The effect of nonsteroidal anti-inflammatory drugs on muscle recovery and strength after injury

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The Effect of Nonsteroidal Anti-inflammatory Drugs on
Muscle Recovery and Strength after Injury

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2009
Acknowledgements

I would like to acknowledge the ongoing support and guidance given to me by my advisor, Dr. Mark Weiner, throughout the development of this project. I would also like to thank Jolene Miller for all of her help with my many formatting questions.
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**Introduction**

Nonsteroidal anti-inflammatory drugs (NSAIDs) are medications used to treat inflammation, mild pain, and fever. This class of drugs is commonly prescribed as treatment for chronic pain, dental pain, dysmenorrhea, gout, headache, tendonitis, bursitis, rheumatoid arthritis, and osteoarthritis (Vieson, 2003). NSAIDs work by inhibiting the synthesis of prostaglandins, which promote inflammation and pain. These drugs are among the most widely prescribed medications, generating between 35 and 70 million prescriptions in the United States per year, while the world market for NSAIDs is reported to be a $6 billion per year industry (Bruno & Carter, 2004).

NSAIDs have commonly been exploited for their analgesic and anti-inflammatory properties in the treatment of exercise-induced muscle injury. Exercise-induced muscle injury is a common problem in sports and in the workplace (Mishra, Friden, Schmitz, & Lieber, 1995). These injuries are primarily due to eccentric contractions of the muscle and cause the release of enzyme muscle markers into circulation. In order for the muscle to be repaired after an injury, satellite cells must become activated and inflammatory mediators mobilized to the injured muscle (McArdle, Katch, & Katch, 2001).

Since acute inflammation initiates repair in muscle tissue, research has been conducted to study the effects of NSAIDs in anti-inflammatory doses on muscle recovery and strength. The studies employ different methods of eccentric contraction-inducing muscle injury and utilize several different NSAIDs after injury. Each study has evaluated different markers of muscle injury and recovery and the effect that NSAIDs have on these markers after injury. Research has primarily focused on recovery of the muscle cell histologically, influx of inflammatory
mediators, satellite cell proliferation, delayed onset muscle soreness (DOMS), and force generation after muscle injury.

Due to the increasing use of NSAIDs, it is imperative to determine if NSAID inhibition of inflammation is delaying muscle from repairing itself after injury. If present, this process is then leading to subsequent delay of muscle recovery and regeneration of muscle strength. Individual studies examining the use of NSAIDs after eccentric contraction-induced muscle injury have shown either no measurable consequence, a definitive support of, or evidence against this common utilization. This review of the literature examines each individual study and attempts to come to a conclusion regarding this controversial topic.
**NSAIDs**

The use of NSAIDs to alleviate the signs and symptoms of exercise-induced muscle damage has been thoroughly investigated over the past 25 years. The chief role of NSAIDs is to provide analgesia and exert its anti-inflammatory properties. However, acute inflammation initiates repair in muscle tissue, which is necessary for recovery after exercise-induced muscle injury (Kumar, Abbas, Fausto, & Mitchell, 2007). Also, it is difficult to distinguish the analgesic effects of NSAIDs from the anti-inflammatory effects when evaluating strength and soreness after exercise-induced muscle injury. Therefore, the precise role of NSAIDs in regards to muscle injury has been studied and many different markers of muscle damage, inflammation, and muscle recovery have been measured and evaluated.

NSAIDs are commonly used after muscle injury for their ability to suppress the signs and symptoms of inflammation. The anti-inflammatory activity of NSAIDs is mediated chiefly through the inhibition of cyclooxygenase (COX), which converts arachidonic acid to prostaglandins (Furst & Ulrich, 2007). Prostaglandins work by promoting inflammation and pain, which are obvious indications of muscle damage. Rodemann and Goldberg, using indomethacin, determined that muscles can synthesize prostaglandins and this synthesis can be inhibited by NSAIDs. This study confirmed that arachidonic acid causes production of prostaglandins, which leads to protein degradation, and indomethacin inhibited this degradation by inhibiting prostaglandin production (Rodemann & Goldberg, 1982). This study was in agreement with Trappe et al. who found that ibuprofen suppresses the normal increase in prostaglandin-F$_{2\alpha}$ (PGF$_{2\alpha}$ ) after resistance exercise, which may substantially influence the anabolic actions of this type of exercise (Trappe, Fluckey, White, Lambert, & Evans, 2001).
Therefore, NSAID inhibition of COX leads to the inhibition of prostaglandins, which in turn relieves the pain and inflammation of a muscle injury.

There are two isoforms of COX: COX-1 is constitutively expressed and COX-2 is an immediate early response to gene products in inflammatory and immune cells (Smyth & Fitzgerald, 2007). NSAIDs non-selectively inhibit both COX enzymes, while COX-2 inhibitor drugs have been developed and are selective for COX-2. Some NSAIDs, such as aspirin, indomethacin, and piroxicam, have proven to be more effective in inhibiting COX-1, while ibuprofen and meclofenamate inhibit COX-1 and COX-2 equally (Furst & Ulrich, 2007).

The production of COX-2, but not COX-1, is essential for early muscle regeneration after injury (Bondesen, Mills, Kegley, & Pavlath, 2004). Bondesen et al. found that after a traumatic injury to the tibialis anterior muscle in mice, COX-2 was elevated eight-fold in comparison with the serum levels of COX-1, which remained constant with pre-injury levels. The animals in this study were chronically treated with either a COX-1 or COX-2 inhibitor. During the first seven days after injury, the number of regenerating muscle fibers was indifferent in comparison with the control in animals chronically treated with a COX-1 inhibitor. However, in animals treated with a COX-2 inhibitor, myofiber regeneration was attenuated for the first week following injury. When treated seven days after the tibialis anterior injury with a COX-2 inhibitor, there was no change in the recovery of the muscle. This study indicates that the presence of COX-2 is most critical immediately post-injury and validates its role in early muscle regeneration.

While all NSAIDs operate through inhibition of cyclooxygenase, their differences lie primarily in their structure (Imboden, et al., 2007). This difference in structure contributes to varied half-lives within this class of drugs. Some drugs, such as ibuprofen, have a half-life of only two hours, while drugs like nabumetone possess a half-life of 24 hours (Furst & Ulrich,
2007). In the studies that are examining the effect of NSAIDs on muscle recovery, different drugs are used, but all are used at anti-inflammatory doses and are dosed accordingly with their half-lives.
Inflammation

The inflammatory response is necessary for healing to be initiated and prostaglandins play a large role in the inflammatory process (Magee, Zachazewski, & Quillen, 2007). Prostaglandins exert effects at the location of muscle damage, including mediation of vasodilation and causing an increase in vascular permeability, pain, and fever (Magee, et al., 2007). Therefore, with NSAID inhibition of prostaglandin production, the inflammatory process is temporarily blunted and cannot mediate tissue repair.

The inflammatory process involves many other chemotactic factors in addition to prostaglandins. These include leukocytes, cytokines, oxidants, macrophages, and neutrophils (Kumar, et al., 2007). Macrophages are central to the healing process because they produce substances that modulate the inflammatory response. Macrophages also play a role in satellite cell proliferation, which contributes to muscle regeneration (Cantini, et al., 1994). In early inflammation, neutrophils, macrophages, and other leukocytes clean the wound site by phagocytosis, debriding the injured area of necrotic tissue, debris, and foreign material within 24 hours. These mediators then continue to act for the next two to five days (Magee, et al., 2007).

