

# Utility of the heated lidocaine/tetracaine patch in the treatment of pain associated with shoulder impingement syndrome: a pilot study

Richard Radnovich<sup>1</sup>  
Thomas B Marriott<sup>2</sup>

<sup>1</sup>Injury Care Medical Center, Boise, ID, USA; <sup>2</sup>Pain Group, Nuvo Research US, Salt Lake City, UT, USA

**Introduction:** Pain control is an important first step in the treatment of shoulder impingement syndrome (SIS) because fear of pain must be removed as an obstacle to participation in an appropriate physical therapy program.

**Methods:** Adult patients with SIS-associated pain of at least 2 weeks' duration and who had an average pain score of  $\geq 4$  on the zero- to ten-point Numeric Pain Rating Scale were eligible to enroll in this 2-week pilot study. Patients were treated with the heated lidocaine/tetracaine (70 mg/70 mg) patch (HLT patch) placed over the site of shoulder tenderness each morning and evening for a period of 2 to 4 hours. Average and worst pain during the previous 24 hours and shoulder range of motion were assessed at baseline and on Day 14. Results were expressed as change and percent change from baseline to Day 14. This pilot study was not powered for rigorous statistical analysis.

**Results:** Twenty patients (seven male, 13 female; average age  $51.2 \pm 10.8$  years [mean  $\pm$  standard deviation]) enrolled in this study, and 18 patients completed the protocol. The mean average pain score at baseline was  $5.5 \pm 1.1$  (range 4 to 8). In the per-protocol population, average and worst pain scores declined by  $2.4 \pm 2.0$  and  $3.7 \pm 2.7$  points, respectively. Two-thirds of the patients demonstrated a clinically meaningful  $\geq 30\%$  decline in average pain score, and half of the patients demonstrated a  $\geq 50\%$  decline in average pain score. Shoulder internal rotation increased by  $29.7^\circ \pm 21.8^\circ$  and abduction increased by  $40.0^\circ \pm 44.2^\circ$ . Application-site erythema was reported by ten patients at some time during the study.

**Conclusion:** Patients treated with the HLT patch for 14 days demonstrated clinically meaningful improvement in pain intensity and range of motion. Further controlled research is necessary to characterize the efficacy and tolerability of the HLT patch in the treatment of SIS.

**Keywords:** SIS, HLT patch, range of motion, pain intensity

## Introduction

Persistent shoulder pain or stiffness is a common reason for consulting with primary care physicians. In the Netherlands, shoulder complaints in general practice have been estimated at 12 to 25 per 1000 visits per year, and in England and Wales the estimate is 6.6 per 1000 visits.<sup>1</sup> A systematic review of the medical literature found that the point prevalence of shoulder pain in adults aged  $<70$  years was between 7% and 27%, and the lifetime prevalence was 7% to 67%.<sup>2</sup> Direct health care costs attributable to shoulder pain and dysfunction are high. In the USA, an examination of the *Medical Expenditure Panel Survey* for the year 2000 revealed a total direct-cost estimate of US\$7 billion with a mean cost per care episode of US\$1667 and US\$3011 for outpatient and hospital-based settings, respectively.<sup>3</sup>

Correspondence: Richard Radnovich  
Injury Care Medical Center,  
4850 North Rosepoint Way,  
Suite 100, Boise, ID 83713, USA  
Tel +1 208 939 2100  
Fax +1 208 939 4411  
Email [dr.radnovich@injurycaremedical.com](mailto:dr.radnovich@injurycaremedical.com)

Shoulder impingement syndrome (SIS) is a common cause of shoulder pain and dysfunction and is typically caused by an impingement of the rotator cuff tendon under the acromion,<sup>4,5</sup> although other pathologies may contribute.<sup>6,7</sup> Initial treatment of SIS is conservative and consists of oral nonsteroidal anti-inflammatory drugs (NSAIDs) and supervised physical therapy regimens,<sup>5,6</sup> with the goal of reducing pain and inflammation, healing the rotator cuff, and improving shoulder function.<sup>8</sup> It has been estimated that about two-thirds of subjects with SIS will demonstrate a satisfactory response to NSAIDs and physical therapy.<sup>8</sup> If symptoms persist, subacromial injection of lidocaine and a corticosteroid may be indicated to relieve pain and allow physical therapy to continue.<sup>5,6,9</sup> However, despite their frequent use, a meta-analysis of randomized clinical trials evaluating subacromial injection of corticosteroids for SIS concluded that these injections may provide a limited and short-term benefit.<sup>10</sup>

