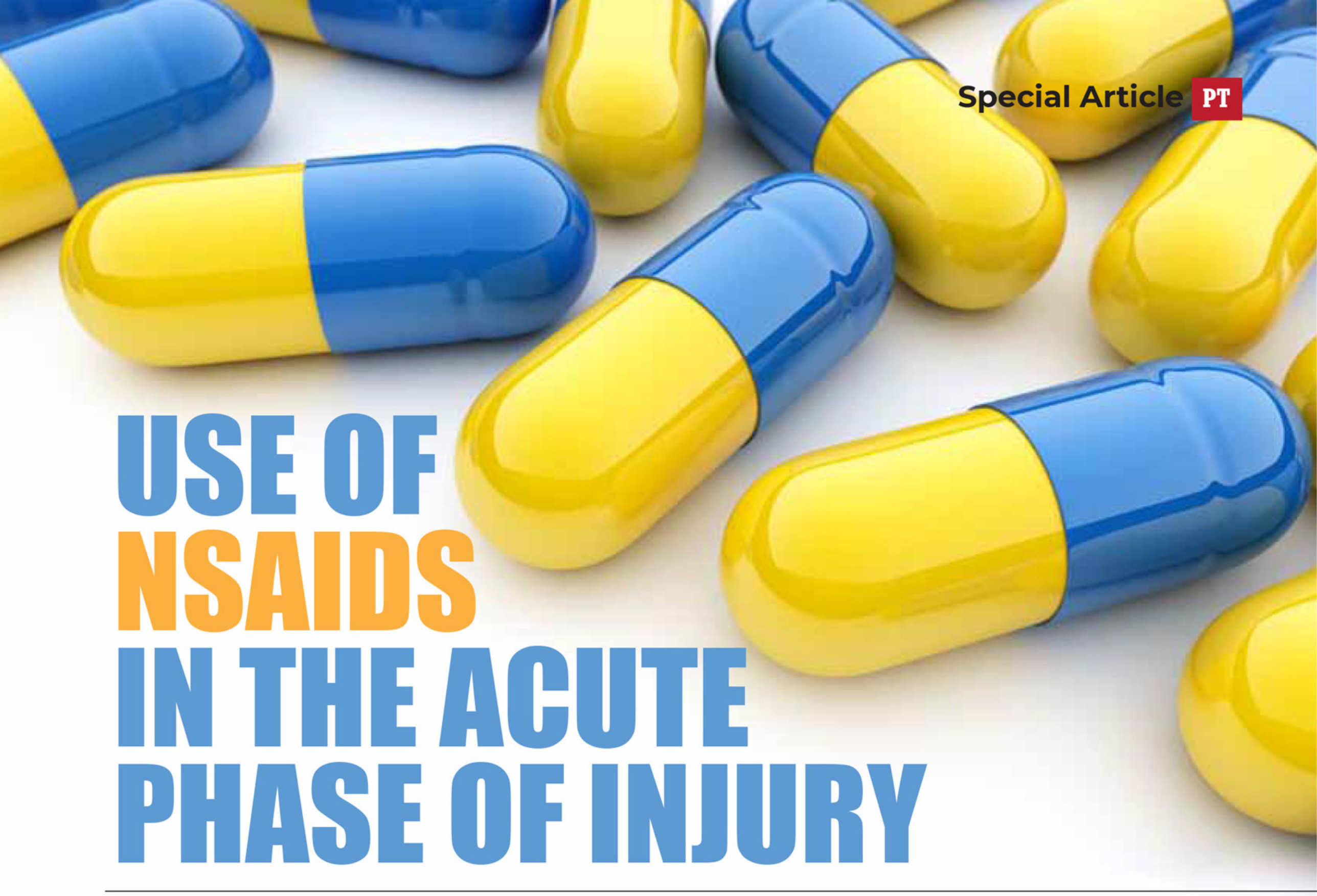

USE OF NSAIDS IN THE ACUTE PHASE OF INJURY

Delays Muscle Healing, Increases Fibrosis and May Potentially Endanger the Patient

RESEARCH COMMENTARY

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Part 1: The Use of Anti-inflammatory Medications in Physical Therapy

Pharmacological management of musculoskeletal pain is a common treatment modality, and may include both short and/or long-term non-steroidal anti-inflammatory drugs (NSAIDs) or short term steroidal anti-inflammatory drug (SAID) administration.