Macrophages have been considered in clinical trials studying the effect of NSAIDs after exercised-induced muscle injury to see if they, like prostaglandins, are affected by NSAID use. Cheung and Tidball determined that administration of ibuprofen prior to muscle loading increased the concentration of ED2+ macrophages, which have been associated with muscle regeneration and repair (Cheung & Tidball, 2003). The same year, Peterson et al. found that macrophage concentrations were significantly elevated after exercise in individuals who consumed ibuprofen, acetaminophen, or placebo. However, the macrophage levels were not significantly different between groups, indicating the influx of macrophages occurs after exercise.
regardless of NSAID use (Peterson, et al., 2003). The increased macrophage levels in these two studies may indicate that inflammation due to exercise-induced muscle damage is not hindered by NSAID use. However, macrophages are not specific to muscle injury because they are mediators of all types of inflammation. Therefore, the presence of macrophages is only one component in measuring the response of injured muscle tissue to NSAIDs.
Exercise-induced muscle injury

Exercise-induced muscle injury damages stress susceptible muscle fibers and leads to an increase in serum muscle enzymes and the development of muscle soreness (Clarkson & Tremblay, 1988). The muscle enzyme released into the serum after exercise-induced muscle injury is creatine kinase, a marker of muscle damage. Creatine kinase is elevated immediately following eccentric-contraction induced injury and is still elevated approximately 48 hours after injury (Armstrong, Ogilvie, & Schwane, 1983; Malm, et al., 2004). However, the rise in creatine kinase after exercise-induced muscle injury is only significant after the first bout of exercise. Muscle rapidly adapts to exercise and less damage is inflicted to the muscle after a subsequent bout of the same type of exercise, so there is not a significant rise in creatine kinase (Hirose, et al., 2004; Stupka, Tarnopolsky, Yardley, & Phillips, 2001).

Studies have been inconsistent in showing whether NSAIDs affect creatine kinase levels after muscle injury. It has been demonstrated that anti-inflammatory doses of ibuprofen significantly reduced creatine kinase activity compared to placebo when ingested before and after exercise (Pizza, Cavender, Stockard, Baylies, & Beighle, 1999). However, Lecomte et al. found that plasma creatine kinase levels were elevated for both naproxen sodium and placebo groups in recreationally active males following eccentric exercise. There was not a significant difference in the creatine kinase elevations between the NSAID-treated and placebo groups (Lecomte, Lacroix, & Montgomery, 1998). This latter result was reproduced in a 160km run with endurance-trained ultramarathoners (Nieman, et al., 2006). However, ultramarathoners are likely to have an attenuated rise in creatine kinase because their muscles have adapted to repetitive exercise. Since these studies utilized subjects who are likely to have different levels of
muscle injury after exercise, it is difficult to make a conclusion regarding the role of NSAIDs on creatine kinase after exercise-induced muscle injury.

Exercise-induced muscle injury may also be affected by the timing of NSAID use. The Pizza et al. study administered the NSAID prophylactically and post-exercise while the Lecomte et al. study only dispensed the NSAID after exercise. The study that administered the NSAID both before and after exercise resulted in decreased creatine kinase levels, while the study with only post-exercise NSAID use did not have lower levels of creatine kinase. The Nieman et al. study administered the NSAID ibuprofen prophylactically, during exercise, and post-race, but the individuals who used ibuprofen were habitual users, which may have affected results. This breakdown of research outcomes mildly supports the theory that prophylactic NSAID use reduces the amount and possibly even the occurrence of exercise-induced muscle injury and inflammation.
Delayed-onset muscle soreness

Exercise-induced muscle injury frequently leads to muscular discomfort known as delayed-onset muscle soreness (DOMS). Temporary soreness may persist for several hours immediately post-exercise, whereas the residual DOMS appears 24 to 48 hours after unaccustomed or strenuous exercise and is characterized by perceived soreness and muscle weakness (McArdle, et al., 2001). DOMS can be attributed to a number of factors: minute tears in muscle tissue, muscle spasms, overstretching, tearing of the muscle’s connective tissue harness, acute inflammation, or any combination of these factors (McArdle, et al., 2001). Physiologically, DOMS can be objectively measured by an increase in serum creatine kinase, influx of inflammatory mediators, and a rise in lactate dehydrogenase (LDH) (Kumar, et al., 2007). DOMS is also relevant clinically because it is a subjective measure of the effectiveness of NSAIDs.

Delayed-onset muscle soreness is frequently treated with the use of NSAIDs. It has commonly been concluded that NSAIDs significantly reduce perceived muscle soreness at some point during recovery after muscle injury (Baldwin, Stevenson, & Dudley, 2001; Dudley, et al., 1997; Lecomte, et al., 1998; O'Grady, et al., 2000; Sayers, Knight, Clarkson, Van Wegen, & Kamen, 2001; Tokmakidis, Kokkinidis, Smilios, & Douda, 2003). Several studies have found no change in perception of DOMS with NSAID use (Bourgeois, MacDougall, MacDonald, & Tarnopolsky, 1999; McAnulty, et al., 2007; Nieman, et al., 2006; Pizza, et al., 1999). However, the assessment by McAnulty et al. did not control NSAID dosage during exercise, which the study acknowledges and notes may be a cause for its results.

Timing of drug administration is crucial to the relief of soreness (Hasson, et al., 1993). Hasson et al. found that muscle soreness perception was significantly less for at least the first
two days after injury when ibuprofen was ingested four hours before exercise and again on two occasions after the injury. When ibuprofen was not given until 24 hours after the injury, the subjects did not have a significant reduction in soreness until 48 hours after exercise. In other studies, as long as an NSAID was given within 24 hours after the injury, there was reduction in DOMS at some point over the next week (Baldwin, et al., 2001; Lecomte, et al., 1998; Sayers, et al., 2001). There is no evidence that treating DOMS with an NSAID causes an increase in perceived muscle soreness.
Satellite Cells

The process of injury and repair in muscle after exercise-induced muscle injury also involves the activation of satellite cells. Satellite cells are necessary for myofiber regeneration, which usually begins three to six days post injury and peaks around seven to fourteen days (Magee, et al., 2007). These normally quiescent myoblasts will proliferate and differentiate to function in regenerative cellular growth, possible adaptations to exercise training, and recovery from injury (McArdle, et al., 2001).

The presence of satellite cells after muscle injury is an indication that an inflammatory response is present. As a mediator of inflammation, macrophages contribute to this rise in satellite cell number. While satellite cells will proliferate mildly in a normal muscle environment, they significantly increase in number when macrophages are present (Cantini, et al., 1994).

Satellite cells flourish both after muscle injury and in response to repetitive exercise training (Appell, Forsberg, & Hollmann, 1988). The number of satellite cells begins to increase within 24 hours after a single bout of eccentric contractions in both young and older subjects (Dreyer, Blanco, Sattler, Schroeder, & Wiswell, 2006). The increase in cell number is more dramatic in younger individuals because they have increased muscle mass in comparison with older individuals. Regardless of the age of the individual, satellite cells increase in response to muscle injury and exercise.

