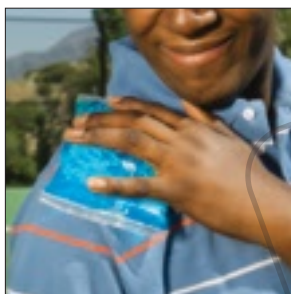


Sean N. Martin, DO  
Christopher P. Paulson, MD  
Eglin Air Force Base Family  
Medicine Residency, Eglin Air  
Force Base, Fla

William Nichols, MLS  
Eglin Air Force Base, Fla



### FAST TRACK

## Cryotherapy is better than heat for initial treatment of acute muscle strain

# Does heat or cold work better for acute muscle strain?

### Evidence-based answer

Cryotherapy is better than heat for treating acute muscle strain (strength of recommendation [SOR]: **C**, consensus, usual practice, and expert opinion).

Insufficient patient-oriented evidence exists regarding use of heat to treat acute soft-tissue injuries.

### Evidence summary

A comprehensive review of the literature revealed no studies that compare heat and cryotherapy to treat acute soft-tissue injury. Well-designed human trials of general management of acute soft-tissue injury are rare.<sup>1</sup>

Cryotherapy has been the recommended initial treatment for muscle strain for more than 30 years, based generally on expert opinion and physiological models, not clinical trials.<sup>2</sup> Theoretically, cryotherapy controls hemorrhage and tissue edema, whereas heat enhances the inflammatory response.<sup>2</sup>

### One human RCT and animal studies find benefits from cold

A 2007 review evaluated 66 publications and found only 1 randomized controlled trial conducted on humans.<sup>3</sup> The intervention in this trial involved applying cold gel 4 times a day for the first 14 days after the injury. The control group received a room-temperature gel application; neither group was aware of the temperature differential.

The study found significant reduction in pain at rest, pain with movement, and functional disability at intervals of 7, 14,

and 28 days postinjury ( $P < .001$ ) among patients receiving cold-gel applications. Patients receiving cold-gel treatment also reported increased satisfaction with treatment compared with the controls. At 28 days, cold-gel treatment patients scored 71 on a 100-point satisfaction scale compared with 44 for controls ( $P < .001$ ).<sup>3</sup> Inconclusive results or significant design flaws limited the validity of all other trials cited in this review.<sup>3</sup>

Laboratory studies on rats have also demonstrated beneficial effects of cryotherapy after simulated soft-tissue injuries.<sup>4,5</sup> One study cited a significant reduction in inflammatory cells, based on histologic examination, in 43 rats between 6 and 24 hours after trauma.<sup>4</sup> A second study of 21 rats showed improvement in associated physiological components with cryotherapy, but no statistically significant improvement in edema.<sup>5</sup>

### How cold is too cold?

Most authorities recommend empiric treatment with cryotherapy during the acute inflammatory phase—the first 24 to 48 hours after injury.<sup>6</sup> Although not rigorously studied, some sources recommend applying cold to the involved muscle for

