deficiency anemia, prolonged prothrombin time, thrombocytopenia Hepatic: Hepatitis (reversible), hepatotoxicity, increased serum transaminases Hypersensitivity: Anaphylaxis, angioedema Neuromuscular & skeletal: Acetabular bone destruction, rhabdomyolysis, weakness Otic: Hearing loss, tinnitus Renal: Increased blood urea nitrogen, increased serum creatinine, interstitial nephritis, renal failure (including cases caused by rhabdomyolysis), renal insufficiency, renal papillary necrosis Respiratory: Asthma, bronchospasm, dyspnea, hyperventilation, laryngeal edema, noncardiogenic pulmonary edema, respiratory alkalosis, tachypnea	(Lilja et al., 2018)
Indomethacin	Central nervous system: Headache Gastrointestinal: Vomiting Hematologic & oncologic: Postoperative hemorrhage Cardiovascular: Presyncope, syncope Central nervous system: Dizziness, depression, drowsiness, fatigue, malaise, vertigo Dermatologic: Pruritus, hyperhidrosis, skin rash Endocrine & metabolic: Hot flash Gastrointestinal: Epigastric pain, heartburn, nausea, dyspepsia, constipation, diarrhea, abdominal pain, decreased appetite Otic: Tinnitus Miscellaneous: Swelling (postprocedural)	
Naproxen	Cardiovascular: Edema, palpitations Central nervous system: Dizziness, drowsiness, headache, vertigo	

	Dermatologic: Pruritus, skin rash, ecchymoses, diaphoresis Endocrine & metabolic: Fluid retention, increased thirst Gastrointestinal: Abdominal pain, constipation, nausea, heartburn, diarrhea, dyspepsia, stomatitis, flatulence, gastrointestinal hemorrhage, gastrointestinal perforation, gastrointestinal ulcer, vomiting Hematologic & oncologic: Hemolysis, purpura, anemia, prolonged bleeding time Hepatic: Increased liver enzymes Ophthalmic: Visual disturbance Otic: Tinnitus, auditory disturbance Renal: Renal function abnormality Respiratory: Dyspnea	
Fosinopril	Central nervous system: Dizziness Cardiovascular: Orthostatic hypotension, palpitations Central nervous system: Headache, noncardiac chest pain, fatigue Endocrine & metabolic: Hyperkalemia Gastrointestinal: Diarrhea, nausea and vomiting Hepatic: Increased serum transaminases Neuromuscular & skeletal: Musculoskeletal pain, weakness Renal: Increased serum creatinine, renal function decompensation (patients with bilateral renal artery stenosis or hypovolemia) Respiratory: Cough, upper respiratory infection	(Cesari et al. 2009)
Etanercept	Dermatologic: Skin rash Gastrointestinal: Diarrhea Infection: Infection Local: Injection site reaction (bleeding, bruising, erythema, itching, pain, or swelling; mild to moderate and usually decreases with subsequent injections) Respiratory: Upper respiratory tract infection, respiratory tract infection Miscellaneous: Antibody development (non-neutralizing), positive ANA titer Dermatologic: Pruritus, urticaria Hypersensitivity: Hypersensitivity reaction Miscellaneous: Fever	
Infliximab	Central nervous system: Headache Gastrointestinal: Abdominal pain, nausea Hematologic & oncologic: Anemia Hepatic: Increased serum ALT Immunologic: Increased ANA titer, antibody development (double-stranded DNA), antibody development (more immunogenic when given as a single induction dose, episodic treatment, and monotherapy) Infection: Infection (serious infection, abscess) Respiratory: Upper respiratory tract infection, sinusitis, cough, pharyngitis Miscellaneous: Infusion related reaction Cardiovascular: hypertension Central nervous system: Fatigue, pain Dermatologic: Skin rash, pruritus Gastrointestinal: Dyspepsia Genitourinary: Urinary tract infection Hematologic & oncologic: Leukopenia Hypersensitivity: Hypersensitivity reaction, delayed hypersensitivity (plaque psoriasis), serum sickness Infection: Candidiasis Neuromuscular & skeletal: Arthralgia Respiratory: Bronchitis, pneumonia Miscellaneous: Fever	

Source: UpToDate® (Accessed on July 02, 2018.)