With endurance training, satellite cells quickly begin to adapt to the constant stimulation. In a study of older men that trained for four times a week for fourteen weeks on a bike, basal levels of satellite cell number in muscle significantly increased by the end of the training period (Charifi, Kadi, Feasson, & Denis, 2003). This study also concluded that the increase in satellite
cell number can be attributed to an increase in skeletal muscle function in older men. The increase in satellite cell number also contributed to a significant amount of skeletal muscle hypertrophy in the participants.

It has been proven that satellite cells flourish after exercise. However, satellite cells are significantly decreased after exercise with the use of naproxen (an NSAID) and a COX-2 inhibitor (Mendias, Tatsumi, & Allen, 2004). The satellite cell response has also been found to be significantly attenuated when indomethacin was ingested prior to endurance exercise (Mackey, et al., 2007). Since satellite cells are required for muscle repair, the lack of a rise after injury hinders the regeneration of myofibers. Although it is expected, this outcome is not consistently reproduced. Results from another study indicated no significant difference between treated and control animals in satellite cell proliferation after naproxen sodium treatment (Thorsson, Rantanen, Hurme, & Kalimo, 1998). The latter study administered naproxen prophylactically and post-injury, while the Mackey et al. only dosed the NSAID prophylactically and Mendias et al. only post-injury. These results are conflicting and lead to the conclusion that satellite cells cannot be the only objective measured after exercise, other markers of muscle injury must also be considered.
Support of NSAID use

Many studies have shown support of NSAID use for the treatment of exercise-induced muscle injury. These studies administered NSAIDs after the eccentric exercise regimen and many times prophylactically as well. The results from these evaluations failed to find that NSAIDs interfered with muscle regeneration and strength gain after eccentric contraction-induced muscle injury. Instead, the studies discussed found that NSAID use pre-, during, or post-exercise was beneficial to the injured muscle in one or more ways: inflammation was lessened, serum creatine kinase elevations were blunted, DOMS reduced, and strength was either gained or decreased less compared to placebo. Clinically, these studies advocate NSAID use primarily for its role in decreasing muscle soreness after exercise-induced muscle injury.

According to a study performed by O’Grady et al., there is strong evidence to support NSAID use. In this study, the experimental group received diclofenac sodium for two weeks before and two weeks after strenuous unaccustomed exercise and had resolution of DOMS after only four days (O’Grady, et al., 2000). This is in stark contrast to the placebo group, which had significant perceived soreness for seven days. Creatine kinase levels were significantly reduced in the diclofenac sodium group, relative to placebo, at two out of three measurements taken in the two weeks following exercise. The other measurement taken, which was done two days after exercise, showed no difference in creatine kinase levels between the placebo and diclofenac sodium group. Finally, O’Grady et al. found histological evidence of necrotic myofibers and inflammation in the muscle of the placebo group after exercise, while neither of these indicators of muscle damage was found in the myofibers of the NSAID-treated group. In summary, this study reveals that administration of an NSAID before and after exercise-induced muscle injury
has a protective effect on the muscle and reduces DOMS and serum creatine kinase relative to placebo.

Another study found similar histological results when an NSAID was ingested prior to exercise-induced muscle injury. In the experimental group treated with ibuprofen beginning eight hours prior to muscle injury, there was a significantly lower amount of necrotic muscle fibers compared to the control group and to the group that received ibuprofen beginning after injury (Cheung & Tidball, 2003). Administration of ibuprofen beginning eight hours before injury also caused a significant increase in ED2+ macrophages, which are associated with muscle regeneration. It is speculated that this increase in ED2+ macrophages may have worked in combination with the NSAID to decrease the number of necrotic muscle fibers in the injured tissue (Cheung & Tidball, 2003).

In a randomized, controlled trial using naproxen sodium after muscle injury, there was a positive correlation between NSAID use and DOMS and strength recovery (Lecomte, et al., 1998). When muscle soreness peaked three days after exercise, the NSAID group had significantly lower perceived soreness than the placebo group. Quadriceps peak torque after exercise at 60°/s, but not at 180°/s or 300°/s, was significantly higher in the NSAID-treated group relative to placebo, indicating the possibility of a slight benefit in performance with NSAID use. There was not a significant difference in creatine kinase levels between groups during any of the four measurements taken. It is important to consider that the NSAID was not ingested until 24 hours after exercise and this may or may not have had an effect on the measured results. Also, while it is significant that torque increased in the NSAID users at 60°/s, since it did not increase at 180°/s or 300°/s it must be contemplated that the increase at 60°/s was purely due to the analgesic effects of the NSAID. It is known that analgesic benefits appear soon
after ingestion, but anti-inflammatory levels of NSAIDs in the blood typically aren’t achieved until several days after ingesting the first dose (Pizza, et al., 1999). Therefore, the point when the analgesic effects of an NSAID overlap with its anti-inflammatory effects is difficult to distinguish, presenting a limitation in this study.

Both prophylactic and therapeutic administration of ibuprofen can be beneficial after eccentric contraction-induced muscle injury, but prophylactic use produces earlier recovery (Hasson, et al., 1993). In an experiment by Hasson et al., the group of subjects receiving prophylactic ibuprofen ingested their first dose just four hours prior to exercise and the therapeutic group of subjects had their first dose 24 hours after exercise. Twenty-four hours after the exercise bout, the prophylactic group had significantly less decline from baseline in isometric force production by the injured muscle. There was also decreased muscle soreness perception compared to the therapeutic, placebo, or control groups, indicating clinical significance for NSAID use prior to exercise. Forty-eight hours after exercise, the prophylactic and therapeutic groups had significantly less decrease in force production and lower muscle soreness perception, relative to the placebo and control groups. A limitation to this study is that muscle soreness, torque, and damage were only measured for 48 hours after the eccentric contraction-induced muscle injury. It would be advantageous to conduct this study for a longer period of time to learn the effect of long-term NSAID use on muscle after injury. Also, once again it must be considered that the decrease in muscle soreness and the less significant decline in force production among the NSAID users could have been due to analgesic effects of the drug. However, for the participants, the analgesic effects are impossible to differentiate from the anti-inflammatory properties of the drug.
While most evaluations of eccentric contraction-induced injury analyzed damage to leg muscles, a study by Sayers et al. evaluated injury of the elbow flexors instead. The protocol included a relatively large number of participants, with 48 integrated into the final results, further validating the outcome. Ketoprofen was administered in either 100mg or 25mg doses. When ingested 36 hours after injury, ketoprofen-100mg and ketoprofen-25mg attenuated muscle soreness 10% and 19%, respectively, while a placebo decreased soreness only 1%. It is not especially significant that the larger dose of ketoprofen decreased soreness less because soreness is a subjective measure. A similar result was found when maximal isometric force (MIF) of the injured muscle was measured after exercise: ketoprofen-100mg increased MIF 16%, ketoprofen-25mg increased MIF 9%, and placebo decreased MIF 9%. This increase in MIF after ketoprofen administration represents strength gain, presumably attributable to the NSAID. However, since different doses were used, whether it was the anti-inflammatory or analgesic effects of the NSAID that produced these results remains undetermined and as mentioned before, difficult to distinguish. This is only a small limitation to the study. The fact that this study measured upper extremity muscles instead of the more commonly measured lower extremity muscles may also contribute to some variation in results. Regardless, the significant outcomes lead researchers to conclude that ketoprofen administered after injury decreases muscle soreness and improves force recovery (Sayers, et al., 2001).

