APPENDIX: HUMAN STUDIES OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS, ACETAMINOPHEN AND CRYOTHERAPY.

A note on the tables: Papers were identified by multiple-iteration searches of relevant terms ("cryotherapy," "NSAIDs," "DOMS," "hypertrophy," "soft tissue injury," etc), on Pub Med and Google Scholar, followed by searches of related and referenced articles. Basic science and animal studies were not tabulated, nor were clearly irrelevant studies. I reviewed and included papers only if the full text was reasonably accessible and they were published in the last 20 years. (I have a life and a job and everything.) I made no attempt to grade the quality of the studies. The purpose of the exercise was not to conduct an exhaustive survey nor to rate the evidence, but rather to evaluate the claim that the literature has reached a consensus on the use of NSAIDs and cryotherapy in the setting of training injury and soreness.

To this end, I include a summary column indicating whether the paper could be reasonably interpreted as supporting the use of the therapy. This was an ***entirely implicit assignment***, based on my own understanding of the paper, and made solely by me, without the use of any objective decision instrument or scoring system. ***The assignment was guided based on the assumption that the reader derives some relief from the therapy in question, unless the paper substantially challenged the palliative efficacy of that therapy.*** For example, if the paper offered strong evidence of a robust maladaptive impact of the therapy, this would override the palliative assumption, and the recommendation assigned would be No (N). If the paper offered no evidence of maladaptive impact, or evidence of a positive impact, the palliative assumption would take precedence, and the recommendation assigned would be Yes (Y). If the paper offered weak evidence of adaptive or maladaptive impact, the assignment would be Maybe (M), Maybe Yes (MY), or Maybe No (MN), depending on my own implicit evaluation of the paper and the reliability of its findings. If the paper substantially challenged the palliative efficacy of the the therapy and identified no other robust adaptive benefit, this overrode the palliative assumption, and the recommendation was No. (The reader may obviously have different ideas if she gets relief from the therapy, but this assignment decision was made to ***err on the side of the AAI argument***).

Just be perfectly clear: this is all ***very presumptuous on my part***; this "scoring" was completely implicit, unscientific and loosey-goosey; and it was done ***only*** to highlight the diverse conclusions and lack of consensus in the literature, while making the tables more accessible to the truncated attention span of North American readers. The reader is strongly advised to take all of this with a shaker of salt, and is invited to read the articles tabulated here and ***make his or her own conclusions…*** always a Good Idea**.**

TABLE 1: HUMAN STUDIES OF NSAIDs AND RELATED DRUGS FOR SOFT-TISSUE INJURIES AND MUSCLE SORENESS. DB=double blind. R=randomized. PC=placebo-controlled. RCT=randomized controlled trial. CxT= crossover trial. MA = meta-analysis. For information on the recommendation assignments in the right-hand column, see the Appendix Notes.

CITATION	STUDY TYPE	CONCLUSIONS	NSAIDs: Y,N,M
1990s			
Various treatment techniques on signs and symptoms of delayed onset muscle soreness. Gulick DT et al. *J Athlet Train* 1996;31(2):145-52.	**RCT**	The authors report no benefit of an NSAID (oxaprozin), ice, stretching, high velocity concentric exercise, or sublingual or topical ***A. montana*** extract on DOMS induced by eccentric forearm contractions. In fact, NSAID and ***A. montana*** "appeared" to impede recovery. No long-term practically relevant outcomes were assessed.	**N**
Anti-inflammatory doses of ibuprofen: effect on neutrophils and exercise-induced muscle injury. Pizza FX, Cavendar D, Stockard A. *Int J Sports Med* 1999; 20(2): 98-102.	**RPCT**	"Anti-inflammatory doses of ibuprofen reduced CK activity but not the neutrophil response or other indirect markers of muscle injury during recovery from eccentric arm exercise." There was no impact on isometric strength or soreness. No long-term variables were studied.	**Y**
2000s			
Effect of ketoprofen on muscle function and sEMG activity after eccentric exercise. Sayers SP, Knight CA, Clarkson PM, et al. *Med Sci Sports Exerc* 2001; 33(5): 702-10.	**RT**	Ketoprofen had no impact on reducing post-exercise increases in myoelectric activity. It improved soreness compared with placebo.	**Y**
Managing delayed-onset muscle soreness: Lack of effect of selected oral systemic analgesis. Barlas et al, *PhysMedRehabil* 2000;81:966-72.	**DBPCRT**	No beneficial effect of aspirin, codeine (?) or paracetamol in reducing DOMS induced in nondominant elbow flexors by repeated eccentric contractions. No study of impact on adaptation or healing.	**N**
Nonsteroidal anti-inflammatory therapy after eccentric exercise in healthy older individuals. Baldwin AC.*J Gerontol Med Sci* 2001;56A(8)M510-13.	**DBCT**	Naproxen sodium decreased muscle injury, strength loss and soreness after eccentric knee extensions in 15 elderly (aged approx 60 years) men and women. The authors conclude that this therapy may be beneficial in older patients during the early stages of increased physical activity. No assays of long-term adaptation were undertaken.	**Y**

