

Nocturnal Cramps and Introduction of a Novel Topical Therapy

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Review of Pathophysiology, Etiology, and Therapeutic Approaches to Nocturnal Cramps**Authors**

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ABSTRACT

Nocturnal leg and foot cramps are reported by more than half of the U.S. population over age 50, with varying frequency, but of those reporting the ailment, up to 20% experience nightly episodes, with attendant sleep disruption which can exacerbate other medical conditions. While there is a widespread belief, even among many clinicians, that hypohydration and electrolyte depletion from exercise are the primary causes of leg cramps, there is strong evidence that neither of these is a primary factor in either exercise-induced or nocturnal muscle cramping. Many commonly used prescription drugs have an impact on muscle physiology and can cause or exacerbate cramps. There is good evidence that the physiological and neurological impact of muscle fatigue, and associated changes in muscle biochemistry, including lactic acid accumulation, are one key factor in nocturnal cramping. A new topical approach to the condition has shown early evidence of its potential to address nocturnal cramping, due to its demonstrated ability to increase oxygen availability and reduce lactic acid levels in muscle tissue.

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Nocturnal cramps represent a common medical challenge in patients age 50 and up, with a higher incidence as individuals age⁽¹⁾. Up to 60% of adults over 50 years of age report a history of night cramps, usually in the calf or thigh, but sometimes the foot. Up to 20% of those experiencing nocturnal cramps have nightly episodes, which can be severe enough to warrant medical treatment.⁽²⁾ While nocturnal cramping is not as common in younger populations, 7% of children in one study had experienced at least one cramping episode within the prior 12 months.⁽³⁾

Nocturnal cramping episodes vary in severity, but for many patients the experience is both painful and debilitating. While the average duration of a nocturnal cramp is nine minutes, the initial event is frequently followed by recurrent episodes and residual pain that may last for up to one week.⁽⁴⁾ For many older patients, nocturnal cramping is a nightly experience, and the attendant sleep disruption can exacerbate other medical conditions, including a negative impact on immune response, cognitive ability, and cardiovascular health.^(5,6,7)

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Physiopathology Considerations:

Most cases of nocturnal cramping are considered idiopathic. Several myopathic, neurological, and metabolic causes have been suggested⁽²⁾, but none have been firmly established. Some studies suggest muscle fatigue can be a primary cause of nocturnal cramping. For example, studies show a correlation between higher-than-normal exercise intensity and onset of nocturnal cramping in endurance athletes.⁽⁸⁻⁹⁾

While there remains a common perception that dehydration and electrolyte depletion can be factors in both exercise-associated muscle cramps (EAMC) and nocturnal cramping, several studies have demonstrated that these are not likely causes. Among patients with nonalcoholic cirrhosis, one study demonstrated that leg cramps are not related to changes in the levels of creatinine, calcium, magnesium, sodium, potassium, zinc, glucose, alanine transaminase, total bilirubin, or albumin⁽¹⁰⁾. Because of the prevalence of nocturnal cramps in patients with some neurological disorders, such as Parkinson's, nerve dysfunction is also suspected in the etiology of cramping⁽¹¹⁾. But in one study in veterans' hospitals, of all patients exhibiting recurrent nocturnal cramping, 75% also had peripheral vascular disease and 62% had coronary artery disease, suggesting that hypoxia could also be a factor in the condition.⁽¹²⁾

At least one study suggests an evolutionary cause for cramping. This "squatting" hypothesis suggests that the modern habit of sitting at rest or at toilet, rather than squatting like our ancestors, leads to muscle and tendon shortening due to inadequate

stretching, and puts the individual at risk for developing leg cramps.⁽¹³⁾ It has also been proposed that leg cramps occur when a maximally contracted muscle is stimulated, thus shortening the muscle beyond physiological tolerance. This theory suggests that in the nocturnal recumbent position, the foot is passively in plantar flexion and the calf muscle fibers are already maximally shortened, so uninhibited nerve stimulation leads to cramping.⁽¹⁴⁾

It is also unclear why cramps are as painful as typically reported, but this may be because the demands of the overactive muscle greatly exceed metabolic supply, causing a rapid relative ischemia and accumulation of metabolites.⁽²⁾

It is known that nocturnal cramping is more prevalent in pregnant women (and slightly more prevalent, overall, in women versus men), as well as patients with vascular problems from diabetes, cirrhosis, lumbar canal stenosis, neuropathy, myopathy, motor neuron disease, and those undergoing hemodialysis. However, many older patients develop daily severe nocturnal cramps and have none of these underlying conditions, and are otherwise healthy.