The preceding results were in agreement with another study that found naproxen sodium to reduce perceived muscle soreness and improve recovery (Dudley, et al., 1997). Four days post-exercise, the naproxen-treated group in this study had significantly reduced soreness and less of a decline in their one-repetition maximum contraction, suggesting enhanced muscle regeneration with naproxen sodium. Also similar to the trial above, the NSAID in this study was
not administered until after the exercise-induced injury had occurred. However, this study employed a testing field of only eight subjects, which is relatively small and somewhat lessens the validity of the results.

Positive effects of NSAIDs as treatment for muscle injury can also be found in the older population. A study by Baldwin et al. (2001) looked at older men and women and determined the effect of naproxen sodium administration after muscle injury for this unique population. Even though the subject age was atypical, the results of this study are very much analogous to what aforementioned researchers ascertained. After only three days, older participants who ingested naproxen sodium after exercise had significantly decreased soreness and less of a decline from their baseline isometric strength measurement. Once again, naproxen sodium use attenuated injury and loss of muscle function and therefore resulted in less strength loss and reduced soreness during recovery.

A study at the University of Thrace found that ibuprofen ingestion after an eccentric exercise regimen causes decreased soreness perception and reduced creatine kinase activity after 48 hours (Tokmakidis, et al., 2003). This study also found that maximal strength, vertical jump performance, and knee range of motion (ROM) decreased significantly after exercise and there was not a significant difference between the ibuprofen and placebo groups. This evidence reveals ibuprofen is beneficial to decrease soreness and muscle damage, but does not assist in restoring muscle function after injury. The decrease in soreness and muscle damage is most advantageous clinically, when the damaged muscle group needs to be utilized soon after the injury.

While the studies formerly presented found evidence in support of NSAID use, some studies discerned only a slight advantage in their utilization. Donnelly et al. detected no
difference between diclofenac sodium and placebo groups except that muscle soreness was reduced at several points with the use of diclofenac sodium (Donnelly, McCormick, Maughan, Whiting, & Clarkson, 1988). At the very least, the reduction in soreness is clinically significant for prescription NSAID use. A study in 1999 identified the only advantage to naproxen sodium use was an earlier return to baseline for maximum volumetric contraction of the injured muscle (Bourgeois, et al., 1999). This suggests that NSAIDs hasten muscle regeneration. Participants in both of the aforementioned studies received their first dose of the NSAID prior to exercise, promoting prophylactic NSAID use for both its clinical and histological advantages.

As mentioned earlier, another common measurement of the influence of NSAIDs on muscle recovery is the number of satellite cells present in the injured muscle. However, none of the studies with results that support NSAID use measured satellite cells. Interestingly, all of the studies that did measure satellite cells found either no consequence to NSAID use or discovered that NSAID exploitation hinders muscle recovery (Mackey, et al., 2007; Mendias, et al., 2004; Rahusen, Weinhold, & Almekinders, 2004; Thorsson, et al., 1998).

The studies listed above display evidence to support NSAID use for the treatment of exercise-induced muscle damage. When taken prophylactically, NSAIDs were found to decrease serum creatine kinase, decrease perceived muscle soreness and hasten its resolution, decrease necrosis, increase ED2+ macrophages to help with reparation of the muscle, and cause less of a decline in force production by the muscle after exercise-induced muscle injury (Bourgeois, et al., 1999; Cheung & Tidball, 2003; Donnelly, et al., 1988; Hasson, et al., 1993; O'Grady, et al., 2000). When the NSAID was ingested after eccentric contraction-induced muscle injury, decreased soreness, quicker resolution of soreness, and less of a decline in muscle strength relative to placebo were all reported (Baldwin, et al., 2001; Dudley, et al., 1997; Lecomte, et al.,
Whether the NSAID was used prophylactically or therapeutically, the results indicate that there is clear clinical advantage with its use. However, of the studies that support therapeutic use, one had only eight test subjects and another tested the elbow flexors instead of the more common quadriceps. These are small limitations, since so many other studies were able to reproduce their results.

In evaluation of the studies that support NSAID use, there is substantial evidence supporting the clinical advantages obtained with NSAIDs. One of the most compelling conclusions of these supporting studies is that the use of NSAIDs causes less of a decline in muscle strength after injury and permits improved performance. However, it must be considered that the subjects in these studies were able to perform post-exercise muscular contractions closer to their baseline strength due to the analgesic effects of the NSAID (Mishra, et al., 1995). The analgesic benefits appear soon after ingestion, but anti-inflammatory levels of NSAIDs in the blood typically aren’t achieved until several days after the initial dose (Pizza, et al., 1999). If this is the case, then it is possible that the subjects in the placebo-treated groups did not contract their muscles to their maximum ability due to discomfort or pain. This result is plausible since DOMS was lessened and resolved sooner with NSAID treatment (Baldwin, et al., 2001; Dudley, et al., 1997; Hasson, et al., 1993; Lecomte, et al., 1998; Sayers, et al., 2001; Tokmakidis, et al., 2003). However, analgesic and anti-inflammatory effects of NSAIDs are nearly impossible to differentiate for both the researcher and the subject with the exercise-induced muscle injury. Therefore, the analgesic effects of NSAIDs are predominantly only significant for the measurement of DOMS.

Results that are likely indisputable include the lack of histological evidence of muscle necrosis and less of a rise in serum creatine kinase in NSAID-treated muscles compared to
control or placebo-treated muscles. A previously discussed study performed by O’Grady et al. (2000) boasted both of these results. However, this study began administering diclofenac sodium a full two weeks prior to exercise. It is speculated that the duration of treatment may have had a protective effect on the muscle following eccentric exercise (Pizza, et al., 1999). So far, the effects of prolonged NSAID administration on exercise-induced muscle damage have not been reported (O'Grady, et al., 2000). Another study found a similar lack of muscle necrosis, but only in subjects treated with NSAIDs prophylactically and not those who began treatment at the time of injury (Cheung & Tidball, 2003). In this study, the prophylactic dose was given only eight hours prior to injury, so protective effects are less of a concern.

The decrease in perceived soreness and DOMS and its quick resolution compared to placebo is also fairly indisputable. NSAIDs inhibit prostaglandins, which promote pain, so it is logical that DOMS is hindered with their use. Some studies to be discussed later failed to uphold this statement (Bourgeois, et al., 1999; Donnelly, Maughan, & Whiting, 1990; Nieman, et al., 2005). However, these studies had limitations in their design which will be discussed in the following chapters.