CITATION	STUDY TYPE	CONCLUSIONS	NSAIDs: Y,N,M
The effects of ibuprofen on delayed onset muscle soreness and muscular performance after eccentric exercise. Tokmakidis SP,et al. *JSCR* 2003;17(1):53-59.	**RPCT**	Nineteen subjects performed eccentric leg curls and got sore hamstrings. They were randomized to ibuprofen or placebo. The ibuprofen group had less soreness and lower CK release and peripheral WBC count, but no differences in maximal strength, vertical jump performance, or knee ROM. "The results of this study reveal that intake of ibuprofen can decrease muscle soreness induced after eccentric exercise but cannot assist in restoring muscle function."	**Y**
2010s			
The effect of nonsteroidal anti-inflammatory drug administration on acute-phase fracture-healing: a review. Kurmis et al. *J Bone Joint Surg* 2012;94:815-23.	**SR**	The authors conducted a review of 316 relevant studies. The available clinical evidence does not substantiate the concern raised by animal studies, and suggests that NSAIDs are safe and effective for pain control after fracture, without an adverse effect on fracture healing. "Although increasing evidence from animal studies suggests that COX-2 inhibition suppresses early fracture healing, in vivo studies involving human subjects have not substantiated this concern….balance of evidence in the available literature appears to suggest that…NSAID(s are)… safe and effective supplement to post-fracture pain control, without…increased risk of…disrupted healing."	**Y**
Effect of ibuprofen and acetaminophen on post-exercise muscle protein synthesis. Trappe et al. *Am J Phyiol Endocrinol Metab* 2001; 282:E551-6.	**RPCT**	24 males received a ***maximal dose*** of medicine or placebo after 10 eccentric reps at 120% 1RM. Postexercise fractional synthesis rate appeared to be increased in all three groups, but reached statistical significance only in the placebo group. Differences were of unclear practical significance. Muscle breakdown was not effected by any regimen. ***The authors did not investigate which proteins were affected*** (i.e., muscle protein, inflammatory protein, etc), and no functional assessments (strength, pain control, time to return to function etc) were undertaken. "The long-term influence of this acute response after resistance exercise for individuals who chronically consume these (or similar) drugs cannot be determined from this study."	**MN**
Influence of acetaminophen and ibuprofen on skeletal muscle adaptations to resistance exercise in older adults. Trappe et al. *Am J Physiol Regul Integr Comp Physiol* 2011;300:R655-62.	**RDBPCT**	"Drug consumption unexpectedly increased muscle volume and muscle strength to a greater extent than placebo." No change in muscle protein content, water content or myosin heavy chain distributions were observed on muscle biopsy. Medication did not inhibit, and in fact appeared to ***enhance***, muscle hypertrophy and strength gains in older adults.	**Y**