**NSAIDs, Aspirin, and Warfarin**- Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of case-control and cohort design have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. These studies have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when Pristiq is initiated or discontinued. **Ethanol**- A clinical study has shown that desvenlafaxine does not increase the impairment of mental and motor skills caused by ethanol. However, as with all CNS-active drugs, patients should be advised to avoid alcohol consumption while taking Pristiq. **Potential for Other Drugs to Affect Desvenlafaxine**-Inhibitors of CYP3A4 (ketoconazole)- CYP3A4 is a minor pathway for the metabolism of Pristiq. Concomitant use of Pristiq with potent inhibitors of CYP3A4 may result in higher concentrations of Pristiq. **Inhibitors of other CYP enzymes**- Based on *in vitro* data, drugs that inhibit CYP isozymes 1A1, 1A2, 2A6, 2D6, 2C8, 2C9, 2C19, and 2E1 are not expected to have significant impact on the pharmacokinetic profile of Pristiq. **Potential for Desvenlafaxine to Affect Other Drugs**- Drugs metabolized by CYP2D6 (desipramine)- *In vitro* studies showed minimal inhibitory effect of desvenlafaxine on CYP2D6. Clinical studies have shown that desvenlafaxine does not have a clinically relevant effect on CYP2D6 metabolism at the dose of 100 mg daily. Concomitant use of desvenlafaxine with a drug metabolized by CYP2D6 can result in higher concentrations of that drug. **Drugs metabolized by CYP3A4 (midazolam)**- *In vitro*, desvenlafaxine does not inhibit or induce the CYP3A4 isozyme. Concomitant use of Pristiq with a drug metabolized by CYP3A4 can result in lower exposures to that drug. **Drugs metabolized by CYP1A2, 2A6, 2C8, 2C9, and 2C19**- *In vitro*, desvenlafaxine does not inhibit CYP1A2, 2A6, 2C8, 2C9, and 2C19 isozymes and would not be expected to affect the pharmacokinetics of drugs that are metabolized by these CYP isozymes. **P-glycoprotein Transporter**- *In vitro*, desvenlafaxine is not a substrate or an inhibitor for the P-glycoprotein transporter. The pharmacokinetics of Pristiq are unlikely to be affected by drugs that inhibit the P-glycoprotein transporter, and desvenlafaxine is not likely to affect the pharmacokinetics of drugs that are substrates of the P-glycoprotein transporter. **Electroconvulsive Therapy**-There are no clinical data establishing the risks and/or benefits of electroconvulsive therapy combined with Pristiq treatment. **USE IN SPECIFIC POPULATIONS: Pregnancy**- Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. **Teratogenic effects** - Pregnancy Category C- There are no adequate and well-controlled studies of Pristiq in pregnant women. Therefore, Pristiq should be used during pregnancy only if the potential benefits justify the potential risks. **Non-teratogenic effects**- Neonates exposed to SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), or SSRIs (Selective Serotonin Reuptake Inhibitors), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome [see *Warnings and Precautions* (5.2)]. When treating a pregnant woman with Pristiq during the third trimester, the physician should carefully consider the potential risks and benefits of treatment [see *Dosage and Administration* (2.2)]. **Labor and Delivery**- The effect of Pristiq on labor and delivery in humans is unknown. Pristiq should be used during labor and delivery only if the potential benefits justify the potential risks. **Nursing Mothers**- Desvenlafaxine (O-desmethylenlafaxine) is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Pristiq, a decision should be made whether or not to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Only administer Pristiq to breastfeeding women if the expected benefits outweigh any possible risk. **Pediatric Use**- Safety and effectiveness in the pediatric population have not been established [see *Box Warning and Warnings and Precautions* (5.1)]. Anyone considering the use of Pristiq in a child or adolescent must balance the potential risks with the clinical need. **Geriatric Use**-Of the 3,292 patients in clinical studies with Pristiq, 5% were 65 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out. For elderly patients, possible reduced renal clearance of desvenlafaxine should be considered when determining dose [see *Dosage and Administration* (2.2) and *Clinical Pharmacology* (12.6) in the full prescribing information]. **Renal Impairment**- In subjects with renal impairment the clearance of Pristiq was decreased. In subjects with severe renal impairment (24-hr CrCl < 30 mL/min) and end-stage renal disease, elimination half-lives were significantly prolonged, increasing exposures to Pristiq; therefore, dosage adjustment is recommended in these patients [see *Dosage and Administration* (2.2) and *Clinical Pharmacology* (12.6) in the full prescribing information]. **Hepatic Impairment**-The mean  $t_{1/2}$  changed from approximately 10 hours in healthy subjects and subjects with mild hepatic impairment to 13 and 14 hours in moderate and severe hepatic impairment, respectively. No adjustment in starting dosage is necessary for patients with hepatic impairment.