In summary, significant evidence exists to support the clinical use of NSAIDs as treatment for exercise-induced muscle injury. There are some limitations, such as the unknown extent of the analgesic benefits of NSAIDs, that put into question the supposed strength gains produced by the drug (Mishra, et al., 1995). The possible effects of long-term administration of NSAIDs are also uncertain, simply because they have been explored in only one study (Pizza, et al., 1999). There aren’t any studies measuring satellite cells that uphold the use of NSAIDs as advantageous, but there also are not any studies which denounce NSAID use due to satellite cell response. Timing of NSAID administration is also a factor and seems to play a crucial role in
recovery (Hasson, et al., 1993). From the studies discussed above, prophylactic NSAID use has produced more clinically significant results than therapeutic use, but therapeutic use still reduces muscle soreness and causes less of a decline from baseline strength. In summary, the limitations to the discussed studies are few and significant evidence has been produced to support the clinical use of NSAIDs both before and after exercise-induced muscle injury.
Conflict with NSAID use for the Treatment of Muscle Injury

There have been numerous studies that suggest NSAIDs delay muscle recovery and hinder strength gain. Almekinders et al. (1986) investigated the healing process of muscle strains and the effect of piroxicam in the eleven days following injury. The control group in this study displayed proof of muscle regeneration after only four days, whereas the piroxicam-treated group showed only slight restoration at this point. The control group also had significantly less aberration from baseline muscle strength in the first few days post-injury. It was determined that muscle strains continue to weaken in the early post-injury period and that piroxicam administered post-injury delayed the inflammatory reaction and muscle regeneration.

NSAIDs have been shown to blunt protein metabolism in animals (Rodemann & Goldberg, 1982). In 2002, Trappe et al. performed a verifiable study on the effect of ibuprofen on human post-exercise muscle protein synthesis (Trappe, et al., 2002). Based on microscopic analysis of the vastus lateralis muscle, it was determined that the muscle protein fractional synthesis rate (FSR) was unchanged after exercise in the ibuprofen-treated group. This was in discord with the control group that had increased FSR after exercise, suggesting muscle protein synthesis and eventually muscle growth. This study also found no significant differences in creatine kinase elevations and perceived muscle soreness between the NSAID-treated and control groups. This evidence concludes that NSAID use beginning at the time of injury attenuates muscle protein synthesis and possibly inhibits the normal anabolic response to eccentric contraction exercise training.

At 2004 study determined that COX-2 is essential for early muscle repair after injury (Bondesen, et al., 2004). In 2005, Soltow et al. further investigated this conclusion, but expanded their research by incorporating NSAIDs into their study and by also analyzing strength
gain. Fourteen days after overloading the plantaris muscle, ibuprofen-treated rats exhibited muscles that were only 29% larger than baseline muscle. In contrast, control rats muscles were 60% larger than the normal, untreated muscle. For L-NAME, a COX-2 inhibitor, muscles 14 days after injury were 42% larger, but the control muscles were 87% larger than the baseline muscle. These results confirmed that COX is necessary for a muscle to reach its full extent of hypertrophy after exercise and that both ibuprofen and L-NAME blunted skeletal muscle hypertrophy when compared to control animals (Soltow, et al., 2006).

Time-dependent effects of NSAIDs also play a crucial role in strength gain. In 1995, unprecedented research was conducted to examine the time-dependent effects of NSAIDs on eccentric contraction-induced injury by following the subjects for 28 days post-injury (Mishra, et al., 1995). It was concluded that flurbiprofen administered after exercise resulted in short-term improvement of muscle strength 3 and 7 days post-injury, but there was a subsequent deficit in muscle strength 28 days after injury. The short-term improvement in this study was represented by lower creatine kinase values and faster recovery of torque generation in the NSAID-treated subjects at 3 and 7 days after exercise. At 28 days after injury, there were no significant differences between treated and control animals for creatine levels. It is proposed that by suppressing the initial inflammatory reaction, the drug permits improved performance early post-injury. However, suppressing the inflammatory process may have also curbed the stimulus needed for cellular remodeling and strength gain. This result is compounded by evidence from another study: inflammation is necessary for resultant skeletal muscle hypertrophy after exercise-induced muscle injury (Soltow, et al., 2006).

Research in 2004 found that COX-2 expression by satellite cells is blunted after exposure to NSAIDs following exercise-induced muscle injury (Mendias, et al., 2004). In this study,
when injured muscle cells were exposed to either a COX-2 inhibitor or naproxen sodium, satellite cells failed to proliferate, differentiate, and fuse. There was no attenuation in satellite cell production for the muscles that were injured, but not exposed to an NSAID. Since satellite cells are needed for muscles to regenerate, NSAID inhibition of satellite cells can lead to a delay in muscle recovery and eventual inhibition of muscle hypertrophy.

As discussed earlier, endurance training elicits an increase in satellite cell number (Charifi, et al., 2003). In a study by Mackey et al. (2007), endurance trained athletes ingested either indomethacin or a placebo beginning four days prior to a 36km run. After the run, biopsies were taken on three occasions and were analyzed for satellite cells. The NSAID-users had no change in satellite cell number compared to their baseline measures, while the placebo group had a 27% increase in satellite cell number as early as eight days post-exercise. These results suggest that the ingestion of NSAIDs prior to eccentric contraction-induced muscle injury inhibits satellite cell proliferation in endurance trained athletes.

A couple of studies found only one difference each between NSAID-treated and control subjects (Donnelly, et al., 1990; McAnulty, et al., 2007). McAnulty et al. found no significant differences between groups for any of the markers of muscle injury or oxidative stress, except for an increase in DOMS one day after injury for NSAID-users. However, this study did not control dosage or the type of NSAID used, so this odd increase in DOMS with NSAID use should likely be considered an exception to the rule. Donnelly et al. found that DOMS ratings and maximum contraction following exercise did not differ between NSAID-treated and untreated subjects following a downhill run. However, it was found that creatine kinase elevations and urea concentration were both significantly greater in ibuprofen-users compared to non-users. The
The authors of this study were surprised by the latter results and attribute them to the effects of ibuprofen on plasma volume and protein content.

The evidence presented in this chapter strongly advocates against NSAID use for the treatment of exercise-induced muscle injury. Whether taken prophylactically or after exercise, NSAIDs were found to inhibit satellite cell proliferation and more importantly to attenuate long-term strength gains and impede the anabolic action normally produced by eccentric exercise (Almekinders & Gilbert, 1986; Mackey, et al., 2007; McAnulty, et al., 2007; Mendias, et al., 2004; Mishra, et al., 1995; Soltow, et al., 2006; Trappe, et al., 2002). The goal of eccentric exercise is typically to increase muscle mass, and these results have indicated that NSAIDs will disrupt this process for up to 28 days, the longest time period studied. Therefore, NSAIDs are erasing some of the benefits normally associated with eccentric exercise, in exchange for slight reduction in DOMS and a possible decrease in total muscle damage. However, the decrease in soreness and muscle damage is significant clinically and remains one of the reasons that NSAIDs are so commonly prescribed for muscle strains and sprains and other muscle injuries. After a muscle injury, only a small percentage of NSAID users are concerned with satellite cell inhibition and delay of strength gain, so the information presented in this chapter is of little consequence to the majority of NSAID users and their prescribing clinician.
**NSAIDs Role in Muscle Recovery is not Significant**

Additional studies have essentially found no consequence in using NSAIDs for the treatment of eccentric contraction-induced muscle injury. In a study by Pizza et al. (1999), ibuprofen was taken for five days prior to exercise and continued for ten days after. Creatine kinase levels were reduced three days post-injury for the ibuprofen group relative to the placebo group. However, there was no difference between groups for neutrophil count, isometric strength, soreness, and arm angles. Therefore, post-exercise strength and inflammation were apparently unaffected by NSAID use.