It is also known, through neurological and electromyographic studies, that all leg and foot cramps initiate from the spontaneous firing of groups of anterior horn cells adjacent to the spinal nerve roots followed by contraction of motor units in the axon at the rate of approximately 300 times per second⁽¹⁵⁾, a rate considerably higher than normal muscle contraction. Since the normal relaxation of muscles after contraction results from the action of adenosine triphosphate (ATP) on the myosin heads to

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properly detach from actin filaments, it is possible that some dysfunction in ATP muscle metabolism, or a temporary shortage or lack of ATP, may also contribute to extended cramping events, but further studies of this mechanism are needed.

Medication-Related Etiologies:

Many drugs used for therapeutic interventions can cause unexpected toxicity in muscle tissue, often leading to significant morbidity and disability. Myotoxic drugs can cause myopathies through a variety of mechanisms by directly affecting muscle organelles such as mitochondria, lysosomes, and myofibrillar proteins; altering muscle antigens and generating an immunologic or inflammatory reaction; or by disturbing the electrolyte or nutritional balance, which can subsequently impact muscle function. Muscle tissue seems particularly susceptible to drug-related injury because of its mass, high blood flow, and mitochondrial energy metabolism²⁷. The drugs showing the strongest correlation to cramping are intravenous iron, conjugated estrogens, such as reloxifen (Evista), naproxen, and teriparatide (Forteo). An apparent increased incidence of nocturnal cramping has also been reported with clonazepam (Klonopin), citalopram (Celexa), celecoxib, gabapentin, statins, diuretics, long-acting beta agonists, and zolpidem (Ambien), which ironically is frequently prescribed for the insomnia associated with nocturnal cramping. Twenty-one of the fifty most commonly prescribed medications list muscles cramps and spasms as a side effect.

Therapeutic Considerations:

There is little research on how treating underlying medical conditions impacts the symptom of nocturnal cramps. Nonetheless, the occurrence of repeated nocturnal cramping episodes provides an important opportunity for clinicians to diagnose and treat potentially underlying conditions such as venous insufficiency, peripheral vascular disease, and peripheral neuropathy.

In terms of strictly treating the symptoms of nocturnal cramping themselves, current guidelines from the American Academy of Neurology (AAN) identify a few candidates for treating the condition, including a calcium channel blocker, diltiazem (Cardizem) and vitamin B complex, while at the same time indicating that evidence for their efficacy is weak. While many physicians continue to prescribe either gabapentin (Neurotin) or magnesium supplements, the AAN's position is that available evidence fails to support their utility for nocturnal leg cramps in older patients⁽¹⁶⁾. The American Academy of Family Physicians adds the muscle relaxant, carisoprol, to the above list, and while there is some weak evidence for its efficacy for cramps, the use of a potentially habit-forming drug that is known to impair reaction time and other mental processes makes its use for this condition problematic. There is some evidence that magnesium supplementation is helpful in preventing nocturnal cramps in pregnant women, which could reflect the hypokalemia that frequently accompanies pregnancy.⁽¹⁷⁾

Looking at non-pharmaceutical approaches, no current treatments for leg cramps have been proven both safe and effective. Passive stretching and deep tissue massage are

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harmless, patient-controlled maneuvers that are sometimes suggested despite limited proof of effectiveness. One randomized study of patients discontinuing quinine showed no effect from stretching; however, gastrocnemius stretching has long been recommended to prevent leg cramps. Forceful stretching also is thought to inhibit and relieve an acute cramp, and the mechanism of dorsiflexing the foot may be helpful, and some report the physical compression of the cramped muscle with a solid flat object during the acute phase provides more rapid resolution. Anecdotal evidence suggests that mild exercise, such as a few minutes on a stationary bicycle or treadmill before bedtime, can relieve nocturnal leg cramps. If muscle fatigue is a cause, graded exercise and/or physical therapy might be of benefit for some patients, particularly as a longer term therapy.⁽²⁾