**OVERDOSAGE: Human Experience with Overdosage**- There is limited clinical experience with desvenlafaxine succinate overdosage in humans. In premarketing clinical studies, no cases of fatal acute overdosage of desvenlafaxine were reported. The adverse reactions reported within 5 days of an overdose > 600 mg that were possibly related to Pristiq included headache, vomiting, agitation, dizziness, nausea, constipation, diarrhea, dry mouth, paresthesia, and tachycardia. Desvenlafaxine (Pristiq) is the major active metabolite of venlafaxine. Overdose experience reported with venlafaxine (the parent drug of Pristiq) is presented below; the identical information can be found in the *Overdosage* section of the venlafaxine package insert. In postmarketing experience, overdose with venlafaxine (the parent drug of Pristiq) has occurred predominantly in combination with alcohol and/or other drugs. The most commonly reported events in overdose include tachycardia, changes in level of consciousness (ranging from somnolence to coma), mydriasis, seizures, and vomiting. Electrocardiogram changes (e.g., prolongation of QT interval, bundle branch block, QRS prolongation), sinus and ventricular tachycardia, bradycardia, hypotension, rhabdomyolysis, vertigo, liver necrosis, serotonin syndrome, and death have been reported. Published retrospective studies report that venlafaxine overdosage may be associated with an increased risk of fatal outcomes compared to that observed with SSRI antidepressant products, but lower than that for tricyclic antidepressants. Epidemiological studies have shown that venlafaxine-treated patients have a higher pre-existing burden of suicide risk factors than SSRI-treated patients. The extent to which the finding of an increased risk of fatal outcomes can be attributed to the toxicity of venlafaxine in overdose, as opposed to some characteristic(s) of venlafaxine-treated patients, is not clear. Prescriptions for Pristiq should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose. **Management of Overdosage**-Treatment should consist of those general measures employed in the management of overdose with any SSRI/SNRI. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal should be administered. Induction of emesis is not recommended. Because of the moderate volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for desvenlafaxine are known. In managing an overdose, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the Physicians Desk Reference (PDR).

This brief summary is based on Pristiq Prescribing Information W10529C002, revised April 2008.

the first 4 hours after injury at intervals of 10 to 20 minutes every 30 to 60 minutes.<sup>6</sup>

The literature focuses more on the optimal temperature for cryotherapy than on the duration and frequency of therapy.<sup>7</sup> Temperatures below 15° to 25°C may actually result in vasodilatation rather than vasoconstriction.<sup>7</sup>

## Evidence for heat is limited

A 2006 Cochrane review that addressed treatment of lower back muscular strain, not soft-tissue injuries in general, found moderate evidence that heat therapy reduces pain by 17% and disability in the acute setting ( $P=.001$ ).<sup>8</sup> The review also cited 2 head-to-head trials that compared heat and cryotherapy; however, the study designs were poor and the results were contradictory.<sup>8</sup>

## Recommendations

Authoritative textbooks consistently recommend applying ice for initial treatment of musculoskeletal and soft-tissue strains.<sup>9</sup> ■

## Acknowledgments

The opinions and assertions contained herein are the private views of the authors and not to be construed as official or as reflecting the views of the United States Air Force Medical Service or the United States Air Force at large.

## References

- Hubbard TJ, Denegar CR. Does cryotherapy improve outcomes with soft tissue injury? *J Athl Train*. 2004;39:278-279.
- Kalenak A, Medlar CE, Fleagle SB, Hochberg WJ. Athletic injuries: heat vs cold. *Am Fam Physician*. 1975;12:131-134.
- Collins NC. Is ice right? Does cryotherapy improve outcome for acute soft tissue injury? *Emerg Med J*. 2008;25:65-68.
- Hurme T, Rantanen J, Kalimo H. Effects of early cryotherapy in experimental skeletal muscle injury. *Scand J Med Sci Sports*. 1993;3:46-51.
- Schaser K, Disch AC, Stover, JF, et al. Prolonged superficial local cryotherapy attenuates microcirculatory impairment, regional inflammation, and muscle necrosis after closed soft tissue injury in rats. *Am J Sports Med*. 2007;35:93-102.
- Kellett J. Acute soft tissue injuries—a review of the literature. *Med Sci Sports Exerc*. 1986;18:489-500.
- McMaster WC, Liddle S, Waugh TR. Laboratory evaluation of various cold therapy modalities. *Am J Sports Med*. 1978;6:291-294.
- French SD, Cameron M, Walker BF, Reggars JW, Esterman AJ. A Cochrane review of superficial heat or cold for low back pain. *Spine*. 2006;31:998-1006.
- Griffin LY. *Essentials of Musculoskeletal Care*. 3rd ed. Rosemont, Ill: American Academy of Orthopaedic Surgeons; 2005:134.