Naproxen sodium was formerly reported to have both positive and negative effects on muscle post-injury (Baldwin, et al., 2001; Dudley, et al., 1997; Mendias, et al., 2004). However, it has also been found to have no significant effect whatsoever (Bourgeois, et al., 1999; Thorsson, et al., 1998). Bourgeois et al. examined the effects of naproxen sodium on delayed-onset muscle soreness, creatine kinase level, and inflammatory cell number and found no significant difference between the treated and control groups for any of these markers. In this study, however, moderately trained subjects were used and trained subjects are likely to have an attenuated creatine kinase and inflammatory cell release after repeated exercise (Stupka, et al., 2001).

A couple of evaluations found no difference between treated and control animals in satellite cell proliferation after NSAID treatment (Rahusen, et al., 2004; Thorsson, et al., 1998). However, the mechanism of injury in both of these studies was a contusion injury and not due to eccentric contractions. The physiological difference in this type of injury may have affected results, so it is not clear that NSAIDs truly have a negligible effect on satellite cell number.
A study of ultra-marathoners found that creatine phosphokinase, cytokines and delayed-onset muscle soreness were all elevated after a 160km race, but the elevations were not significantly different between NSAID users and non-users (Nieman, et al., 2005). While this study had a large number of subjects, the groups of NSAID users and non-users were disproportionate, with 72% reportedly using an NSAID. Also, the dosage of the NSAID was not controlled, so it is not known if subjects were taking doses that may have had more or less of an impact on the measured markers. These limitations in the design of the study stimulated the authors to revamp it. The second study performed by Nieman et al. (2006) controlled the dosage of the NSAID and approximately 50% of subjects were reported as NSAID users. This time, ibuprofen use resulted in significantly higher levels of cytokines, neutrophils, and leukocytes, which are all indicators of inflammation. There was no significant difference in creatine kinase elevations and DOMS between NSAID users and non-users. These results are somewhat similar to the first study and in basically denounce NSAID use due to a lack of evidence of substantial benefit with their utilization.

Whether taken prophylactically or post-exercise, NSAIDs have been shown to have no significant role in the creatine kinase response of injured muscles (Bourgeois, et al., 1999; Donnelly, et al., 1988; Hasson, et al., 1993; Lecomte, et al., 1998; McAnulty, et al., 2007; Nieman, et al., 2006; Trappe, et al., 2002). Since creatine kinase is one of the markers of muscle damage, the deficiency of a significant difference in creatine kinase level between NSAID treated and untreated subjects in so many studies implies that NSAIDs do not play a role in protection from muscle damage. However, creatine kinase in not only significant in muscle injury because a rise in creatine kinase may also reflect heart or brain injury. McAnulty et al. found that in addition to creatine kinase, NSAID use did not diminish any oxidative stress
markers after exercise. However, this study did not control the dosage of the NSAID, so results are limited.

Macrophages and neutrophils, key inflammatory markers, did not differ in number between ibuprofen users and non-users after eccentric contractions of the knee flexors (Peterson, et al., 2003). In this study, ibuprofen was ingested beginning right after exercise. A large drawback in this study is that inflammatory cells were only measured once, 24 hours after exercise. Since the ingestion of ibuprofen was after exercise, it would have taken time for the NSAID to reach a steady state concentration in the blood, so results after 24 hours, had they been taken, may have been significant. This lack of long-term measurement limits the outcome reported in this study.

While the evidence presented in this chapter argues that NSAIDs do not play a significant role on muscle post-injury, limitations exist within nearly every study. Whether it was lack of control of NSAID dosage, mechanism of injury, length of the study, or the characteristics of the subjects, all of the studies except one, by Pizza et al., had an identifiable weakness. Therefore, there is not enough evidence to uphold the supposed outcome that NSAIDs have no effect on muscle recovery and strength after eccentric contraction-induced injury.
Conclusion

Although the pharmacology of NSAIDs and the processes of inflammation and of muscle recovery after eccentric contraction-induced muscle injury have been established, it has proven difficult to confirm their interactions with one another. Studies have been performed and come to a variety of conclusions: NSAIDs improve muscle recovery, NSAIDs hinder muscle recovery, and NSAIDs do not have a significant effect on muscle post-injury. After intense review, limitations were found in some of the studies and the recommendation for the use of NSAIDs as treatment for exercise-induced muscle injury is primarily based on its clinical benefits.

Many of the studies evaluated have outcomes that strongly favor the utilization of NSAIDs. Studies performed by O’Grady et al. (2000) and Cheung & Tidball (2003) both administered NSAIDs prophylactically and therapeutically and found evidence of decreased necrosis in the muscles of NSAID users post-exercise. This histological evidence cannot be disputed. However, both of these studies utilized NSAIDs prior to exercise and the protective effect of NSAIDs has yet to be researched. Future research is needed in order to assess the benefits and drawbacks of long-term NSAID use because for now, the longest study performed measured results for only 28 days post injury (Mishra, et al., 1995).

Several of the studies that supported NSAID use brought into question the extent of the analgesic effect of NSAIDs. Most studies administered the NSAID post-injury and claimed to decrease muscle soreness and cause either less of a decline from baseline strength measurements or strength gain with NSAID use (Baldwin, et al., 2001; Dudley, et al., 1997; Hasson, et al., 1993; Lecomte, et al., 1998; Sayers, et al., 2001; Tokmakidis, et al., 2003). The decrease in perceived soreness is rather indisputable since it results from both the analgesic and anti-inflammatory effects of NSAID, due to the inhibition of prostaglandins. The strength benefits,
however, are not as clear. It is possible that the reason NSAID users were able to perform
superiorly post-injury was simply because less pain was experienced with NSAID use or that the
pain felt by non-users caused them to perform inferiorly. The analgesic effects of NSAIDs occur
quickly after ingestion, but the anti-inflammatory effects take several days to acquire (Pizza, et
al., 1999). However, as discussed many times, we cannot distinguish these two effects.
Regardless of whether it is due to a reduction in pain or inflammation, NSAID users are able to
perform closer to baseline sooner than non-users after exercise-induced muscle injury (Hasson,
et al., 1993; Sayers, et al., 2001).

In addition to reducing muscle soreness and providing protection from muscle damage,
NSAID use is also supported because of its role in reducing creatine kinase levels, increasing the
concentration of ED2+ macrophages, and reducing inflammation (Bourgeois, et al., 1999;
Tokmakidis, et al., 2003). While these latter measurements are less significant clinically, they
lead to a reduction in pain and soreness, which are two of the most important clinical complaints
after exercise-induced muscle injury. These important factors, along with additional studies that
indicate NSAIDs enhance recuperation, lead to support of NSAID use for the treatment and

Of the few studies that found no consequence with NSAID use, there were limitations in
all but one. The use of trained subjects, a very short study length, contusion injuries, and no
monitoring of NSAID dosage were some of the errors found that likely affected results
(Bourgeois, et al., 1999; Nieman, et al., 2005; Nieman, et al., 2006; Peterson, et al., 2003;
Rahusen, et al., 2004; Thorsson, et al., 1998). Also, the results that were produced in these
studies are fairly small findings in comparison with other studies and varied from one study to
another. One common finding was that creatine kinase levels were frequently unaffected by NSAID use (Bourgeois, et al., 1999; Donnelly, et al., 1988; Hasson, et al., 1993; Lecomte, et al., 1998; McAnulty, et al., 2007; Nieman, et al., 2006; Trappe, et al., 2002). This indicates that NSAIDs did nothing to protect muscles from damage during exercise. In total, the results of these studies are uncertain at best and other than the observation regarding creatine kinase, the idea that NSAIDs do not play a significant role in muscle recovery after injury is weakly supported.

