

# Questioning the use of NSAIDs Given Inflammation is a Perfectly Healthy Response Following Acute Musculoskeletal Injuries

Written by: Dr. Bahram Jam, PT

Advanced Physical Therapy Education Institute (APTEI), Thornhill, ON, Canada  
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Nonsteroidal anti-inflammatory drugs (NSAIDs) are often prescribed in the treatment of musculoskeletal injuries and are one of the most commonly used medications worldwide. It is estimated that more than 30 million people take NSAIDs daily for a variety of conditions ranging from headaches to low back pain (LBP) (McGettigan & Henry 2013).



Ibuprofen is the most commonly used NSAID in North America while diclofenac is the most popular throughout the world (McGettigan & Henry 2013). Interestingly a 2013 review recommended that due to its high cardiovascular toxicity, diclofenac be removed from worldwide markets (McGettigan & Henry 2013). In fact it is well documented that all forms of NSAIDs are associated with potential adverse gastrointestinal (GI), renal, hepatic, and cardiovascular effects (Hunt et al 2007).

In 1998 *The American Journal of Medicine* stated the following:

*"Conservative calculations estimate that approximately 107,000 patients are hospitalized annually for NSAID-related GI complications and at least 16,500 NSAID-related deaths occur each year among arthritis patients alone in the USA, 4,000 deaths in Great Britain and 1,650 deaths in Germany. The figures of all NSAID users would be overwhelming, yet the scope of this problem is generally under-appreciated."* (Singh et al 1998)

The use of prescription NSAIDs is reported to be the 15<sup>th</sup> most common cause of death in the United States and it is conservatively calculated that in the last 3 decades 300,000 people in the United States have died from GI complications due to NSAIDs (Wolf et al 1999).

Before I begin my likely controversial discussion on the use of NSAIDs, it is appropriate to clearly state that I am certainly not making a blanket statement that all NSAIDs are inappropriate for all medical conditions. In fact, there are studies supporting their benefit with respect to pain and functional improvements in various conditions such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, gout, and tension headaches. These and many other conditions where NSAIDs may be appropriate to use have one thing in common; they are *not* a natural inflammatory response to an acute soft tissue injury following a specific trauma.



Admittedly, there are several high quality studies supporting the use of various NSAIDs on patients post soft-tissue injuries (*although conflicting*). There are systematic reviews supporting the use of NSAIDs for back pain (Chung et al 2013, Griffin et al 2002) and many other soft tissue injuries (Jones & Lamdin 2013). Then again the Cochrane database concludes that there is insufficient and conflicting evidence to support the use of NSAIDs in treating lateral elbow pain (Pattanittum et al 2013).

Despite the evidence, my goal is to have clinicians continue to question and scrutinize the use of NSAIDs on soft-tissue injuries. Sure you may think that *“this Bahram Jam guy is being hypocritical; in one breath he promotes evidence-based practice and in another breath he is questioning clear medical evidence”*.

I will reply with, sure there are studies supporting the use of NSAIDs on soft-tissue injuries and that is precisely why health care providers support their use, however the studies look at the short-term symptomatic recovery; what they **fail to do is look at the long-term effects and recurrence rates** with and without NSAIDs. At the expense of faster recovery, what effects do NSAIDs have on the actual quality of the bone, tendon, ligament or muscle repair?

Based on 65 clinical trials, the Cochrane database clearly supports the use of NSAIDs for patients with non-specific LBP (Roelfs et al 2008), hence nearly every patient with acute LBP almost instantaneously consumes either over the counter or prescription NSAIDs in order to hasten their recovery.



Following an acute episode of LBP, the recurrence rate within 1-year is up to 72% (Klenerman et al 1995), and there has yet to be study investigating if the use of NSAIDs is in any way associated with the risk of recurrence.

Similarly a study supported the use of NSAIDs for patients post acute ankle sprain (Slatyer et al 1997) yet ankle sprain recurrence within 1-year is up to 33% (Hupperets et al 2009). Again, there has yet to be study investigating if the use of



NSAIDs is in any way associated with the risk of recurrence.

The million dollar question remains, **could the use of NSAIDs post-acute musculoskeletal injuries actually increase the risk of recurrence due to inadequate repair?**



The correct answer remains unknown as the studies, primarily involving rats and rabbits, give conflicting results. However, in this biased paper I shall summarize a number of studies concluding that NSAIDs significantly reduce the quality and strength of bones and soft-tissues during healing.

Firstly, in a study (Warden et al 2006) 60 rats received a controlled incision of their knee medial collateral ligament (MCL) simulating an acute grade II MCL sprain. After 2 weeks they demonstrated that compared to the control group, the rats who received NSAIDs (celecoxib) 5 days a week had **significantly delayed healing** where the MCL could **absorb 33% less energy before tearing**.