CITATION	STUDY TYPE	CONCLUSIONS	NSAIDs: Y,N,M
Ingestion of low-dose ibuprofen following resistance exercise in post-menopausal women. Candow et al. *J Cachexia Sarcopenia Muscle* 2012 DOI 10.1007/s13539-012-0077-3	**RCT**	Postmenopausal women demonstrated no significant difference in strength gain or lean body mass whether they took ibuprofen or placebo after resistance exercise. Analgesic efficacy was not assessed.	**M**
The effect of nonsteroidal anti-inflammatory drugs on tissue healing. Chen and Dragoo. *Knee Surg Sports Traumatol Arthrosc* 2012; DOI 10.1007/s00167-012-2095-2	**SR**	"Short-term, low-dose use of NSAIDs and COX-2 inhibitors does not appear to have a detrimental effect following soft tissue injury, but is inhibitory in cases involving bony healing….Clinically, the prudent use of anti-inflammatory medications following sports medicine injuries and surgeries appears to be a reasonable option in clinical practice unless bone healing is required."	**MY**
The effects of ibuprofen on muscle hypertrophy, strength, and soreness during resistance training. Krentz et al. *Appl Physiol Nutr Metab* 2008;33:470-75.	**RDBPCT**	Ibuprofen did not impair muscle hypertrophy or strength in young men and women after resistance training.	**Y**
A COX-2 inhibitor reduces muscle soreness, but does not influence recovery and adaptation after eccentric exercise. Paulsen et al. *Scan J Med Sci Sports* 2010;20:e195-207.	**DBPCT**	Subjects who took celecoxib had less soreness than the placebo group, but no difference in serum creatine kinase levels or tissue levels of radiolabled leukocytes (WBCs), monocytes, macrophages or satellite cells.	**Y**
Influence of acetaminophen and ibuprofen on in vivo patellar tendon adaptations to knee extensor resistance exercise in older adults. Carroll CC et al. *J Appl Physiol* 2011;111:508-15.	**RDBPCT**	Patellar tendon anatomical and biophysical properties were assessed with MRI and ultrasound coupled with force measurements before and after training in older adults training with knee extensor exercises. Patellar cross-sectional area (CSA) was unchanged in the placebo and ibuprofen groups and increased in the acetaminophen group. However, tendon deformation and strain, while unaffected except in the placebo and ibuprofen groups, increased in the acetaminophen group. No long-term practical outcome measures were assessed.	**MY (Ibuprof)** **MN (Acet)**

CITATION	STUDY TYPE	CONCLUSIONS	NSAIDs: Y,N,M
Nonsteroidal anti-inflammatory drug or glucosamine reduced pain and improved muscle strength with resistance training in a randomized controlled trial of knee osteoarthritis patients. Peterson SG et al. *Arch Phys Med Rehabil* 2011;92:1185-93.	**DBRCT**	36 men and women with knee osteoarthritis, 50-70 yo, were randomly assigned to ibuprofen, glucosamine or placebo during 12 weeks of quad training. The authors report that "In patients with knee OA, NSAID or glucosamine administration during a 12-week strength-training programdid not improve muscle mass gain, but improved maximal muscle strength gain in comparison with treatment with placebo. However, we do not find that the benefits are large enough to justify taking NSAIDs or glucosamine."	**MY**

TABLE 2: HUMAN STUDIES OF CRYOTHERAPY. DB=double blind. R=randomized. PC=placebo-controlled. RCT=randomized controlled trial. CxT= crossover trial. MA = meta-analysis.For information on the recommendation assignments in the right-hand column, see the Appendix Notes.

