AN EXPLORATION OF NEW THERAPEUTIC OPTIONS
FOR NOCTURNAL LEG CRAMPS

by

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Abstract

THE PROBLEM: Rest cramps (also known as nocturnal leg cramps) are painful muscle contractions, typically in the legs or feet, that occur during prolonged rest - most often while in bed at night. Although common in older adults, safe and effective treatment options are lacking.

OPPORTUNITY AND METHOD #1: Magnesium supplements are readily available and widely marketed to consumers for cramp prophylaxis. However the efficacy of magnesium for this indication is unclear and existing clinical trials are limited by the well recognized poor bioavailability of oral magnesium. To better assess the potential efficacy of magnesium in cramp prophylaxis I conducted a (N=46) double-blind, placebo-controlled RCT on community-dwelling rest cramp sufferers to determine whether a more reliable delivery method (5 consecutive days intravenous infusion of 20 mmol magnesium sulfate) could reduce the frequency of rest cramps. I additionally determined whether the response to treatment varied with the extent to which infused magnesium was retained (as measured by 24-hr urinary magnesium excretion) and performed a Cochrane Systematic Literature Review to find and synthesize all relevant randomised trials.

OPPORTUNITY AND METHOD #2: Anecdotal evidence suggested several medications might promote muscle cramping. If true, cramp sufferers using these drugs could potentially gain cramp relief through therapeutic substitution or reduction of these agents. To investigate this potential cramp link I searched BC Ministry of Health databases containing diagnostic and prescribing information on the 4.2 million residents of British Columbia to determine,
using sequence symmetry methods, whether quinine starts (i.e. new cramp treatment) increased in the year following introduction of the three most commonly prescribed medications with a link to muscle cramps (diuretics, statins and inhaled long-acting beta2-agonists).

CONCLUSION: Although its role in pregnancy-associated rest cramps remains unclear, magnesium supplementation does not meaningfully reduce the frequency of rest cramps in older adults. Alternatively, for some cramp sufferers, reduction or discontinuation of select cramp promoting medications (inhaled long-acting beta2-agonists, potassium-sparing diuretics and thiazides) may be a useful therapeutic maneuver. Over a 13 year period 60.3% of quinine users (cramp sufferers) received at least one of these medications. In contrast, statin and loop-diuretic cramp associations were clinically unimportant.
Preface

With the exception of the assistance of Dr. C. Laird Birmingham in helping to design the magnesium infusion RCT, Robert McCollom who performed the randomization and maintained the blind of the magnesium RCT, the Pharmacoepidemiology Group (Dr. Colin Dormuth, Greg Carney and Richard Morrow) who helped me access and orient to using the Ministry of Health data, and the general guidance offered by my supervisor, Dr. Karim Khan, and my supervisory committee (Dr.’s Khan and Birmingham and Dr. Maureen Ashe), I was solely responsible for the conception, design, conducting, analyzing and writing up of all research in this dissertation. This includes the writing of all grant applications, patient consents, protocols, ethics applications, Health Canada clinical trial application and manuscripts for publication; the production of all study materials (e.g. cramp diaries, pamphlets, advertisements); the performing of all recruitment and clinical trial coordination (including all patient interviews and examinations); and the performing of all data analysis and all custom SAS programming used to analyze Ministry of Health Data.

The magnesium RCT and quinine pharmacoepidemiologic study both received approvals from the University of British Columbia Clinical Research Ethics Board (CREB# H06-03345 and CREB# H11-00670). The magnesium RCT also received Health Canada approval (No Objection Letter #9427-R1243-21C) to use IV magnesium outside of its approved indication.
Three publications resulted from the work described in this dissertation to date and include:


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In addition to my PhD Supervisory Committee (Dr. Karim Khan, Dr. Maureen Ashe, Dr. Laird Birmingham), I would also like to acknowledge the helpful comments and insights of my University Examiners (Dr. James McCormack, Dr. Robert Rangno), my External Examiner (Dr. Michael Kjaer) and the Chair of my examining committee (Dr. Kellogg Booth).
Dedication

To Griffin and Cady

May you both find your passion.
Chapter 1: Introduction

1.1 Research Chronology

In the summer of 2005 I was, and had been for about 15 years, a full time family physician with a traditional office and hospital based practice in Richmond, BC. At that time, several of my patients had been complaining of very bothersome nocturnal leg cramps and I had been looking for alternatives to quinine - which these patients had not found effective. While pursuing solutions for these patients I came to appreciate (as will be outlined in greater detail towards the end of this chapter) that while oral magnesium was being marketed to patients over the counter for cramp prophylaxis, evidence to support this use was conflicting. Additionally, even if magnesium replacement had potential efficacy, the observed effectiveness of oral magnesium replacement would presumably be hampered by the well recognized poor bioavailability of oral magnesium supplements.

As fate would have it, at the same time as I was appreciating this gap in the literature, the Vancouver Coastal Health Research Institute initiated and advertised their first Team Grants competition. This competition enabled a novice researcher who was backed by an experienced mentor to apply for research funding to answer a clinical question. I decided to apply for this grant and I approached Dr. Laird Birmingham, a prominent local internist who is widely regarded as an expert on electrolyte disorders (including disorders of magnesium), about mentoring me for this competition. My proposed project was a cramp prophylaxis RCT where the intervention was a series of intravenous infusions similar to the protocol used in our health authority to treat magnesium deficiency. I had felt that, with the better bioavailability of intravenous magnesium, this would be a more definitive trial. I was successful in this competition and was awarded a 2006 Team Grant in the spring of 2006.
Over the coming 8 months, while continuing to work full time in my family practice, I wrote the study protocols and applications necessary to obtain approvals from Health Canada to use magnesium off label; wrote the application to the UBC Clinical Research Ethics Board to gain ethics approval; wrote the study consent forms; created information pamphlets and posters for recruiting; created cramp diaries for patient recording and created all interview forms (for recruitment and exit interviews).