Pain control is an important first step in the treatment of SIS because fear of pain may contribute to the original pathology as a result of fear of movement, avoidance of movement, and eventual disuse.<sup>11,12</sup> Thus, pain and fear of pain must be removed as obstacles to participation in appropriate physical therapy and exercise programs. One possible adjunct in the management of SIS-associated pain is the heated lidocaine/tetracaine (70 mg/70 mg) patch (HLT patch) that contains a eutectic mixture of the two drugs and has an integrated oxygen-activated heating component that enhances the dermal delivery of the anesthetic agents.<sup>13,14</sup> The HLT patch is approved in the USA and Europe and is indicated for use on intact skin to provide local dermal analgesia for superficial venous access and superficial dermatological procedures.<sup>14</sup> The depth and duration of anesthesia observed in a controlled study of the patch<sup>15</sup> suggest that it may be useful in the relief of pain associated with musculoskeletal structures lying close to the surface of the skin, as has been reported for other patches for the dermal delivery of local anesthetics.<sup>16–19</sup> Thus, here we report an open-label pilot study that was designed to investigate the utility of the HLT patch in reducing pain and improving shoulder function in patients with SIS.

## Methods

### Ethics

The study protocol was reviewed and approved by the Quorum Review Institutional Review Board (Seattle, WA, USA). All study subjects provided signed informed consent prior to engaging in any study activities.

## Patient population

Adult patients ( $\geq 18$  years old) with pain associated with SIS of at least a 2-week duration were eligible to enroll in the study. Additional inclusion criteria included tenderness at the site of rotator cuff tendons, positive Hawkins' and Neer's signs, and an average pain score of  $\geq 4$  on the zero- to ten-point Numeric Pain Rating Scale<sup>20</sup> over the past 24 hours.

Exclusion criteria included topical pain medication applied to the treatment area within 3 days of the screening visit, use of injected pain medication within 14 days of the screening visit, allergies or contraindications to any of the study drug components, clinically significant illness within 14 days of the screening visit, use of any class I antiarrhythmic agent, history of severe hepatic disease, and participation in a study of an unapproved drug within 30 days of the screening visit. Patients who had filed a SIS-associated disability claim or were receiving disability benefits due to SIS were ineligible for the study, as were women who were pregnant, breastfeeding, or not using appropriate birth control.

## Study design

This open-label study was conducted at the Injury Care Medical Center (Boise, ID, USA) and was carried out in accordance with the Good Clinical Practice guidelines. At the screening visit, patients underwent a problem-based physical examination, and medical history and concomitant medication use were recorded. Enrolled patients were instructed to apply the HLT patch to the site of tenderness twice daily (about every 12 hours) for periods of 2 to 4 hours. Each evening, patients were instructed to record average and worst pain intensity during the previous 24 hours in their study diary using the Numeric Pain Rating Scale,<sup>20</sup> an eleven-point rating scale in which a score of 0 indicates no pain and a score of 10 represents the worst pain imaginable. Pain interference with general activity, normal work, and sleep during the previous 24 hours was also recorded using a similar eleven-point scale in which a score of 0 represents no interference and a score of 10 represents complete interference. In addition, they were instructed to record the use of any concomitant medications during the previous 24-hour period. Limits of internal rotation and abduction of the shoulder were assessed with a goniometer at baseline and on Day 14. On Day 14, patients were asked to grade their satisfaction of treatment by choosing one of the following categories: very dissatisfied, dissatisfied, no preference, satisfied, or very satisfied.

Patients were allowed to use acetaminophen for acute SIS pain that was not effectively treated by the HLT patch

or for other minor pain (eg, headache). However, patients who used acetaminophen for SIS pain on two consecutive days were not included in the per-protocol population. NSAIDs were not allowed during the study, nor were any topically applied medications for the treatment of SIS pain.

## Safety

All 20 patients who enrolled in the study received at least one treatment with the HLT patch and were included in the safety population. Adverse events (AEs) were monitored throughout the study. Erythema at the application site was evaluated at the final study visit (Day 14) by medical personnel using a five-point scale (0 = no erythema, 1 = very slight erythema, 2 = well-defined erythema, 3 = moderate to severe erythema, 4 = severe erythema [beet redness] to slight eschar formations [injuries in depth]).