CITATION	STUDY TYPE	CONCLUSIONS	LOCAL CRYOTX: Y,N,M
1990s			
Various treatment techniques on signs and symptoms of delayed onset muscle soreness. Gulick DT et al. *J Athlet Train* 1996;31(2):145-52.	**RCT**	The authors report no benefit of an NSAID (oxaprozin), ice, stretching, high velocity concentric exercise, or sublingual or topical ***A. montana*** extract on DOMS induced by eccentric forearm contractions. No long-term practically relevant outcomes were assessed.	**N**
Effect of cryotherapy on muscle soreness and strength following eccentric exercise. Paddon-Jones DJ, Quigly BM. *Int J Sports Med* 1997; 18(8): 588-93.	**CT**	After performing 64 eccentric elbow flexions with each arm, 8 resistance trained males did five 20 minute immersions in a cold-water bath (1 deg C) interspersed with 60 minute rests. No significant difference between cryo-treated or control arms were noted for soreness, limb volume, isometric torque, isokinetic torque, or any other variable. No long-term assay of adaptive response was undertaken.	**MN**
2000s			
The use of ice in the treatment of acute soft-tissue injury: a systematic review of randomized controlled trials. Bleakley et al. *Am J Sports Med* 2004; 32(1)251-61	**MA**	Analysis of twenty-two studies meeting inclusion criteria yielded marginal evidence that ice plus exercise was most effective after acute ankle injury or surgery. Ice appeared to add little to compression, but this finding was restricted to hospitalized (post-operative) patients. Data on ice after closed soft-tissue injury was sparse. "Many more high-quality trials are needed."	**MY**
Ice-water immersion and delayed-onset muscle soreness: a randomised controlled trial. Sellwood et al. *Br J Sports Med* 2007;41:392-7.	**DBPCRT**	"The protocol of ***ice-water immersion**** used in this study was innefectual in minimising markers of DOMS in untrained individuals.This study challenges the use of this intervention as a recovery strategy by athletes." ***The study did not address local cryotherapy*** for injury or DOMS.	**MN***
Efficacy of cold gel for soft tissue injuries: a prospective randomized double-blinded trial. Airaksenen, et al. *Am J Sports Med* 2003;31(5)680-4.	**DBPCRT**	Cold gel therapy was safe and effective at reducing pain, compared to placebo, when applied to patients with sports-related soft-tissue injuries.	**Y**
Does cryotherapy improve outcomes with soft tissue injury? Hubbard and Denegar. *J Athlet Training* 2004;39(3):278-79.	**SR**	A systematic review of 22 RCTs, all of relatively low quality, suggested that cryotherapy was effective in reducing pain. Its effectiveness relative to other therapies and its impact on patient-oriented outcomes remains somewhat unclear.	**MY**

CITATION	STUDY TYPE	CONCLUSIONS	LOCAL CRYOTX: Y,N,M
Ice therapy: how good is the evidence? MacAuley DC. *Int J Sports Med* 2001; 22(5):379-84.	**SR**	This systematic review suggests that intermittent application of ice is effective, but notes decreased motor function and reflex activity after ice is applied.	**M**
The efficcy of ice massage in the treatment of exercise-induced muscle damage. Howatson G, et al. *Scand J. Med Sci Sports* 2005;15:416-422.	**PCCT**	Compared to a sham ultrasound therapy (the placebo) ice demonstrated no difference in reduction of discomfort, indirect serum markers of muscle damage (CK, Mb), or enhancement of function. No long-term outcome variables were assessed.	**MY**
Is ice right? Does cryotherapy improve outcome for acute soft tissue injury. Collins NC, *Emerg Med Journal* 2008;25:65-68.	**SR, sorta.**	This implicit review of both human and animal studies concluded—contrary to its own findings—that the literature contains insufficient evidence to suggest that cryotherapy is useful. See **detailed analysis** in the main body of the article.	**N**
The effects of various therapeutic measures on shoulder strength and muscle soreness after baseball pitching. Yanagisawa O, Miyanaga Y, Shiraki H et al. *J Sports Med Phys Fitness* 2003; 43(2):189-201.	**RCT**	Participants were randomized to one of 4 groups after throwing 98 pitches: ice (IT), light exercise (LSE), ice + light exercise (ILSE), and control (CON). The investigators report that both IT and ILSE had a positive effect, and that ILSE (ice + light exercise) was the optimal therapy.	**Y**
2010s			
A comparison of topical menthol to ice on pain, evoked tetanic and voluntary force during delayed onset muscle soreness. Johar et al. *Int J Sports Phys Ther* 2012;7(3):314-22.	**RT**	A topical menthol preparation displayed better analgesia and permitted greater force generation than ice. No placebo (non-treatment) group was incorporated into the study, so we know nothing about how these two therapies compared with no therapy at all. Investigators were blinded, but obviously patients could not be. No long-term end-points were studied.	**M**