Since Physical Therapists are commonly the first point of contact in the musculoskeletal care of a patient, they should be knowledgeable in the administration and effects of various pharmacological musculoskeletal treatments. Since January 1, 2015, all 50 states, the District of Columbia, and the US Virgin Islands allow patients to see a licensed physical therapist directly. However, in many states limited or provisional conditions restrict the clinical access patients have to PTs. These restrictions can have an unnecessary impact on the needs of the patient which can delay care, delay full rehabilitation and increase costs.[1]

NSAIDs are very commonly used in the management of various types of pain, particularly musculoskeletal pain. According to a 2014 study *"over 90 million prescriptions for NSAIDs were filled and 23 million Americans were estimated to be using over-the-counter NSAIDS, [which] gives a total of 113 million American NSAIDS users annually"*.[2]

Despite the real and perceived benefits of NSAIDs, there are risks associated with their use. Use of NSAIDs has been associated with *"NSAID induced gastrointestinal pathology (gastropathy), accounting for over 70,000 hospitalizations, and 7,000 deaths annually in the US for patients with rheumatoid arthritis (RA)."*[3]

Thus, NSAID use is extremely common, potentially dangerous, and can even be fatal. Physical Therapists are often asked by their patients if they should take over the counter (OTC) anti-inflammatory medications. In fact, in-depth discussions on the topic are more often held between the physical therapist and the patient compared to potentially limited discussions between the physician and the patient.[4]

In 2013, Physical Therapists in the United Kingdom were the first to be able to prescribe NSAID's.[5] Physical therapists in many other countries, including the United States, are not legally allowed to prescribe medications, yet many PTs will recommend or emphasize their use and/or defer to the physician for advice.

Despite the common use of NSAIDs in musculoskeletal patients seen by Physical Therapists, unfortunately, many physical therapists knowledge of NSAID use is lacking.[6,7] From a personal perspective, the PTs authoring this Research Commentary feel that an in-depth knowledge of the cellular processes of anti-inflammatory medications was lacking after their first professional degrees. After having received transitional Doctorates of Physical Therapy degrees and with over 44 years of combined experience, their knowledge base of clinical pharmacology has increased somewhat, but both still feel it is lacking in clinically relevant foundational areas of pharmacology.

The APTA website states that 'the outcome competencies of the graduate of a post professional DPT program are most analogous to those of the current professional (entry-level) DPT standard.[8] As business owners, employers and mentors providing clinical instruction to entry-level DPTs, it is apparent that PTs knowledge of supplementary use of anti-inflammatory medication is lacking and the basis of use confirms the lack of knowledge.

A 2016 article by Norland et al in Physical Therapy discusses the disconnect between basic science research, the DPT curriculum, and its application into clinical practice.[9]

Many physical therapists will promote anti-inflammatory medications (e.g., ibuprofen, naproxen sodium, etc.) rather than analgesic medications (e.g., acetaminophen), and suggest NSAID use during the crucial acute period of inflammation necessary for tissue healing.

However, the value of NSAID use in acute injuries is complex and may be detrimental to tissue repair. The type of injury, stage of injury, and location of the injury should be taken into consideration to fully understand the impact of this modality. A review of the mechanism and type of injury and inflammatory processes are also needed to further understand NSAID applications in clinical practice.

Part 2: The Physiology of Inflammation and Muscle Repair (Adapted from Duchesne et al 2017)

Skeletal muscle accounts for approximately 30-40% of total body mass and movement is produced by contraction of long cylindrical cells called myofibers. Myofiber cells are impacted by trauma and different conditions and the nuclei of these myofibers are terminally post-mitotic (cannot divide further). Satellite cells are adult muscle stem cells which ensure muscle regeneration and without these, skeletal muscle cannot regenerate after injury. Satellite cells are inactive in resting muscle.

After an injury (day 0), resting satellite cells activate and turn into myoblasts. These myoblasts cells proliferate extensively for a few days (peaking at day 3). These myoblasts stop proliferating to differentiate. They either fuse to the damaged myofibers or fuse together to form myotubes, immature myofibers (day 4-7). Over the next few weeks, these newly formed myofibers grow into mature myofibers. Satellite cells then return to their resting state.