## Data analysis

This pilot study was designed to provide information to guide further research into the use of the HLT patch in the treatment of pain associated with SIS and was not powered for rigorous statistical analysis. Therefore, no hypothesis testing was performed. All results are presented using descriptive statistics.

## Results

A total of 20 patients were enrolled in the study and 19 patients completed it. One patient was lost to follow-up due to incarceration. All patients were Caucasian. Seven patients were male and 13 were female. The average age of the patients was  $51.2 \pm 10.8$  years (range 31 to 75 years). The mean baseline average pain score was  $5.5 \pm 1.1$  (range 4 to 8). The per-protocol population included 18 subjects; one subject was lost to follow-up and provided no efficacy data, and one subject used acetaminophen on two or more consecutive days for SIS pain.

The effects of the HLT patch on measurement of SIS pain are presented in Table 1. In the per-protocol population, average and worst pain scores decreased by  $2.4 \pm 2.0$  and  $3.7 \pm 2.7$  points, respectively, from baseline to Day 14. Similar changes were seen for the pain interference scores (Table 1). The cumulative response rate for percent decrease in average pain score (ie, percent improvement in average pain intensity) is shown in Figure 1. Two-thirds of the per-protocol population demonstrated at least a 30% decrease in average pain scores, and 50% of this population demonstrated at least a 50% reduction in average pain.

**Table 1** Changes in pain scores and pain interference scores in the per-protocol population

Parameter	Baseline	Day 14	Change from baseline	% change from baseline
N	18	18	18	18
Average pain	$5.5 \pm 1.1$	$3.1 \pm 2.2$	$-2.4 \pm 2.0$	$-45.0 \pm 39.5$
Worst pain	$7.8 \pm 1.2$	$4.2 \pm 2.8$	$-3.7 \pm 2.7$	$-47.0 \pm 35.6$
Pain interference				
General activity	$5.9 \pm 1.5$	$3.4 \pm 3.0$	$-2.4 \pm 3.4$	$-39.1 \pm 47.5$
Normal work	$6.2 \pm 1.4$	$3.8 \pm 3.4$	$-2.3 \pm 3.4$	$-37.8 \pm 49.4$
Sleep	$6.7 \pm 2.1$	$3.4 \pm 2.8$	$-3.3 \pm 3.2$	$-44.9 \pm 48.1$

**Note:** Numbers are expressed as mean  $\pm$  standard deviation.

The effect of treatment on shoulder range of motion is shown in Figure 2. In the per-protocol population, internal rotation increased by a mean  $29.7^\circ \pm 21.8^\circ$  during the study. Similarly, abduction increased by a mean  $40.0^\circ \pm 44.2^\circ$ .

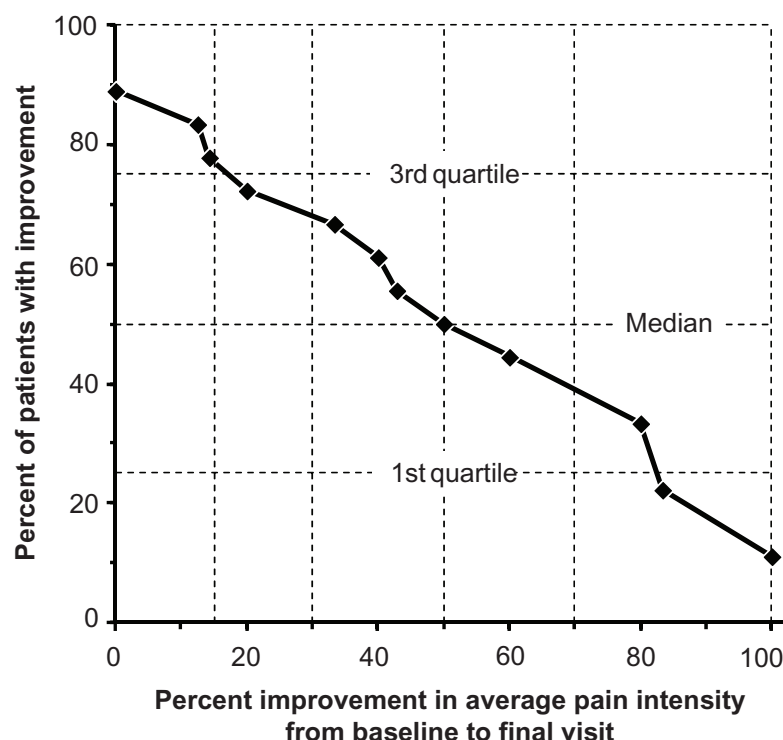
On Day 14 in the per-protocol population, eight patients (44.4%) indicated they were “very satisfied” with their HLT patch experience and two patients (11.1%) were “satisfied.” Two patients (11.1%) were “very dissatisfied” and three patients (16.7%) were “dissatisfied.” Three patients (16.7%) expressed “no preference.”