Finally, the research that criticizes NSAID use is significant and focuses primarily on the delay in muscle regeneration, inhibition of satellite cells, and the blunted skeletal muscle hypertrophy associated with NSAIDs. NSAIDs inhibit COX-2, which is necessary for muscle regeneration (Bondesen, et al., 2004). The studies that condemn NSAID utilization for the treatment of exercise-induced muscle damage exhibit this important fact over and over. These studies found evidence that NSAID use blunted protein synthesis, inhibited skeletal muscle hypertrophy, attenuated the satellite cell response, and essentially negated the anabolic results normally produced after eccentric exercise (Almekinders & Gilbert, 1986; Mackey, et al., 2007; Mendias, et al., 2004; Mishra, et al., 1995; Soltow, et al., 2006; Trappe, et al., 2002). This evidence also suggests that inflammation, which is attenuated with NSAID use, is necessary for muscle repair and strength gain. There were few limitations discovered in any of these studies, solidifying these conclusions. It is also important to note that all of these studies, except for that by Mackey et al., administered NSAIDs immediately post-injury as opposed to prophylactically. While the musculoskeletal disadvantages of NSAID are significant histologically, these important findings are most likely to be significant only to athletes, those who frequently exercise, and habitual NSAID users. The adverse effects on muscle growth associated with
NSAID use are not likely important factors to most clinicians when prescribing NSAIDs. They are also not imperative facts for the average individual who suffers a muscle injury and simply seeks relief from pain and soreness.

It can be concluded that NSAID use for the treatment of exercise-induce muscle injury is partially detrimental due to the hindrance of skeletal muscle repair and hypertrophy, but that clinically these effects are less important. The inhibition of muscle growth after exercise is primarily important for athletes and individuals who are exercising in order to gain strength and muscle mass. It is also important for those who will be using NSAIDs habitually, since we do not know the long-term effect of NSAIDs on muscle. However, most NSAID-users are not concerned with these side-effects and continue to use NSAIDs. Therefore, for an individual simply seeking relief from pain and soreness associated with muscle injury and not concerned with the inhibition of muscle hypertrophy associated with NSAID use, this class of drugs is recommended. Clinically, NSAIDs continue to be the mainstay of treatment for a variety of muscular aches and pains and their role has been supported after this review of the literature.
References


Chapter 36. Nonsteroidal Anti-Inflammatory Drugs, Disease-Modifying Antirheumatic Drugs, Nonopioid Analgesics, & Drugs Used in Gout.


Table 1. Effect of NSAIDs on Muscle Recovery and Strength after Exercise-Induced Muscle Injury