With all these materials complete, in Jan 2007 I began recruiting for my RCT by placing posters in the offices of 21 Richmond British Columbia family physicians. Since I needed the community to be aware of this trial, and since I had limited funds, I also wrote a description of the trial which I sent to local media. This resulted in interviews for the Richmond Review and Vancouver Sun newspapers, as well as a CBC radio interview (Almanac). These interviews substantially boosted enrolment, although I ultimately also needed to write advertisements for the trial which were placed in local newspapers. I conducted all interviews and examinations to determine patient eligibility as well as all exit interviews. All recruitment, magnesium infusion and follow-up occurred between Jan 2007 and Oct 2008.

During 2007 I also became aware of the clinical scholar program in the UBC Dept of Family Practice. This was a competition that offered financial support and mentorship in research methods to successful applicants. I applied to the program with the same project and was successful in gaining support for the period mid 2007 to mid 2009. Dr. Karim Khan was in charge of the Clinical Scholar program and provided me additional mentorship for the project during that time.
Coming to the realization that I had a passion for clinical research, and that I wanted to pursue it for the remainder of my career, I asked Dr. Khan in Jan 2008 if he would be willing to serve as my supervisor if I returned to UBC to pursue a PhD. Dr. Khan was willing and I submitted an application to the UBC Dept of Experimental Medicine which led to my entering my current PhD program in Sept 2008.

I continued to work part-time in my clinical practice while I took a variety of courses at UBC over a period of 2 years. This included the two required core courses in experimental medicine (which teach grant writing and presentation skills and provide an overview of research methods and current perspectives on disease etiology). I also took courses in Biostatistics and Clinical Trial Design and Analysis and I audited a course in Neurophysiology. In addition to these UBC courses I also took a course in how to perform systematic reviews provided by the Centre for Clinical Epidemiology and Evaluation (C2E2) at the Vancouver Coastal Health Research Institute.

During 2008 I had an idea for a related project and approached Dr. Colin Dormuth, a researcher who had experience with, and (at the time) access to, the linked BC Ministry of Health databases. I proposed to Dr. Dormuth to collaborate on a pharmacoepidemiologic exploration of BC Ministry of Health data that could substantiate anecdotal evidence (largely case reports) that certain commonly used medications were cramp promoting. I proposed doing this not by using diagnostic coding for muscle cramps (which I believed would be poorly documented in physician fee-for-service data) but by looking at new prescriptions for quinine – which would serve (given it is prescribed almost exclusively to treat nocturnal leg cramps) as a very specific marker for new or escalating cramp treatment. Dr. Dormuth liked the idea and suggested that I employ a method known as sequence symmetry. As a result I
learned this research method, wrote the protocol for data extraction, and data was obtained for me to work on by Dr. Dormuth’s research group at the end of 2008. During 2008 I also applied for, and was successful in obtaining, a CIHR PhD award in the area of research on aging based on these projects.

During 2009, in addition to taking courses, I performed the data analysis for the magnesium RCT and began learning to program in SAS. In 2010 I took courses, wrote and submitted the magnesium RCT manuscript for publication (accepted by the Journal of Gerontology Nov 2010) and wrote SAS code for the quinine pharmacoepidemiology project. During 2011, I completed analysis of the quinine data and wrote and submitted the resulting manuscript (published in the Archives of Internal Medicine in Dec 2011). In late 2011, I presented this work in Banff as a “distinguished presentation” at the North American Primary Care Research Groups annual meeting. In 2011, I also arranged to collaborate with a group of researchers with experience in meta-analysis on the Cochrane Systematic Review1 entitled “Magnesium for Skeletal Muscle Cramps”. This review permitted me to thoroughly integrate the literature on magnesium for the prophylaxis of skeletal muscle cramps with my own work on magnesium. I wrote the title application and subsequent protocol for this review – which was accepted for publication by the Cochrane Neuromuscular Diseases Working Group mid 2007. I subsequently worked on all elements of the full systematic review which I completed and submitted to Cochrane in January 2012 (where it is currently under editorial review). Since that time I have been working on this dissertation.
1.2 Overview of this Dissertation

Nocturnal leg cramps (also known as rest cramps) are a common and distressing problem in older adults for which current treatment options are inadequate. This body of work looks to improve clinical knowledge relevant to the treatment of rest cramps in two ways:

1. Evaluating the efficacy of a common non-prescription product marketed for cramp prophylaxis (oral magnesium supplements) – both by means of systematic literature review and by conducting a randomized controlled trial of magnesium prophylaxis given by a highly reliable delivery method (IV infusion).

2. Determining whether commonly used medications with anecdotal links to muscle cramping (diuretics, statins and inhaled long-acting beta2-agonists) associate with cramp treatment on a population level through the use of linked British Columbia Ministry of Health databases.