No serious AEs were reported during the study and no patients withdrew from the study due to AEs. A total of 36 AEs were reported by 14 patients (70%) during the study; all were mild or moderate in severity. Ten subjects reported application-site erythema at some time during the study. On Day 14, Grade 2 and Grade 1 erythema was observed in three and six patients, respectively. Other application-site AEs included irritation and pruritus in two patients each and dermatitis, induration, pain, rash, swelling, and urticaria in one patient each.

## Discussion

In this pilot study of the initial treatment of patients with SIS, 2 weeks of treatment with the HLT patch resulted in improvement in pain scores, pain interference scores, and range of motion (Table 1 and Figure 1). The majority of patients were “satisfied” or “very satisfied” with the HLT patch. The HLT patch was generally well tolerated.

The magnitude of the pain response in the present study is within the range considered clinically meaningful. For example, Farrar et al<sup>20</sup> analyzed the results of ten double-blind studies of patients with pain that used an eleven-point numerical pain rating scale. In their analysis, a change of  $-1.74$  points or  $-27.9\%$  was associated with “much or very much” improvement. As shown in Figure 1, two-thirds of



**Figure 1** Response distribution of percent improvement of final average pain (N = 18). Two subjects had 0% improvement: one patient demonstrated no change from baseline and one patient demonstrated an increase in average pain intensity from baseline to final visit.

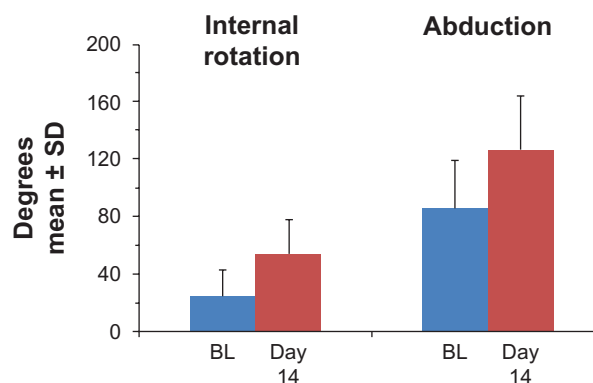
the patients in the present study demonstrated at least a 30% decrease in average pain score, suggesting that the HLT patch produced clinically meaningful improvement in most patients.

Pain or fear of pain may directly contribute to the pathophysiology of SIS.<sup>12</sup> This concept, which has been described as the “fear-avoidance model” of musculoskeletal pain, is defined as a catastrophic misinterpretation of pain resulting in increased fear of pain, fear of movement, avoidance, and hypervigilance.<sup>12</sup> This behavior initiates and perpetuates a vicious cycle that leads to an elevation of chronic pain and long-term disability. Lentz et al<sup>12</sup> studied 142 subjects with unilateral shoulder disorders and assessed pain-related fear with the Tampa Scale of Kinesiophobia. They found that pain-related fear was statistically significantly associated with self-reported disability after controlling for demographics, pain intensity, and other physical impairment measures. Based on the fear-avoidance model theory, the reduction in pain observed in the present study may have had the direct effect of improvement in range of motion (Figure 2).

Conservative therapy for SIS involves supervised physical therapy including stretching and gradual strengthening of the shoulder musculature.<sup>21</sup> However, pain control is an essential component of a successful physical therapy program.<sup>9,21</sup> Initial pain management typically involves NSAIDs or

acetaminophen,<sup>9</sup> and if symptoms persist, a subacromial injection of corticosteroids can be administered in combination with a local anesthetic.<sup>9</sup>

The term “shoulder impingement syndrome” is often used indiscriminately to describe various conditions of chronic shoulder pain or discomfort. The disease it describes is part of a continuum of rotator cuff tendinopathy characterized by mucoid degeneration, collagen loss, and disorganization.<sup>22,23</sup> Histopathologic examinations of symptomatic rotator cuff tendons have inconsistently shown evidence of inflammation despite substantial degenerative changes in the tendons.<sup>22</sup>



**Figure 2** Shoulder range of motion at baseline and after 14 days of treatment with the heated lidocaine/tetracaine patch.