There are also home remedies for cramps that some patients feel are effective, as evidenced by a simple Google search. Apple cider vinegar, pickle juice, a bar of soap (Irish Spring is often mentioned) under the sheets, cream of tartar, a golden rod stems and flowers in tea, black strap molasses, mustard, a copper ring on the first digit of the cramping leg, each have their proponents. While one study indicated rapid relief of electrically-induced cramping in hypohydrated adults through the administration of pickle juice, the relief obtained could not have reflected any electrolyte effect, because its impact was much more rapid than can be explained by increased bioavailability of sodium or any other substance in the juice⁽¹⁸⁾. Another study which measured plasma electrolytes,

osmolality and fluid volume showed no change during a 60 minute interval after ingestion of pickle juice.⁽¹⁹⁾ Therefore, it has been hypothesized that the strong taste of the juice produces a neurally mediated reflex that originates in the oropharyngeal region and acts to inhibit the firing of alpha motor neurons of the cramping muscle. Subsequent studies have shown that neither hypohydration nor a drop in electrolytes impacts the incidence and frequency of cramping⁽⁹⁻¹⁰⁾, this neurological effect could be the reason why athletes, in particular, are likely to feel that pickle juice is beneficial.

Quinine, Past and Present:

The medication most prescribed for nocturnal cramping during the 20th century has been quinine, a naturally occurring alkaloid found in the bark of the *cinchona officinalis* plant. Quinine was also the primary treatment for malaria, prior to the development of synthetic drugs for the disease. In 1994, based on safety concerns, the FDA ordered the removal of all over-the-counter cramping products containing quinine from the U. S. market. Qulaquin, the sole remaining prescribed quinine-containing prescription product in the U.S., was approved by the FDA solely for the treatment of uncomplicated malaria in 2005, under the orphan drug rule. In 2006, 324,000 patients were prescribed Qulaquin, off-label for the treatment of painful muscle cramps and spasms. In 2008 the FDA issued a warning of hematologic events including death with Qulaquin. In 2010 the FDA issued a REMS (Risk Evaluation and Mitigation Strategy) for the manufacturers of all quinine containing substances

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resulting in significantly reduced prescribing of Qulaquin for nocturnal cramps. In a research letter entitled “Association Between Long-term Quinine Exposure and All-Cause Mortality” published in the May 2017 edition of JAMA, authors Laurence Fardet, MD, PhD; Irwin Nazareth, MD and PhD; Irene Petersen, PhD reported that even small amounts of quinine exposure over time can lead to serious hematologic events, as many patients drink tonic water and other quinine containing substances to manage cramps and spasms²⁸.

Quinine presents an even greater risk for pregnant patients, many of whom suffer from persistent nocturnal cramping. Assessment in Germany, responsible for the preparation of expert reports and recommendations on food safety for that country, published its own warning about the safety of quinine-containing beverages, such as tonic water, for pregnant women. While the amounts of quinine allowed by the German and U.S. regulatory agencies are low, the German agency pointed to an incident where the offspring of a pregnant woman, who had consumed up to a liter a day of tonic water during her pregnancy, displayed significant health issues. They also noted other pregnant women who reported an apparent hypersensitivity to quinine, which manifested itself as tinnitus and issues with vision. Out of an abundance of caution, they recommend that all pregnant women avoid beverages containing even small amounts of quinine (in both the U.S. and Germany, the maximum amount of quinine allowed in beverages is 85 ppm)⁽²⁵⁾. Quinine in larger (standard adult) doses is certainly contraindicated for pregnant women, as both photosensitivity and

deafness have been reported in neonates of mothers taking the drug.⁽²⁶⁾

Despite the numerous warnings and actions taken by the FDA, there is at least one oral homeopathic remedy containing quinine for leg cramps on the shelf in drug stores and homeopathic vendors throughout the U.S. The ingredient list for this product includes ‘*cinchona officinalis*’, the primary species of cinchona with the highest quinine content, at 3-8% of total weight. However, information on the manufacturer’s website states that while the FDA does not allow the use of quinine in over-the-counter products, their product qualifies for its inclusion under the FDA’s “microdosing” allowance for homeopathic remedies, and that the amount of quinine in one dose of the product is 4000 times less than the amount in a 6 ounce serving of tonic water.