The remainder of this introduction will start by describing muscle cramps more generally and then give the reader a broad overview of the prevalence, differential diagnosis, etiology and treatment of the one particular cramp syndrome upon which this work is based – nocturnal leg cramps. At the end of this overview, more specific and detailed information will be provided related to the two questions my experimental work addresses. These two questions being:

1) Are magnesium supplements efficacious in providing rest cramp prophylaxis?
2) Do diuretics, statins or inhaled long-acting beta2-agonists promote muscle cramping?
1.3 Definition of Skeletal Muscle Cramp

Skeletal muscle cramps are sudden, involuntary, painful and palpable skeletal muscle contractions that can last anywhere from seconds to many minutes\(^2\). At times such cramps will respond acutely to stretch of the involved muscle\(^3\). They can occur in a variety of clinical settings and are often discussed in the context of those settings (e.g. pregnancy-associated muscle cramps or exercise-associated muscle cramps)\(^4\). The cramp itself, however, appears similar in each case and has a distinct electromyographic (EMG) appearance (termed “cramp discharge” by the American Association of Neuromuscular and Electrodiagnostic Medicine) which distinguishes it from other pathologic conditions that involve muscle tightening (e.g. focal dystonia, contracture, myotonia)\(^5\). During a cramp, unlike during a maximal voluntary contraction, only a subset of motor units are firing at any given time (a motor unit being a single motor neuron and the various muscle fibres that it innervates)\(^6,7\). These motor units are described as firing at higher rates than can be voluntarily achieved, with the individual motor units involved migrating around the muscle belly over the duration of the cramp\(^8\). The collective firing of motor units during a cramp starts off more slowly, builds to a plateau, and then tapers off gradually, with irregular firing patterns as the cramp discharge extinguishes. A given episode of cramp usually involves a single muscle, but occasionally can involve more than one. Over the 48 to 72 hours following muscle cramping the involved muscle can be tender, and the serum creatine kinase can be elevated\(^9\).

1.4 Diagnosing Muscle Cramps in the Clinic

Diagnosing muscle cramps is not difficult but the term “cramp”, similar to the word “flu”, is often used inconsistently by patients when describing their symptoms. Care needs to be taken
to ensure that other conditions causing soft tissue limb pain are not mistakenly being referred to as “cramping” (e.g. statin myopathy, polymyalgia, deep venous thrombosis). True cramps are episodic, with abrupt onset / offset and palpable muscle tightening. Such a description will usually correctly differentiate a true muscle cramp amongst the many other potential causes of leg pain.

However this generalization does not always hold true. Some rare conditions do produce focal intermittent muscle pain along with an associated muscle tightening and yet they are not true muscle cramps. These conditions include contracture and occupational cramp. Contracture is an electrically (EMG) silent tightening of muscle that occurs following prolonged exertion of the same muscle in individuals who are unable, because of an inborn error of metabolism, to effectively utilize glycogen to make ATP (e.g. McArdle’s disease). In this instance energy cannot be provided to return calcium to the sarcoplasmic reticulum and the existing muscle contraction cannot be relaxed. Occupational cramp (e.g. writer’s cramp, pianist’s cramp) is a misnomer for a condition which is really a focal dystonia. This condition occurs in individuals who have spent many years refining the fine hand motor control required for certain tasks. In this condition, when attempting the trained activity, both agonist and antagonist muscles begin to contract and cause the fingers to curl, freeze, move jerkily or undergo tremor.

True cramps can also occur as part of more generalized peripheral nerve hyperexcitability syndromes. Such syndromes can be inherited or acquired (e.g. upon the development of voltage gated potassium channel antibodies) and are usually termed, in increasing degree of hyperexcitability and symptomotology, either “benign fasciculation syndrome”, “cramp fasciculation syndrome” or “neuromyotonia” (also called Isaac’s
syndrome). In addition to cramps and fasciculations, neuromyotonia is characterized by muscles that are slow to relax during exertion (myotonia) and by myokymia, which appears clinically as an intermittent quivering of the involved muscle belly and on EMG is seen to be single motor units undergoing repetitive and recurrent firing (2 to 60 Hz) for several seconds at a time interrupted by pauses of several seconds. Generalized peripheral nerve hyperexcitability and cramping can also occur as part of tetany (brought on by hypocalcemia or alkalosis) and generalized increased muscle tone (not true cramps) can be brought on by tetanus (as a result of a bacterial toxin which blocks inhibitory neurotransmission in the central nervous system).

Finally, it is also worth mentioning that restless leg syndrome and rest cramps can sometimes be confused because of the similarity in their names. However they are distinctly different conditions. Restless leg syndrome is not painful and has no palpable muscle tightening, rather it is an unpleasant sensation of 'needing to move' one's legs that prevents relaxation.

1.5 Clinical Presentations of (True) Muscle Cramp

True muscle cramps can occur in association with a variety of diseases, both neurologic and metabolic. Neuromuscular diseases associated with cramp are those involving the lower motor neuron (amyotrophic lateral sclerosis, recovered poliomyelitis, nerve root compression, polyneuropathy). In contrast, diseases of the muscle or central nervous system are not associated with cramping. Some metabolic diseases (cirrhosis, uremia, hypothyroidism, hypoadrenalism) and some medications (e.g. diuretics, inhaled beta-agonists) are associated with muscle cramps, as is total parenteral nutrition (TPN) and
haemodialysis (especially if large volumes of fluid are being removed)\textsuperscript{12, 13}. It is believed that acute extracellular volume loss is a cause of muscle cramping (e.g. “heat cramps”, or cramps following vomiting / diarrhea), which might also explain the dialysis association\textsuperscript{4}. In addition to these stresses and associated diseases, there are also congenital disorders such as Machado-Joseph disease that involve, amongst other neurologic problems, frequent muscle cramping\textsuperscript{14}. Acquired disorders of frequent cramping and fasciculation have also been described (acquired neuromyotonia) and are believed to be immune mediated by the development of potassium channel antibodies\textsuperscript{15-17}.