**Abbreviations:** BL, baseline; SD, standard deviation.

Khan et al<sup>22</sup> failed to show histopathological evidence of inflammation, while Murphy and coworkers<sup>7</sup> found significant elevation of CD45, a marker of inflammation, in biopsies of the supraspinatus tendon from patients with early stage rotator cuff tendinopathy but not in samples taken from patients with more advanced disease. In addition, immunohistochemical examination of subacromial bursa biopsy specimens from patients with rotator cuff disease shows a clear increase in inflammatory cytokines, as well as in cyclooxygenase 1 and 2, compared with specimens from subjects without SIS.<sup>24,25</sup>

The pathophysiological processes that contribute to the pain of rotator cuff disease are many, and this variation may influence the response to treatment. The less-than-certain role of inflammation in the pathology of SIS calls into question the routine use of systemic NSAIDs, especially in view of their AE profile, and points to the need to explore alternative treatments that target different proposed mechanisms of pain. Other biochemical mediators that may influence nociceptors include glutamate and substance P.<sup>26</sup> Local anesthetics, such as lidocaine and tetracaine, are known to relieve pain by inhibiting the depolarization and firing of sensory nerve fibers through sodium channel blockade and possibly targeting substance P/neurokinin-1 signaling via sodium channel blockade.<sup>27,28</sup> Additionally, high levels of the neurotransmitter glutamate have been identified by in situ microdialysis in patellar and Achilles tendinopathies,<sup>29</sup> and elevated expression of the glutamate receptor N-methyl-D-aspartate (NMDA) receptor type 1 has been associated with tendinopathies.<sup>30,31</sup> The NMDA receptor is reported to be involved in chronic pain disorders, and both lidocaine and tetracaine inhibit this receptor.<sup>32</sup> Thus, it is possible that the HLT patch might attenuate pain in part by blockade of the NMDA receptor. However, without data regarding receptor expression in SIS, this mechanism of action must remain speculative.

The HLT patch is designed to have its primary effect on the skin and underlying subcutaneous tissue, but the present results suggest a drug effect within deeper structures with increased duration of application and twice-daily dosing. Wallace et al<sup>15</sup> reported that a 30-minute application of a single HLT patch resulted in elimination of pain to a mean depth of 8.22 mm, with this peak effect occurring 60 minutes after HLT patch removal. Longer application times, as were used in the present study, might be expected to result in deeper penetration of the lidocaine and tetracaine. Other investigators have shown that topically applied agents can be detected in structures beneath the skin following application. For example, Sekiya et al<sup>33</sup>

found similar concentrations of ketoprofen in semitendinosus muscle and tendon at 14 hours following the administration of either 40 mg by dermal patch or 150 mg administered as a single, sustained-release oral dose, even though mean ketoprofen plasma concentrations were 17-fold higher in patients who received oral doses.

## Study limitations

This study was open-label and of short duration. As no placebo-treated control group was included, it cannot be determined to what degree placebo response contributed to the observed outcomes in this study. Further controlled research is warranted before any firm conclusions can be drawn.

## Conclusion

The latest consensus is that SIS most likely represents a rotator cuff tendinopathy. Given our understanding of the underlying pathophysiology relating to tendinopathies and pain, use of anti-inflammatory agents may not optimally target two recently implicated components of SIS pain: glutamate-NMDA signaling and substance P/neurokinin-1 signaling via sodium channel blockade. In this pilot study, patients with SIS demonstrated clinically meaningful improvement in pain intensity, pain interference scores, and range of motion after 14 days of treatment with the HLT patch, suggesting a potential role in this patient population. Further controlled research is warranted to fully characterize the efficacy and benefit–risk profile of the HLT patch for the relief of pain associated with SIS.

## Acknowledgments

The authors thank ZARS Pharma and Nuvo Research for the support provided for the development of this article. The authors also thank Arnold R Gammaioni, PharmD, of Nuvo Research, for his review for medical accuracy. Professional medical writing and editing assistance was paid for by Nuvo Research and was provided by Edward Weselcouch, PhD, and Diana Talag, MS, ELS, of PharmaWrite (Princeton, NJ, USA). This article was prepared according to the International Society for Medical Publication Professionals' *Good Publication Practice for Communicating Company-Sponsored Medical Research: The GPP2 Guidelines*.