In addition to reduced access for prescription quinine, the muscle relaxant and anti-spasmodic class of medications have been added to the BEERS list. In 1991, Dr. Mark Beers and colleagues published a methods paper describing the development of a consensus list of medicines considered to be inappropriate for long-term care facility residents.³⁰ The American Geriatrics Society Beers Criteria or “Beers list” is now in its fifth permutation. It is intended for use by clinicians in outpatient as well as inpatient settings (but not hospice or palliative care) to improve the care of patients 65 years of age and older. It includes medications that should be avoided, and medications that should be used with extra caution, either in all elderly or in certain populations. New to the latest version is a list of potentially harmful drug-

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drug interactions in seniors, as well as a list of medications that may need to be avoided or their dosage reduced based on renal function. The most common brand names of products added to the Beers List are Soma, Flexeril and Skelaxin, because of their effects on cognition and physical dependency risks, as well as the fact that psychoactive agents can be interpreted as chemical restraints in the long term care setting.

Future and Growing Therapeutic Considerations:

With off-label use of quinine for leg cramps declining, and no other effective alternative identified, it is important to consider again what is known about the pathogenesis of this condition. Given the breadth of evidence that has been published on the causes of leg cramps, what is the consensus? With both dehydration and electrolyte depletion having been shown in several studies to not be causative, the latest research has focused on muscle fatigue, with possible lactic acid accumulation, as the most likely cause of nocturnal cramping. Accordingly, conditions that impact circulation and oxygen delivery to muscles, as noted above, increase the incidence of nocturnal cramps. One of the strongest empirical arguments for this hypothesis is that nocturnal cramps occur primarily in the muscles that have been most heavily used during the day, usually the legs, even in the elderly. Lack of optimal circulation and oxygenation, coupled with other physical conditions that impair oxygenation of neural and muscle tissue, likely are contributory, but even in healthy patients, night cramps are far more

likely to occur in ambulatory than in non-ambulatory patients. The physiological and neurological impact of muscle fatigue, and associated changes in muscle biochemistry, including lactic acid accumulation, are now thought to play a major role in nocturnal cramping.

Recent research at the University of Louisiana Lafayette's Vascular Research Laboratory and at the Applied Science and Performance Institute involving studies of a new topical product, Theraworx Relief™ (Avadim Technologies, Inc., Asheville NC), shows great promise for both prevention of cramps, and rapid relief of acute cramping episodes, support this latest hypothesis on the causes of cramps. The entire mechanism of action of Theraworx Relief™ is not fully understood, but the proposed mechanism is a vascular profusion effect causing an increase in deep tissue blood flow. Theraworx Relief™ increased deep tissue blood flow compared to placebo as detected by Near Infrared Spectroscopy N.I.R.S. a non-invasive diagnostic used during open-heart surgery to monitor intracranial blood flow³¹. Secondly, in a study conducted at the Applied Science and Performance Institute, Theraworx Relief™ was shown to inhibit the accumulation of serum lactate as compared to placebo during exhaustive exercise³². During activity, the accumulation of lactic acid and carbon dioxide will reduce cellular pH as well as interstitial pH due to acid efflux from the muscle cells. The changes in interstitial pH during muscle activity could be an important signal in the regulation of blood flow²⁹. Most recently, in a double blinded placebo controlled trial conducted at the American Sport and Spine Institute, Theraworx

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Relief™ was shown to significantly reduce the incidence and severity of nocturnal cramps and spasms in patients identified as having chronic nocturnal cramps and spasms disorder with three or more episodes per week. These patients also showed improvements in sleep quality, daytime function and quality of life. With the reduced access to prescription medication and the risks associated with other over the counter options having a safe and effective topical non-systemic option has broad utility.

Another topical approach uses instrumental soft tissue mobilization and deep friction

massage which may benefit in adhesive and contracture related conditions. Deep friction massage with instrument-assisted soft tissue mobilization (IASTM) as used in such interventions as Graston Technique®, ASTYM®, or guasha has become increasingly popular in physical therapy practice^{33,34}. IASTM reportedly provides strong afferent stimulation and reorganization of collagen, as well as an increase in microcirculation. This technique has been shown to disrupt rebound and cramp prone conditions.

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