And yet skeletal muscle cramping is more commonly seen in the absence of serious disease – typically in individuals who are either elderly, pregnant, continuing to contract a muscle already at its shortest length, or exercising vigorously\textsuperscript{6}. Exercise-associated muscle cramps occur either during or immediately following intense exercise, usually in the exercising muscle groups\textsuperscript{18}. In contrast, cramps associated with pregnancy or advanced age occur in the legs or feet during periods of prolonged inactivity, such as while lying in bed at night - for which they are termed “rest cramps”, or “nocturnal leg cramps”. Rest cramps associated with aging are a very common problem in general practice and it is this particular cramp syndrome which is the focus of this body of work.

1.6 Rest Cramp Prevalence, Demographics and Disease Associations

Children (Canadian ambulatory care records)\textsuperscript{19}:

Rest cramps can occur over a wide age range. In a review of the ambulatory care records of 2527 healthy Canadian children, 7.3\% had reported a nocturnal leg cramp in the
previous year (although cramps were not reported in children younger than 8 years). The incidence began increasing at age 12 and was highest in the oldest children whose records were examined (16 to 18 years).

*All Adults (Random survey in a Dutch community)*:20,21

A Dutch general population telephone survey (780 respondents age 18 and over) showed that age had little effect on the proportion of the population experiencing a cramp in the previous year (36% overall), although older adults who did report cramps suffered them more frequently. Women were 1.5 times more likely to suffer cramps than men, largely because of twice the incidence of cramping in the feet. Pregnancy was associated with cramping (odds ratio 6.3; 95% confidence interval 1.0 to 38.6), as were complaints of muscular pain or stiffness (odds ratio 2.8; 1.1 to 7.2). The calf was the most commonly affected muscle (involved in 84% of crampers), followed by the foot (in 39% of crampers). Surprisingly, the correlation between muscle fasciculation and cramping (muscle fasciculation having been linked to cramping in EMG studies) was not significant (odds ratio 1.6; 0.9 to 2.8).

*Older Adults (UK general practice registrants)*:22:

Other studies exploring cramp prevalence and demographic associations in the normal population have focused on the elderly. A survey mailed to 250 registrants (218 responding) of a UK general practice registry (60 randomly selected subjects from each decade of age from the 50s to 70s and 65 subjects randomly selected in their 80s and 90s) found that 37% of respondents had experienced a cramp over a 2 month period. This survey
was not rest cramp specific, although cramps occurring during occupational activities were excluded. The prevalence was higher for those over 80 years of age (54%), possibly because the survey used a relatively short 2 month period of recall (i.e. if cramps are more frequent in the elderly then a shorter period of recall could lead to a higher apparent prevalence). The over 80 years age group also rated their cramping as more distressing, with 57% rating their cramps as either a major nuisance or very distressing compared to the remaining 43% rating their cramps as a minor nuisance. No gender difference in the rate of cramping was found. Across all age groups, most respondents (73%) reported cramping either mostly or only at night and the majority experienced symptoms less than once per week. However, 40% experienced rest cramps more than 3 times per week and 6% suffered more than one episode in 24 hours. Subjects who had complained of cramping to their family physician averaged 3 cramps per week and had cramps lasting 13.9 minutes on average. Those who had not reported cramps to their doctor had an average cramp duration of only 6.1 minutes. Cramps were localized to the lower leg, foot or thigh and only rarely to the upper limb or elsewhere. Specific questions about a history of angina or leg claudication were also included in the questionnaire and both were significantly associated with the presence of cramping.

*Older Adults (UK general practice clinic attendees)*:

Another UK general practice study handed questionnaires to 365 outpatient clinic attendees over the age of 65 to determine rest cramp prevalence as well as drug and disease associations. In this survey, where no time interval over which to recall the frequency of cramping was defined, 50% of respondents reported experiencing cramps. There was no difference in prevalence with age but a greater number of females reported experiencing
cramps (56% in females versus 40% in males). The majority (74%) of cramps occurred only 
at night and had a mean duration of 8.4 minutes. Daily (i.e. recurring within a 24 hour 
period) cramps were experienced by 19% and multiple daily cramps by 1.5%. Of the 40% 
who had advised their family physician of their cramps 53% had received treatment. For the 
majority (54%) this treatment was the anti-malarial drug quinine, but analgesics, non-
steroidal anti-inflammatory drugs, topical creams and support stockings were also employed. 
Disease associations were sought for heart disease, diabetes, hypertension, stroke, renal 
disease, arthritis, gout, leg surgery and peripheral vascular disease. Of these, only peripheral 
vascular disease (odds ratio 2.9 p < 0.001) and arthritis (odds ratio 2.3 p < 0.001) had 
significant associations. No drug associations reached significance, with the exception of 
analgesics which had an odds ratio of 2.24 (p = 0.0018) and which the authors attributed to 
cramp treatment.

*Older Adult Males (Ambulatory care records of American veterans)*

A retrospective case-control chart review of 50 male American veterans who took 
quinine sulfate for rest cramps also sought disease and drug associations. Of these, peripheral 
vascular disease was once again associated with cramping (34% in crampers vs. 12% in 
controls, p = .009), as was peripheral neurological deficit (12% vs. 0%, p = .012). Crampers 
were prescribed significantly more medications in general than controls, but no specific 
medication was prescribed more frequently to crampers. Although there are other diseases 
which have been associated with cramps in the literature (e.g. liver disease), these disorders 
may not have occurred with sufficient frequency to reach significance in this small chart 
review.
Older Adult Males (Survey of American Ambulatory Care Clinic Attendees)\textsuperscript{25}:

A survey distributed to 515 attendees of a Denver Veterans Affairs Medical Center (including primary care, internal medicine, diabetes, hypertension and geriatric outpatient clinics) asked about the presence of various leg symptoms, including nocturnal leg cramps. Respondents were 95\% male and 56\% reported experiencing nocturnal leg cramps. Of those reporting cramps 24\% reported them as occurring daily (in conjunction with 26\% reporting cramps 1-4 times per week, 27\% reporting 1-3 per month and 23\% reporting 1-12 per year). Correlations were sought between the presence of nocturnal leg cramps and the presence of self reported peripheral vascular disease, coronary artery disease, hypertension, kidney disease, stroke, diabetes mellitus and hypokalemia. Of these conditions, significant associations were found for peripheral vascular disease (odds ratio 3.49, p = 0.0001), hypokalemia (odds ratio 1.74, p = 0.047) and coronary artery disease (odds ratio 1.68, p = 0.015). The survey also asked what treatments had been used and responses included quinine sulfate (34 patients), diazepam (17 patients), vitamin E (12 patients), amitriptyline (10 patients), phenytoin (9 patients) and diphenhydramine (8 patients). Quinine was reported to be “most effective” in 50\% of those receiving it, whereas “none of the other drugs were described as effective”.

1.7 The Pathophysiology of Muscle Cramps

The precise mechanism behind muscle cramping remains obscure but cramps can generally be agreed to have a neural, rather than muscular origin\textsuperscript{4,6}. In support of this is the observation that diseases of muscle are not associated with muscle cramping (while diseases of the motor neuron are) and that EMG during a muscle cramp shows repetitive high frequency firing of
motor units – a pattern that is highly unlikely to have a muscle origin. Additionally fasciculations (experienced as an irregular muscle twitch and seen on EMG to be single discharges of one motor unit) are associated with the onset and offset of muscle cramping and have been shown to have their origin in the peripheral motor nerve. A central versus peripheral neurologic origin of cramps has been debated but the preponderance of evidence favors a peripheral origin. Those who favor a central origin of cramping point for support to the modulation of cramping by muscle stretch, and also to the observation of increased synchronization of motor units during camp, as being evidence of a central influence. However during a muscle cramp motor units fire at rates (typically 150 Hz) that far exceed the normal rate of centrally driven muscle contraction and neurologic diseases that associate with muscle cramps are diseases of the motor neuron, and not diseases of the central nervous system. It has further been established that muscle cramps can be electrically triggered and sustained by high frequency peripheral nerve stimulation distal to an anesthetic nerve block. Despite this anesthetic isolation of the distal motor nerve and its muscle, normal cramp morphology and a normal cramp response to stretch persisted. These observations suggest that cramps arise in the distal motor neuron.

To date there is no generally accepted theory of muscle cramp etiology. Most speculation on the mechanism behind muscle cramps focuses either on central spinal dysinhibition leading to hyperactivity of motor neurons (though this would appear to be contradicted by the observation of cramps distal to a nerve block) or on an abnormal excitability of distal motor neurons (though how this would occur and be translated into most cramp related observations remains to be worked out). Feedback loops or abnormal interactions between muscle spindle afferents and α-motoneurons have also been
postulated\textsuperscript{31,32}. However none of these theories can explain all of the experimental observations and none has emerged as the clear candidate to explain the phenomenon.

A comprehensive theory of cramp etiology would need to explain:

- The association with aging, pregnancy, exercise and motor neuron disease.
- The observation that a key trigger for non-exercise related cramps is prolonged immobility (i.e. rest cramps).
- The observation that the mean motor unit firing rate during cramp discharges exceeds the mean motor unit firing rate during maximal voluntary contraction\textsuperscript{8,31,33}.
  (Although this observation is contradicted by a more recent study where the mean rates were found to be comparable\textsuperscript{34}.)
- The observation that the time interval between motor units firing during cramp is more variable than during maximal voluntary contraction (at times being less than 10 ms)\textsuperscript{34}.
- The observation of greater synchronous activity between motor units during cramp discharge compared to maximal voluntary contraction\textsuperscript{27}.
- The observation of an out of phase coherence in the firing rates of motor units during cramp compared to maximal voluntary contraction (i.e. the firing rates have a similar modulating pattern with a time lag that is variable amongst motor units but fixed for any two specified motor units)\textsuperscript{34}.
- The observation that stretch of a muscle reduces the frequency of cramp discharges and can sometimes abort a cramp\textsuperscript{3}. 
• The observation that there is a frequency threshold for electrical or magnetic neurostimulation above which a cramp can be artificially induced in most individuals\textsuperscript{3, 35-37}.

• The observation that this stimulus threshold frequency correlates with a predisposition to spontaneous muscle cramping (i.e. lower frequency thresholds are seen in individuals that are prone to spontaneous muscle cramping)\textsuperscript{38}.

• The observation that after an anesthetic nerve block muscle cramps can still be induced by high frequency nerve stimulation distal to that nerve block\textsuperscript{3, 39}.

• The observation that the frequency threshold for inducing a cramp varies with the current state of lengthening of the involved muscle (i.e. stimulation frequencies need to be higher to induce cramp in muscles which are being held in a stretched position)\textsuperscript{3}.

• The observation that cramps involve only a subset of motor units and that the motor units involved migrate gradually around a muscle during the cramp\textsuperscript{8}.

1.8 Current Treatment

Treatments in use for cramp prophylaxis include quinine, prophylactic stretching before going to bed, analgesics, NSAIDs, calcium channel blockers (diltiazem, verapamil), anti-seizure medications (phenytoin, carbamazepine, gabapentin), amitriptyline, baclofen, methocarbamol, diphenhydramine, compressive stockings, mineral supplements (calcium, magnesium, potassium or sodium salts) and vitamin E\textsuperscript{4, 6, 11, 40}. Common lay treatments additionally include apple cider vinegar, pickle juice and the placing of an object such as a bar of soap, horseshoe, potato, or cork under the covers when going to bed at night\textsuperscript{41}. 
The following section on treatment begins with background information on two treatments I believe to be commonly offered to cramp sufferers in Canada (quinine and prophylactic stretching), and then briefly describes the breadth of RCT evidence surrounding other cramp therapies I believe to be less common. At the end of this section on treatment I will also describe in greater depth the two major potential interventions that I explored with my experimental work (those being magnesium supplementation and the discontinuation of cramp promoting drugs).