The Acute Inflammatory Process (3 phases)

1. ONSET

2. DEVELOPMENT

3. RESOLUTION

The Acute Inflammatory Process (3 phases)

1) Onset: Skeletal muscle injury occurs with a disruption of blood vessel integrity and initiation of the blood coagulation cascade. This forms anaphylotoxins, small molecules which trigger the release of substances such as mast cells, from sentinel cells residing in muscle tissue (resident cells). Tissue damage also liberates intracellular proteins and molecules which also activate resident cells. The factors released by mast cells stimulate the proliferation of satellite cells. This early mediation of inflammation starts the coordinated muscle repair process.

2) Development: Neutrophils migrate into injured tissue to phagocytose cell debris. They are followed by blood monocytes which differentiate into macrophages once they reach muscle tissue. Neutrophils also release proteolytic enzymes and reactive oxygen species which can induce secondary damage to healthy tissue adjacent to the injured site. Both neutrophils and macrophages (M1), along with other resident cell types release cytokines (secreted proteins important in cell signaling) which stimulate inflammatory cell recruitment. This phase typically lasts 72 hours.

3) Resolution: Recent discoveries show that inflammation is not a passive process but rather an active process. Macrophages switch from M1 (pro-inflammatory phenotype) to M2 (anti-inflammatory phenotype) two days post injury. M1 macrophages

phagocytose cellular debris and release pro-inflammatory factors for myoblast proliferation. M2 macrophages release anti-inflammatory molecules and growth factors that allow for cessation of myoblast proliferation and start differentiation, fusion and myofiber growth. This switch from M1 to M2 macrophage is essential for resolution of inflammation and promotion of muscle healing.

On the molecular level, pro-inflammatory lipid mediators are replaced by anti-inflammatory lipid mediators. This programmed class switching is due to the enzyme cyclooxygenase-2 (COX-2) which generates both molecules at different stages during the inflammatory process.

The Chronic Inflammatory Process

The persistence of pro-inflammatory cells impairs muscle regeneration and healing, leading to altered repair mechanisms such as muscle fibrosis and fat accumulation. This continuous inflammatory state can be from local or systemic injury.

Systemic: Aging is related to a higher concentration of pro-inflammatory systemic factors. Chronic disorders generate systemic pro-inflammatory factors that impair M1 to M2 macrophage change and resolution of inflammation.

Local: Repetitive local trauma contributes to the formation of scar tissue and/or muscle wasting. M1 macrophages are unable to switch to M2 macrophages and adopt a hybrid phenotype that produces transforming growth factor “beta” which stimulates fibrosis. The release of procachexia factors such as tumor necrosis factor alpha stimulate muscle wasting.