## Disclosure

RR has been a consultant for and has received research funding from Nuvo Research. TBM is a full-time employee of ZARS Pharma, a Nuvo Research company, which markets Synera in the USA. The authors declare no other conflicts of interest in this work.



## References

- van der Windt DA, Koes BW, de Jong BA, Bouter LM. Shoulder disorders in general practice: incidence, patient characteristics, and management. *Ann Rheum Dis*. 1995;54(12):959–964.
- Luime JJ, Koes BW, Hendriksen IJ, et al. Prevalence and incidence of shoulder pain in the general population; a systematic review. *Scand Cardiovasc J*. 2004;33(2):73–81.
- Johnson MP, Crossley KL, O'Neil ME, Al-Zakwani IS. Estimates of direct health care expenditures among individuals with shoulder dysfunction in the United States. Paper presented at the 2004 Annual Meeting of the American Society of Shoulder and Elbow Therapists, September 29–October 2, 2004, New York, NY.
- Neer CS. Anterior acromioplasty for the chronic impingement syndrome in the shoulder: a preliminary report. *J Bone Joint Surg AM*. 1972;54(1):41–50.
- Buss DD, Freehill MQ, Marra G. Typical and atypical shoulder impingement syndrome: diagnosis, treatment, and pitfalls. *Instr Course Lect*. 2009;58:447–457.
- Koester MC, George MS, Kuhn JE. Shoulder impingement syndrome. *Am J Med*. 2005;118(5):452–455.
- Murphy RJ, Kliskey K, Wheway K, Watkins EB, Beard DJ, Carr AJ. Rotator cuff tendinopathy: immunohistochemical changes across the spectrum of pathology. *Br J Sports Med*. 2013;47(9):e2.
- Morrison DS, Frogameni AD, Woodworth P. Non-operative treatment of subacromial impingement syndrome. *J Bone Joint Surg AM*. 1997;79(5):732–737.
- Burbank KM, Stevenson JH, Czarnecki GR, Dorfman J. Chronic shoulder pain: part II. Treatment. *Am Fam Physician*. 2008;77(4):493–497.
- Buchbinder R, Green S, Youd JM. Corticosteroid injections for shoulder pain. *Cochrane Database Syst Rev*. 2003;1:CD004016.
- Leeuw M, Goossens ME, Linton SJ, Crombez G, Boersma K, Vlaeyen JW. The fear-avoidance model of musculoskeletal pain: current state of scientific evidence. *J Behav Med*. 2007;30(1):77–94.
- Lentz TA, Barabas JA, Day T, Bishop MD, George SZ. The relationship of pain intensity, physical impairment, and pain-related fear to function in patients with shoulder pathology. *J Orthop Sports Phys Ther*. 2009;39(4):270–277.
- Sawyer J, Febraro S, Masud S, Ashburn MA, Campbell JC. Heated lidocaine/tetracaine patch (Synera, Rapydan) compared with lidocaine/prilocaine cream (EMLA) for topical anaesthesia before vascular access. *Br J Anaesth*. 2009;102(2):210–215.
- Synera (lidocaine 70 mg and tetracaine 70 mg) topical patch [prescribing information]. Salt Lake City, UT: ZARS Pharma; 2010.
- Wallace MS, Kopecky EA, Ma T, Brophy F, Campbell JC. Evaluation of the depth and duration of anesthesia from heated lidocaine/tetracaine (Synera) patches compared with placebo patches applied to healthy adult volunteers. *Reg Anesth Pain Med*. 2010;35(6):507–513.
- Affaitati G, Fabrizio A, Savini A, et al. A randomized, controlled study comparing a lidocaine patch, a placebo patch, and anesthetic injection for treatment of trigger points in patients with myofascial pain syndrome: Evaluation of pain and somatic pain thresholds. *Clin Ther*. 2009;31(4):705–720.
- Nalamachu S, Crockett RS, Gammaitoni AR, Gould EM. A comparison of the lidocaine patch 5% vs naproxen 500 mg bid for the relief of pain associated with carpal tunnel syndrome: a 6-week, randomized, parallel-group study. *Med Gen Med*. 2006;8(3):33.
- Burch F, Coddling C, Patel N, Sheldon E. Lidocaine patch 5% improves pain, stiffness, and physical function in osteoarthritis pain patients. A prospective, multicenter, open-label effectiveness trial. *Osteoarthritis Cartilage*. 2004;12(3):253–255.