1.8.1 Quinine

The anti-malarial drug quinine is the optical isomer of the cardiac rhythm managing medication quinidine. In addition to its anti-malarial properties, quinine also possesses sodium and potassium channel blocking properties - which might be relevant (via action on motoneuronal cell membranes) to its mechanism of action in cramp prophylaxis\textsuperscript{42-44}. Quinine is the only cramp intervention whose (modest) efficacy is supported by systematic review\textsuperscript{45}. Compared to placebo, over a two-week interval quinine significantly reduced cramp number by 28%, cramp intensity by 10% and number of cramp days by 20%. Cramp duration remained unchanged.

Unfortunately, while quinine is commonly used in Canada for the prophylaxis of nocturnal leg cramps, it has also been associated with significant hematologic and cardiac toxicity and its use as an off-label cramp prophylactic has been actively discouraged by multiple drug regulatory agencies such as the American FDA and its counterparts in Australia and New Zealand\textsuperscript{46-49}. It is effective for some individuals, but safer and more effective treatments are clearly needed.
1.8.2 Stretch

It is important to distinguish between acutely stretching out a cramping muscle in an attempt to abort an ongoing cramp and prophylactically stretching a muscle before going to bed. Many rest cramp sufferers will jump out of bed when a cramp starts and stretch the involved muscle. Although this has not been studied by RCT, there is EMG evidence that stretch of a cramping muscle lowers the rate of motor neuron firing during cramp discharge and the simultaneous observation by the same authors that stretch could often abort experimentally induced cramps\(^3\).

There is also evidence that the length of a muscle influences how prone that muscle is to the induction of cramps. This evidence includes the common observation and demonstration that self-induced cramps can be brought about by maximal contraction of a muscle at its shortest length, as well as the demonstration that, as the length of a muscle is increased, increasing frequencies of electrical stimulation of motor nerves are required for cramps to be experimentally induced\(^3,27\).

Prophylactic stretch, however, is a different story. The recommendation to stretch before bedtime comes from a 1979 letter to the editor of the New England Journal in which it was reported that 44 adults instructed in calf stretching before bed “all reported cure within a week”\(^50\). This trial was uncontrolled and impossible to assess because of the letter’s necessary brevity. Although this letter is often cited, I am unaware of any additional data to support the practice.

In 2005 Coppin et al.\(^51\) reported a peer reviewed 2X2 factorial RCT comparing the same stretching regimen to control leg movements that provided minimal stretch to calf and
foot muscles. All 191 subjects (from 28 British family practices) were current quinine users additionally randomized to continue or discontinue their quinine. This was a pragmatic trial. Subjects continued their assigned interventions for 6 weeks and then chose for themselves to continue those interventions or not for another 6 weeks. At 12 weeks they reported their recollection of the number of cramps over the prior 4 weeks. Not only was there no significant difference in cramp rates related to the stretching recommendation, there was not even a trend to benefit (1.95 more cramps in 4 weeks, p=0.44 95%CI -3.01 to 6.90).

Two systematic reviews include the Coppin paper. The first perceived potential bias from limited blinding (though this would presumably favor the intervention) and from potential benefit to the sham exercise. The second review didn’t share these concerns but rated the risk of bias high largely because the intervention was not obligatory during the final 6 weeks of the trial. This would bias against a demonstration of efficacy but mirrors patient interactions in the real world.

Thus while it appears that stretching may have some acute value in aborting a cramp, and that the current length of a muscle may influence its susceptibility to cramping, prophylactic stretching before bed is likely ineffective.

### 1.8.3 Other Therapies

There are a large number of other cramp treatments, but none towards which the majority of patients or physicians seem to gravitate based on the perception of efficacy. In addition to the Cochrane Collaboration’s review of quinine for muscle cramps, two systematic reviews have looked more broadly at all therapies for muscle cramp. The first was performed by the American Academy of Neurology and limited itself to idiopathic cramps and cramps
associated with neurologic disease\textsuperscript{52}. The second was performed by the Cochrane Collaboration and limited itself to the treatment of pregnancy-associated muscle cramps\textsuperscript{54}. Randomized trials identified by these reviews include:

- A double blind parallel arm RCT (N = 204 ALS patients) of gabapentin 3,600 mg per day versus placebo which found no difference between treatment and placebo on any treatment score\textsuperscript{55}.

- A double-blind parallel arm RCT (N = 28 non-pregnant rest cramp sufferers) of oral vitamin B complex versus placebo which found benefit in the form of remission of symptoms in 86\% of treated subjects but was limited by incomplete documentation of completion and compliance rates\textsuperscript{56}. The use of global cramp severity as the major outcome measure was also questioned (most trials use cramp frequency).

- A double-blind parallel arm RCT (N = 14 non-pregnant rest cramp sufferers) of Naftidrofuryl oxalate 300 mg BID versus placebo which showed benefit but did not adequately account for dropouts\textsuperscript{57}. Naftidrofuryl oxalate is a drug marketed for peripheral vascular disease that is purported to enhance the utilization of glucose and oxygen. Naftidrofuryl is not available for use in North America.

- A double-blind parallel arm RCT (N = 27 non-pregnant rest cramp sufferers) of vitamin E 800 IU each evening versus placebo which found no effect on any cramp measure (mean number of cramps, number of nights with cramps, or sleep disturbance)\textsuperscript{58}.