PART 3: IMPLICATIONS OF NSAID USE

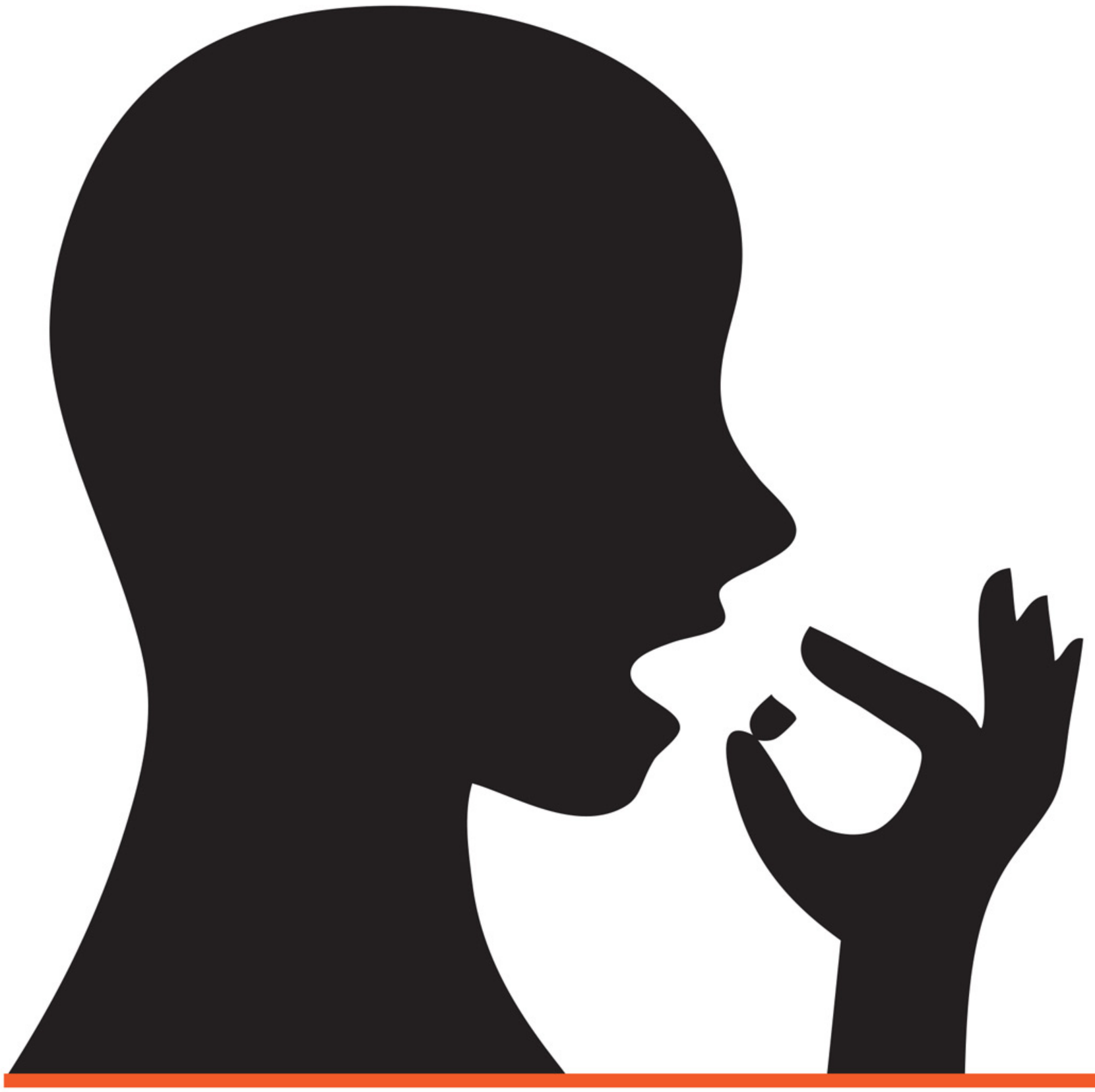
The impact of NSAID's during acute injury can actually have a detrimental effect on muscle healing. NSAID's target the COX-2 enzyme. Inhibition of the COX-2 enzyme impairs both the pro-inflammatory response and the switch to the anti-inflammatory phenotype that resolves inflammation.

Current evidence in acute ankle sprain and hamstring injury suggests that early use will actually reduce the necessary reparative inflammatory response hence leading to a delay in acute healing, muscle regeneration and compromised long-term healing.[10,11]

All phases of the acute inflammatory process after injury contribute to muscle regeneration and any inhibition of this pathway will limit the inflammatory pathways and retard acute muscle healing. Contrary to acute injuries, the use of anti-inflammatory medications may be beneficial in certain chronic muscle disorders.

In asynchronous muscle injury e.g. Duchenne muscular dystrophy (DMD) or repetitive local trauma, SAID administration was shown to restore the balance in the inflammatory process which then promotes improved muscle healing. Unfortunately, these benefits are limited in time and progressively lost with continued use, along with subsequent detrimental effects.

NSAID use in chronic, systemic inflammation was not shown to have any beneficial effects. Depending on the chronic inflammatory state and the type of injury or disease, the use of anti-inflammatory medications with chronic injuries may have beneficial use but adversely effect muscle healing.



The impact of NSAID's during acute injury can actually have a detrimental effect on muscle healing.

Duchesne et al (2017) proposed a concept map for application of anti-inflammatory medications into the clinical setting.