- Kivitz A, Fairfax M, Sheldon EA, et al. Comparison of the effectiveness and tolerability of Lidocaine Patch 5% versus Celecoxib for osteoarthritis-related knee pain: post hoc analysis of a 12-week, prospective, randomized, active-controlled, open-label, parallel-group trial in adults. *Clin Ther*. 2008;30(12):2366–2377.
- Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain*. 2001;94(2):149–158.
- Codsi MJ. The painful shoulder: when to inject and when to refer. *Cleve Clin J Med*. 2007;74(7):473–478, 480.
- Khan KM, Cook JL, Bonar F, Harcourt P, Astrom M. Histopathology of common tendinopathies. Update and implications for clinical management. *Sports Med*. 1999;27(6):393–408.
- Lewis JS. Rotator cuff tendinopathy. *Br J Sports Med*. 2009;43(4):236–241.
- Blaine TA, Kim YS, Voloshin I, et al. The molecular pathophysiology of subacromial bursitis in rotator cuff disease. *J Shoulder Elbow Surg*. 2005;14(Suppl 1):84S–89S.
- Voloshin I, Gelinas J, Maloney MD, O'Keefe RJ, Bigliani LU, Blaine TA. Proinflammatory cytokines and metalloproteinases are expressed in the subacromial bursa in patients with rotator cuff disease. *Arthroscopy*. 2005;21(9):1076.e1–1076.e9.
- Khan KM, Cook JL, Maffulli N, Kannus P. Where is the pain coming from in tendinopathy? It may be biochemical, not only structural, in origin. *Br J Sports Med*. 2000;34(2):81–83.
- Weiser T. Comparison of the effects of four Na<sup>+</sup> channel analgesics on TTX-resistant Na<sup>+</sup> currents in rat sensory neurons and recombinant Nav 1.2 channels. *Neurosci Lett*. 2006;395(3):179–184.
- Li YM, Wingrove DE, Too HP, et al. Local anesthetics inhibit substance P binding and evoked increases in intracellular Ca<sup>2+</sup>. *Anesthesiology*. 1995;82(1):166–173.
- Alfredson H, Forsgren S, Thorsen K, Lorentzon R. In vivo microdialysis and immunohistochemical analyses of tendon tissue demonstrated high amounts of free glutamate and glutamate NMDAR1 receptors, but no signs of inflammation, in Jumper's knee. *J Orthop Res*. 2001;19(5):881–886.
- Schizas N, Lian O, Frihagen F, Engebretsen L, Bahr R, Ackermann PW. Coexistence of up-regulated NMDA receptor 1 and glutamate on nerves, vessels and transformed tenocytes in tendinopathy. *Scand J Med Sci Sports*. 2010;20(2):208–215.
- Schizas N, Weiss R, Lian O, Frihagen F, Bahr R, Ackermann PW. Glutamate receptors in tendinopathic patients. *J Orthop Res*. 2012;30(9):1447–1452.
- Sugimoto M, Uchida I, Mashimo T. Local anesthetics have different mechanisms and sites of action at the recombinant N-methyl-D-aspartate (NMDA) receptors. *Br J Pharmacol*. 2003;138(5):876–882.
- Sekiya I, Morito T, Hara K, et al. Ketoprofen absorption by muscle and tendon after topical or oral administration in patients undergoing anterior cruciate ligament reconstruction. *AAPS PharmSciTech*. 2010;11(1):154–158.

### International Journal of General Medicine

### Publish your work in this journal

The International Journal of General Medicine is an international, peer-reviewed open-access journal that focuses on general and internal medicine, pathogenesis, epidemiology, diagnosis, monitoring and treatment protocols. The journal is characterized by the rapid reporting of reviews, original research and clinical studies across all disease areas.

Submit your manuscript here: <http://www.dovepress.com/international-journal-of-general-medicine-journal>

### Dovepress

A key focus is the elucidation of disease processes and management protocols resulting in improved outcomes for the patient. The manuscript management system is completely online and includes a very quick and fair peer-review system. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.