In a second study (Ferry et al 2007) 200 rats received a controlled incision on their patellar tendons at the inferior pole of the patella. The injured rats were then randomized into 7 groups where they received one of the following analgesics for 2 weeks: ibuprofen, acetaminophen, naproxen, piroxicam, celecoxib, valdecoxib, or control.

At 2 weeks, all the animals were sacrificed, and their patellar tendons were biomechanically analyzed. They demonstrated that the **tendon strength in the control group (no meds) was significantly**

**stronger** and had greater maximum load compared with the celecoxib, valdecoxib, and piroxicam groups.

Here is a summary quote from the paper,

***“Anti-inflammatory drugs, with the exception of ibuprofen, had a detrimental effect on healing strength at the bone-tendon junction” and “Acetaminophen had no effect on healing strength.”*** (Ferry et al 2007)

To continue, here is the third rat study (Dimmens et al 2009) where the Achilles tendons of 60 rats were not only cut, but a 3 mm segment of the tendon was fully cut out and left unrepaired. Post-injury, the rats were given one of two NSAIDs (parecoxib or indomethacin) or placebo for one week. After 2 weeks when the rats were sacrificed, they found that **those who received NSAIDs had impaired tendon healing and had significantly lower Achilles tendon tensile strength** when compared to the control group. Relative to the control group, the **diameter of the tendons were reduced in both NSAID groups.**



In the most recent and fourth study, once again rats received surgical rotator cuff repairs. They showed that those given NSAIDs (meloxicam) between 11-20 days after post-op had **significantly reduced**

**biomechanical strength of their repaired rotator cuff tendon** when compared to the placebo group (Chechik et al 2014).

Enough rat studies, let's take a look at this study (Cohen et al 2006) where 180 rabbits received rotator cuff repairs. Immediately post-op the rabbits were given either placebo or one of two NSAIDs (celecoxib or indomethacin) for 2



weeks post-op. The animals were then sacrificed after 2, 4 and 8 weeks and their rotator cuff tendons were biomechanically and histologically analyzed. There were **significantly lower rotator cuff failure loads in the rabbits who received the NSAIDs** and in fact 5 of the tendons in the NSAID group completely failed to heal whereas all the tendons in the control group healed. **Collagen organization and maturation was significantly poorer in the NSAID group** at 4 and at 8 weeks post-op. Here is a quote from the paper published in the *American Journal of Sports Medicine*,

***“...nonsteroidal anti-inflammatory drugs significantly inhibited tendon-to-bone healing... If the results of this study are verified in a larger animal model, the common practice of administering non-steroidal anti-inflammatory drugs after rotator cuff repair should be reconsidered.”*** (Cohen et al 2006)

Despite all the above-mentioned animal studies, the most recent literature review on this topic concludes that there is insufficient evidence to support that NSAIDs may have a detrimental effect on soft-tissue healing; however there is clear evidence that some NSAIDs have an inhibitory effect on bone healing (Chen & Drago 2013).

Here a sample study (O'Connor et al 2009) where 67 rabbits received fibula osteotomies and were then allocated to receive either placebo medications or NSAIDs (ibuprofen or rofecoxib). After 6 weeks the rabbits were sacrificed and they clearly demonstrated that compared to the placebo group, the fibulas of **rabbits who received NSAIDs had significantly higher percentage of non-union and reduced torsional mechanical strength.**



And to quote the paper published in *The Journal of the American Academy of Orthopaedic Surgeon*,

***“When fracture healing or spine fusion is desired, nonsteroidal anti-inflammatory drugs should be avoided.”*** (Dahners et al 2004).

Here is the only experimental study I could find on the effects of NSAIDs on muscle healing (Mishra et al 1995). This time rabbit plantar flexors were subjected to experimentally induced eccentric contraction muscle injuries, simulating an eccentric overload injury of the hamstrings or gastrocnemius muscle that frequently occurs in athletes (e.g. sprinters).

Following the induced muscle injury, half the rabbits received NSAIDs (ibuprofen) two times a day for six days and the other half served as the control (natural healing). The rabbits' muscles were histologically and structurally analyzed at one week and 4 weeks post injury.



As typically observed in human studies, within one week post injury, those who received NSAIDs had more functional recovery however after 4 weeks the NSAID group had a greater deficit in their muscular force generation when compared to the untreated controls.