• **STEP 1.** Step 1 determines if the condition involves an inflammatory response. Clinicians sometimes lack clarity in chronic pain and chronic inflammation patient presentation. The pain reported with Achilles tendinopathy which has now been shown to not be an inflammatory condition has clinicians still using therapeutic modalities to reduce the 'inflammation', swelling and pain.[12]

• **STEP 2.** If the condition is associated with an inflammatory response, Step 2 is to determine if it is acute or chronic. If acute, do NOT use anti-inflammatory modalities (NSAID's). Physical therapy and analgesic modalities are warranted.

• **STEP 3.** If chronic, Step 3 is to determine if it is local or systemic. If systemic, do NOT use anti-inflammatory (NSAID) modalities. If local, anti-inflammatories can be beneficial (mainly SAID's), however their use should be evidence based and validated for that specific condition. Long term harmful effects should be kept in mind.

Discussion

Physical therapists diagnose and provide therapies for musculoskeletal repair, recovery and rehabilitation. One of our roles as a direct access provider is to be able to discern medical conditions as physical therapy appropriate or not.

Our initial intake of a patient will include a full medical screen to include medication history, present use and the use of pharmacological and supplemental compounds. Since pain is the most reported symptom, the understanding of therapeutic modalities such as anti-inflammatory medications must be taken into account to determine if their use is beneficial in the recovery and resolution of pain and injury.

Oftentimes, we are asked to provide insight into the use of anti-inflammatory or pain medications during the healing process. This line of questioning is an important point during the Maitland Australian Approach to classification of a patient as being pain dominant/irritable or stiff dominant. This classification is an important component in the physical therapist's prognosis and prescription for therapeutic modalities.

One of our roles as a direct access provider is to be able to discern medical conditions as physical therapy appropriate or not.

Evidence exists that physical therapist's knowledge of basic inflammatory processes and the effects of anti-inflammatory modalities is lacking. This Research Commentary highlights information that is necessary for physical therapists in the appropriate management of musculoskeletal injuries. The Duchesne et al (2017) paper discusses physiological processes that occur following injury that should be taken into consideration when considering the use of anti-inflammatory medications.

US Physical therapists cannot prescribe medications but will recommend or discuss the use of over the counter (OTC) medications.[13] However, the literature demonstrates a lack of knowledge in the physical therapist profession regarding cellular physiology during acute and chronic conditions and the impact of these medications. The PT's recommendation of an OTC medication must have the knowledge basis at the forefront in the correct prescription of supplementation.

The PT's lack of legislative understanding and adherence can pose a risk to patient safety and practice guidelines.[14] Consideration must be taken regarding the type of injury (whether inflammation exists), the stage of injury (acute versus chronic) and where the inflammation exists (local versus systemic). These factors will determine the best use of anti-inflammatory medications to minimize adverse effects in tissue healing. Reduction of inflammation without impairment of muscle regeneration must be achieved for optimal tissue healing and should always be the goal.

The concept map proposed by Duchesne et al (2017) gives general guidance to evidence-based use of anti-inflammatory modalities in the treatment of musculoskeletal disorders. Use of this guideline can help in the clinical reasoning and decision making of patient care.

TAKE-HOME MESSAGES

1) NSAID use is extremely common, potentially dangerous, and can even be fatal.

2) The use of anti-inflammatory medications during the acute inflammatory phase of musculoskeletal injuries is NOT recommended as it will delay tissue healing. Physical Therapy and analgesic medication (acetaminophen) use is more efficient for optimal muscle healing during the acute phase.

3) Anti-inflammatory modalities (NSAIDs) are NOT recommended in chronic, systemic inflammatory conditions as they will delay muscle healing.

4) Chronic, local inflammation will benefit from anti-inflammatory medications (SAIDs) but prolonged systemic use can have well documented detrimental side effects.

5) An important question to ask...

"Does early and continuous use of NSAIDs for relatively minor musculoskeletal injuries disrupt the normal inflammatory cascade and potentially increase the patient's risk of developing chronic inflammation and potentially muscle fibrosis?"

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Featured Study:

Duchesne E, Dufresne SS, Dumont N. (2017) Impact of Inflammation and Anti-inflammatory Modalities on Skeletal Muscle Healing: From Fundamental Research to the Clinic. Phys Ther. 2017:97:807-817.

The study can be found here: https://www.ncbi.nlm.nih.gov/pubmed/28789470

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