- A double-blind cross-over RCT (N = 13 non-pregnant rest cramp sufferers) of diltiazem 30mg versus placebo which showed a reduction in cramps over 2 weeks (-5.84 vs. -0.16 p = 0.04) with no effect on cramp intensity\textsuperscript{59}.
• An unblinded parallel group RCT (N = 42 pregnant cramp sufferers) of 1000 mg oral calcium twice daily for two weeks versus no treatment in which a reduction in cramp frequency was noted\textsuperscript{60}.

• A double-blind parallel group RCT (N = 60 pregnant cramp sufferers) of 1000 mg oral calcium or vitamin C twice daily for 3 weeks in which no difference in cramp frequency was found\textsuperscript{61}.

• A double-blind parallel group RCT (N = 150 pregnant cramp sufferers) of Sodium Chloride 45 grams per day versus placebo in which benefit was suggested for sodium chloride in resolution of cramps\textsuperscript{62}.

• A double-blind parallel group RCT (N = 141 pregnant cramp sufferers) of sodium chloride 45 grams per day versus calcium lactate in which no differences between groups was evident\textsuperscript{62}.

• A double-blind parallel group RCT (N = 29 pregnant cramp sufferers) of multivitamin / multimineral supplements versus placebo which suggested more patients with resolution of cramping in the treatment group\textsuperscript{63}.

• A double-blind cross-over RCT (N = 45 non-pregnant rest cramp sufferers) of a 900 mg magnesium citrate pill (approx 100mg elemental Mg) twice daily or matched placebo for 28 days before switching to the alternate therapy. No difference in outcomes was found (number of cramps, cramp duration, cramp intensity, sleep disturbance)\textsuperscript{64}. More detail in Section 1.6.4.6.

• A double-blind cross-over RCT (N = 73 but with 27 dropouts non-pregnant rest cramp sufferers) of either 1830 mg of tri-magnesium dicitrate powder (300 mg elemental magnesium) poured from a sachet into a glass of water, or matched
placebo powder, taken orally each night for 6 weeks before switching to the alternate therapy\textsuperscript{65}. This RCT reported a non-significant trend’’ (p = 0.07) to benefit in reducing cramp frequency. There was no change in severity or duration of cramps. More detail in Section 1.6.4.6.

- A double-blind parallel group RCT (N = 73 pregnant cramp sufferers) of 122 mg elemental magnesium (as Mg lactate and Mg citrate) or matched placebo tablet taken once each morning and twice each evening for 3 weeks\textsuperscript{66}. Magnesium recipients had a greater reduction in cramp frequency and intensity. More detail in Section 1.6.4.6.

These reviews also identified 4 trials in non-pregnant rest cramp sufferers which were uncontrolled. This included open label or uncontrolled trials of gabapentin (N = 30), verapamil (N = 8), intra-muscular lidocaine (N = 24) and the anti-convulsant levetiracetam (N = 20) all of which suggested benefit but which were of limited use because of the absence of a blinded control group\textsuperscript{67-70}.

The American Academy of Neurology Review of rest cramp therapies ultimately recommended: \textit{“Although likely effective (Level A), quinine derivatives should be avoided for routine use in the management of muscle cramps because of the potential of toxicity, but in select patients they can be considered for an individual therapeutic trial once potential side effects are taken into account. Vitamin B complex, Naftidrofuryl, and calcium channel blockers such as diltiazem are possibly effective and may be considered in the management of muscle cramps (Level C). Further studies are needed to identify agents that are effective and safe for the treatment of muscle cramps.”}
The Cochrane review of treatments for pregnancy-associated rest cramps concluded:

“The evidence that calcium reduces cramp is weak and seems to depend on placebo effect. The evidence for sodium chloride is stronger but the results of the sodium chloride trial may no longer be relevant because of dietary changes which include an increased sodium intake in the general population. It is not possible to recommend multivitamins with mineral supplementation, as it is not clear which ingredient, if any, is helping. If a woman finds cramp troublesome in pregnancy, the best evidence is for magnesium lactate or citrate taken as 5mmol in the morning and 10mmol in the evening.”

1.8.4 Magnesium

At the inception of my PhD work I was aware that magnesium was already being marketed directly to consumers for the prevention of muscle cramps and that, as stated above, the author’s of the Cochrane Systematic Review of treatments for pregnancy associated leg cramps had suggested that magnesium had the best evidence for cramp prophylaxis. However I also knew that the Cochrane conclusion was based on a single clinical trial and that trials in older adults had failed to find statistically significant benefit (though one reported what they described as a positive trend). However I also knew that magnesium was poorly bioavailable when taken orally because of poor absorption (hence its use as an osmotic laxative) and I reasoned that the poor bioavailability of oral magnesium might have limited its effectiveness in clinical trials. A better way to determine the efficacy of magnesium to provide cramp prophylaxis was to perform an RCT of parenteral magnesium. For this reason I set out to perform that trial.
The following sections discuss relevant knowledge surrounding magnesium metabolism. Additionally, the reader will find a brief summary of the results of a literature search for randomized trials exploring the use of magnesium to treat skeletal muscle cramps that I performed in the spring of 2006 to evaluate the merit for a clinical trial of intravenous magnesium. It is provided in this introduction to inform the reader as to the state of knowledge at the time my magnesium investigations began. A more up to date and complete version of this review which makes use of my RCT, the results of an unpublished trial, and patient level data from one of the earlier published trials, has recently been submitted to the Cochrane collaboration and appears separately (in full detail) as chapter 3 of this manuscript.