<table>
<thead>
<tr>
<th>Author(s) of study</th>
<th>Methods used</th>
<th>Study groups and timing of NSAID use</th>
<th>Measurement</th>
<th>Results</th>
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<tbody>
<tr>
<td>Almekinders &amp; Gilbert, 1986</td>
<td>- Rat muscle strained by machine and then immobilized - 85 rats</td>
<td>- Therapeutic NSAID(^1) use vs. control</td>
<td>- Wet weight of muscle (measure of edema) - Histological evaluation - Maximum failure load</td>
<td>- Histology showed a delay in inflammatory reaction and muscle regeneration in the NSAID group - Wet weight ↑ significantly less for NSAID group vs. control - Control group had less strength loss and earlier regeneration</td>
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<tr>
<td>Baldwin, et al., 2001</td>
<td>- 64 knee extensions performed - Strength measured before exercise, at day 3 and day 10 - 10 men and 5 women ≈60y/o and not resistance trained</td>
<td>- Therapeutic NSAID use vs. placebo</td>
<td>- Muscle strength before and after EIMI(^2) - Muscle soreness - Muscle injury assessed with MR(^3) imaging</td>
<td>- Strength declined less for NSAID than placebo - ↑ soreness after exercise with placebo vs. NSAID - Placebo users had significantly increased EIMI and edema on MRI on days 3 and 10</td>
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<tr>
<td>Bourgeois, et al., 1999</td>
<td>- Leg press and knee extension - 8 resistance and aerobic trained men</td>
<td>- Prophylactic naproxen sodium use vs. placebo</td>
<td>- DOMS(^4) - CK(^5) level - MVC(^6)</td>
<td>- No significant difference (SD) in elevations of CK or DOMS between placebo vs. NSAID - MVC ↓ for both groups at 24h and still for placebo at 48h – NSAID may help ↑MVC 48h after exercise</td>
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<td>Cheung &amp; Tidball, 2003</td>
<td>- Rats had suspended hindlimb for 10 days, followed by normal loading to induce inflammation - 37 rats</td>
<td>- Prophylactic NSAID vs. therapeutic NSAID vs. control</td>
<td>- Neutrophils - ED1 and ED2+ macrophages - Histological evaluation of muscle</td>
<td>- Prophylactic NSAID use resulted in ↓ muscle necrosis and ↑ macrophage (ED2+) - No significant Δ in the group that received NSAID after muscle loading</td>
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<td>Dudley, et al., 1997</td>
<td>- 10 sets of 7-10 leg extensions at 85% of 1RM(^7) - 2 phases (second phase with other leg) - 9 males, not resistance trained</td>
<td>- Therapeutic NSAID use vs. placebo</td>
<td>- 1 RM - DOMS</td>
<td>- ↑ 1RM at day 4 with naproxen sodium - ↓ DOMS at day 4 with naproxen sodium</td>
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<tr>
<td>Source</td>
<td>Experimentation</td>
<td>Measurements</td>
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<td>Hasson, et al., 1993</td>
<td>- Bench step-ups 20 subjects, males and females not involved in weight training</td>
<td>- Prophylactic NSAID vs. therapeutic NSAID (given 24h after exercise)</td>
<td>- ↑ CK in prophylactic and therapeutic groups at 24 and 48h with no SD - Prophylactic NSAID use resulted in ↓ soreness and less decline from baseline in torque and MVC, with therapeutic results lagging 24h behind</td>
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<td>Lecomte, et al., 1998</td>
<td>- Eccentric leg exercises on days 1, 3, and 4 – (2 testing phases lasting 8d and separated by 1wk) - Exercised vs. control leg - 20 males, not resistance trained</td>
<td>- Therapeutic NSAID use vs. placebo</td>
<td>- ↑ CK in both groups with no SD - ↑ quad strength for NSAID at 60°/s (no SD for 180 and 300°/s) - ↓ DOMS on day 3 with NSAID use</td>
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<tr>
<td>Mackey, et al., 2007</td>
<td>- 36km race - 14 endurance trained athletes</td>
<td>- Prophylactic NSAID use vs. placebo</td>
<td>- ↓ number of SCs after exercise with NSAID use - SCs are increased after exercise without NSAID use</td>
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<td>Mendias, et al., 2004</td>
<td>- Rat muscle cells cultured and exposed to naproxen sodium, COX-1 inhibitor, or COX-2 inhibitor for 96h</td>
<td>- Naproxen sodium (inhibits COX-1 and 2) vs. COX-1 inhibitor vs. COX-2 inhibitor vs. control</td>
<td>- ↓ in SC proliferation with naproxen sodium and COX-2 inhibitor - Inhibition of COX-1 and 2 results in ↓ and differentiation of SCs</td>
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<td>Mishra, et al., 1995</td>
<td>- Rabbit leg has an induced eccentric injury - 45 male rabbits</td>
<td>- Therapeutic flurbiprofen use vs. control</td>
<td>- Flurbiprofen resulted in short term improvement in maximum contraction at 3d and 7d, but deficit at 28d - ↓ CK in flurbiprofen users at 3d and 7d, but not at 28d</td>
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<td>Nieman, et al., 2005</td>
<td>- 160km run - 45 men and 15 women</td>
<td>- NSAID use vs. control - Dosage and type of NSAID not controlled</td>
<td>- CK, DOMS, and cytokines ↑ after race for both groups, but no SD between NSAID users and control</td>
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<td>- CK level - DOMS - Cytokine level</td>
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<td>Study</td>
<td>Intervention</td>
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<tr>
<td>Nieman, et al., 2006</td>
<td>160km endurance run - 54 ultra-marathoners</td>
<td>NSAID use vs. control - Dosage and type of NSAID controlled - CK level - Leukocyte count - Neutrophil count - LPS9 (measure of endotoxemia) - No SD in CK level between ibuprofen users and control - ↑ cytokines, neutrophils, leukocytes, and LPS levels with ibuprofen use</td>
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<td>O'Grady, et al., 2000</td>
<td>20 minutes of step-ups - 54 healthy, physically active men</td>
<td>Prophylactic diclofenac sodium use vs. placebo - NSAID use began 14d prior to exercise - CK level - DOMS - ↓ CK level with diclofenac sodium and ↑ CK with placebo 4d after exercise - CK levels SD 14d after exercise - ↓ DOMS with diclofenac sodium use</td>
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<td>Peterson, et al., 2003</td>
<td>Eccentric contractions of knee extensors - 24 untrained males</td>
<td>Therapeutic ibuprofen use vs. therapeutic ACET use vs. placebo - Macrophage count - Neutrophil count - Macrophages significantly ↑ in all groups 24h after exercise, while neutrophils did not Δ - Inflammatory cell concentrations were unaffected by ibuprofen or ACET use</td>
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<td>Pizza, et al., 1999</td>
<td>2 bouts of one arm exercises done 3wks apart - 10 sedentary males</td>
<td>Therapeutic ibuprofen use vs. control - NSAID ingested for 5d before and 10d after exercise - CK levels - Neutrophil count - DOMS - Isometric strength - Ketoprofen ↓ soreness and ↑ max isometric force recovery compared to placebo - ↑ EMG for all groups after exercise and ketoprofen did not reduce this at all</td>
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<td>Rahusen, et al., 2004</td>
<td>Mice given contusion injury - 96 mice</td>
<td>Tx with COX-2 inhibitor after injury vs. COX-2 inhibitor 24h before injury vs. ACET after injury vs. placebo - Gait disturbance - Wet weight of muscle (measure of edema) - SC count - No significant Δ in SC count with NSAID, ACET, or placebo - Wet weight ↑ for placebo only - Gait disturbance significantly ↑ for placebo group</td>
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<td>Sayers, et al., 2001</td>
<td>50 max eccentric contractions of the elbow flexors - 48 males</td>
<td>Therapeutic 25mg ketoprofen vs. 100mg ketoprofen vs. placebo - All ingested 36h after exercise - Max isometric force - Muscle soreness - EMG↑ - Ketoprofen ↓ soreness and ↑ max isometric force recovery compared to placebo - ↑ EMG for all groups after exercise and ketoprofen did not reduce this at all</td>
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Soltow, et al., 2006
- Rat muscle overloaded (OL) or normal loaded (NL)
- 16 rats
- Therapeutic ibuprofen vs. L-NAME (a COX-2 inhibitor) vs. control
- Muscle protein
- Macrophage count
- Neutrophil count
- Control rats ended up with larger muscles → Hypertrophy blunted by NSAID use
- Macrophages elevated 2x in OL vs. NL muscles
- Neutrophil count didn’t \( \Delta \)

Thorsson, et al., 1998
- Rats hit with mallet to induce contusion
- 4 groups of 12-16 rats each
- Naproxen sodium 6h after injury vs. naproxen sodium 3d after injury vs. 2 control groups
- SC proliferation
- No difference between NSAID and control groups in SC count after injury
- Note: injury was a contusion injury and was not due to eccentric exercise

Tokmakidis, et al., 2003
- 6 sets of 10 reps of leg curls
- 14 men and 5 women who were not training with weights
- Therapeutic ibuprofen vs. placebo
- CK level
- DOMS
- ROM\(^{12}\)
- Leg curl max strength
- Vertical jump performance
- ↓ CK at 48h and ↑DOMS at 24h with NSAID use
- Ibuprofen did not accelerate recovery of ROM, strength, or jump performance

Trappe, et al., 2002
- 10-14 sets of 10 high-intensity eccentric exercises with knee extensors
- 24 sedentary males
- Therapeutic ibuprofen vs. therapeutic ACET vs. placebo
- CK level
- Muscle protein fractional synthesis rate (FSR)
- ↑ CK in all groups after exercise with no SD between groups
- ↑ FSR only in placebo
- Ibuprofen and ACET blunted protein synthesis after exercise

Table 1. ¹ Nonsteroidal anti-inflammatory drug; ² Exercise-induced muscle injury; ³ Magnetic resonance; ⁴ Delayed-onset muscle soreness; ⁵ Creatine kinase; ⁶ Maximum volumetric contraction; ⁷ Repetition maximum; ⁸ Satellite cell; ⁹ Lipopolysaccharide; ¹⁰ Acetaminophen; ¹¹ Electromyelogram; ¹² Range of motion
Abstract

Objective. NSAIDs are commonly prescribed as treatment for inflammation, pain, and fever and work by inhibiting the synthesis of prostaglandins. This review investigates whether the anti-inflammatory actions of NSAIDs hinder muscle repair and strength gain after exercise-induced muscle injury (EIMI). Methods. This review was conducted using MEDLINE and PubMed databases. Results. NSAID use for the treatment of EIMI hinders satellite cell proliferation and skeletal muscle hypertrophy and repair, therefore blunting various benefits of eccentric exercise. Evidence supports short-term NSAID use both prophylactically and post-injury for its ability to reduce inflammation, lower serum creatine kinase levels, and reduce delayed-onset muscle soreness. Use of NSAIDs past 28 days has not been investigated making long-term effects unclear. Conclusion. Clinically, short-term NSAID use is upheld as treatment for inflammation and pain following EIMI. Athletes should recognize that NSAIDs inhibit muscle growth after EIMI. Chronic users should be wary of unknown long-term effects of NSAIDs.