This study demonstrated that although NSAIDs provided short-term improvements in the initial week following the injury, after 4 weeks the rabbits treated with NSAIDs had significantly decreased torque and tension production of their effected muscles. Once again, this study concluded that a **brief course of NSAIDs did provide short-term benefit but it was a decrement in long-term muscle function.**

Here is a direct quote from the above-mentioned paper published in *The Journal of Bone and Joint Surgery*,

***“By suppressing the initial inflammatory reaction, the NSAID permits improved performance in early time-periods but appears to suppress the stimulus that may be needed for cellular remodeling in longer time-periods.”***

A review paper (Ziltener et al 2010) published in the *Annals of Physical and Rehabilitation Medicine* written by sports medicine physicians states,

***“We do not recommend their use (NSAIDs) for muscle injuries”.***

Considering all the aforementioned studies and review papers one may question why there is still controversy over the use of NSAIDs on soft-tissue injuries. Simple: animal studies hold limited value in medicine and human trials have not yet demonstrated the same adverse effects on tissue healing as the speculation has not yet been researched.

As one can appreciate, due to obvious ethical reasons human trials involving experimentally induced injuries followed by in vivo histological examination of the injured muscle, tendon, or ligament is not possible.

However, the one human study that is worth mentioning here involved 364 Australian army recruits who sustained ankle sprains (Slatyer et al 1997). Immediately post-injury the recruits were randomized to receive



either NSAIDs (piroxicam) or placebo. Not surprisingly they clearly demonstrated that those who took the NSAIDs experienced significantly less pain, more rapid functional recovery and had increased exercise endurance. The mean number of military training days lost was 2.7 from the NSAID group and 8.5 from the placebo groups, which proved NSAIDs to be a cost-effective intervention.

If you simply finish reading the paper based on these facts then case closed, a physician is perfectly justified in prescribing NSAIDs for a patient with an ankle sprain and the injured athlete would be crazy not to take NSAIDs considering it clearly reduces pain and improves function. The study then boldly concludes that, NSAIDs should form an integral part in the management of acute ankle sprains. (*Note: Study funded by Pfizer Pty Lt*)

Let's hold on here though. Could the short-term decreases in pain and improvements in function with NSAIDs be at the expense of the injured soft-tissue in the long-term?

The above-mentioned study fails to emphasize the ankle instability and range of motion (ROM) findings that were measured



**Anterior Drawer Test (Ankle):** With the tibia and fibula stabilized, the talus is drawn forward and the degree of laxity is noted and compared to the contra-lateral side.

on day 1, 3, 7 and 14. Initially following the ankle sprains the patients in both groups (NSAID and placebo) had similar ankle laxity using the anterior drawer test.

However at day 3, 7 and 14 the **patients treated with NSAIDs had significantly greater ankle instability** than the placebo group. After 3 days, 74% of the patients given placebo had a reversal of their ankle instability test where their anterior drawer test became negative, compared to 28% of those taking NSAIDs demonstrated the same reversal. After 14 days, the reversal of the anterior drawer test was seen in 97% of the patients given placebo compared to 78% of those taking NSAIDs.

Compared to the placebo group, the patients given NSAIDs had **significantly less ROM** into dorsiflexion, plantar flexion and inversion at 7 and 14 days. Ironically **those treated with NSAIDs subjectively reported greater swelling** at 7 days, 14 days, 3 months and 6 months post injury.

Interestingly there were no differences between the placebo and NSAID group with respect to recovery from ankle bruising.



Although the study reports that the recurrence rate was 25% within the 6 months of the study, regrettably they did not analyze the difference in recurrence between the two groups. It is hypothesized that since the patients in the NSAID group had reduced pain, they may have resumed activity prematurely thereby explaining the increased swelling, loss of mobility and greater ligamentous laxity.

Here is a quote from another paper pushed in *The Open Rehabilitation Journal*;

**“...NSAIDs are no longer recommended for chronic soft-tissue (ligament) injuries, and their use is cautioned in athletes who have ligament injuries.”** (Hauser et al 2013)

**“In the case of acute ligament injuries, NSAIDs should be used for the shortest time possible, if used at all”** (Hauser et al 2013)

I will make a confession that this has been a very biased paper where I have selectively presented the studies that show the potential negative side of NSAID usage. However, from an unbiased view, thus far there is still no definitive scientific evidence to completely dismiss the use of NSAIDs to treat acute soft-tissue injuries.

In conclusion, considering the undeniable cardiovascular and GI risks in the use of NSAIDs, and taking into account the potential hindrance to tissue recovery, we must continue to question the ever growing use of NSAIDs in those post acute soft-tissue injuries.

On a more positive note, there is mounting evidence that EXERCISE and PHYSICAL ACTIVITY have anti-inflammatory benefits. Therefore instead of immediately reaching for the NSAID bottle, perhaps the correct



movement(s) in the right direction(s) performed at the optimum intensity and frequency may be potentially more effective in both short and long-term in individuals post acute soft-tissue injuries.

The follow-up to this paper will review the evidences supporting physical therapists / physiotherapists as the ideal health care providers with the ability to effectively evaluate and efficiently prescribe the optimum daily exercise / movement program following all acute and recurrent musculoskeletal injuries.

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