1.8.4.1 Magnesium Metabolism

Magnesium (Mg) is the fourth most abundant mineral in the human body and a cofactor for more than 300 biochemical reactions, including most reactions utilizing ATP\(^71\). Roughly half (53%) of the typically 900 mmol of total body magnesium is found in bone, with the other half (46%) distributed intracellularly throughout the body’s tissues and organs\(^72, 73\). Only about 1% (10 mmol) is found extracellularly in intravascular or interstitial fluids.

Although intracellular free magnesium levels are tightly controlled there are no hormones which regulate the plasma concentrations of magnesium (unlike calcium, sodium and potassium) and magnesium within the tissues, bone and extracellular spaces is slow to equilibrate\(^73-75\). Only about 20% (180 mmol) of total body magnesium is available to buffer losses\(^72, 76, 77\). Two thirds of this (120 mmol) comes from bone and one third (60 mmol) from skeletal muscle with other tissues being more resistant to magnesium loss. Although 20% of
this available magnesium buffer exchanges over a relatively shorter period of 9 hours, the bulk (80%) exchanges more slowly over about 5 days\textsuperscript{76}.

Magnesium balance is largely maintained by renal excretion\textsuperscript{73, 75, 78, 79}. If oral intake of magnesium falls, plasma magnesium similarly falls and results in less magnesium being filtered through the glomerulus. Lowered intracellular levels of magnesium in the kidney also lead to increased absorption of magnesium such that less than 1 mmol of magnesium will appear in a 24 hour urine collection when Mg deficiency is present\textsuperscript{73}. Although there is also some slight ability to increase magnesium absorption in the gut during times of deficiency, magnesium absorption in the small bowel (the main site of absorption) takes place by both passive diffusion and a saturable active transport mechanism which reaches its maximum capacity at ingested loads of magnesium of 7 mmol\textsuperscript{74, 80-82}. As a result magnesium absorption falls with increasing magnesium load such that 80\% of small Mg loads can be absorbed in contrast to only 20\% of high Mg loads\textsuperscript{82}. For instance, increasing oral magnesium intake 2.5 times above normal dietary intake only increases the amount of magnesium absorbed by one third\textsuperscript{81}. The rate of magnesium absorption is also known to fall with age – being roughly 1/3 less in 70 year olds than in 30 year olds\textsuperscript{83}.

\textit{Putting this in context:}

The above tells us that magnesium is poorly absorbed by the gut and that the rate of magnesium absorption is even lower in the elderly (the same population who are prone to nocturnal leg cramps). It also led me to the speculation that oral magnesium supplements might lack efficacy (especially in the elderly) simply because of poor oral bioavailability.
1.8.4.2 Detecting Magnesium Deficiency

As a result of the slow equilibration of magnesium between tissues, serum magnesium correlates very poorly with tissue magnesium (as determined by muscle biopsy). This is problematic since serum magnesium is the only test readily available to clinicians for the assessment of magnesium deficiency. In the clinic, total body magnesium deficiency could very easily go undetected since these patients may have normal serum magnesium.

Tissue magnesium has also been assessed experimentally using methods such as skeletal muscle biopsy, NMR spectroscopy of P31, and the magnesium load test. NMR spectroscopy takes advantage of the difference in NMR signal of P31 when Mg is bound to ATP to measure the proportion of intracellular Mg-ATP and then estimate the amount of free intracellular Mg from the known rate of dissociation. The magnesium load test relies on giving a magnesium load by intravenous infusion and then measuring the urinary output of magnesium over 24 hours to determine what percentage of magnesium is retained.

Although it is arguably the most convenient method to meaningfully assess for magnesium deficiency, the magnesium load test has not been standardized. The amount of magnesium infused, the duration over which it is given, and the expected normal percentage retention varies considerably in the literature. One protocol, for instance, gives 30 mmol of magnesium in 500 ml D5W over 12 hours and suggests that greater than 30% retention indicates deficit. However a 12 hour test is not practical in the clinic and this has led to shorter infusion intervals being used in the literature. Typically these are 4 to 8 hour infusion protocols that could serve equally well for both therapeutic magnesium replacement and assessment of magnesium status. In our local health authority 20 mmol of magnesium sulfate is given intravenously in 500 ml D5W over 4 hours with greater than 15%...
retention suggesting deficit – however this protocol, adapted from what is in the literature, has not been validated. Another published protocol used a very short, 1 hour infusion, of 0.1 mmol magnesium per kg of total body weight\textsuperscript{97}. Normal values for retention were not established but this study demonstrated that the percentage retention of magnesium correlated well with bone magnesium in elective hip replacement patients. The same study also demonstrated a marked decrease in retention after 4 months of oral supplementation. This agrees well with other work showing a strong correlation between % retention of infused magnesium and the increase in intracellular magnesium on skeletal muscle biopsy following magnesium replacement therapy (replacement therapy consisting of 2 days of IV magnesium infusion and 6 weeks of oral magnesium supplements)\textsuperscript{90}.

\textit{Putting this in context:}

The above tells us that magnesium deficiency is difficult to test for in the clinic and, as a result, could easily be present in cramp sufferers without their physician being aware. It also establishes that magnesium deficiency can be assessed by examining a 24-hour urine for the fractional excretion of an infused magnesium load. This is important because I chose to assess the subjects in my clinical trial for their fractional excretion of magnesium into the urine. Participants retaining greater amounts of the infused magnesium were presumed to be more likely to have magnesium deficiency at baseline and more likely to have a rise in tissue magnesium following their infusions. I reasoned that, if magnesium infusion was effective at providing cramp prophylaxis, retainers of magnesium might display greater benefit.
1.8.4.3 Prevalence of Magnesium Deficiency in the Elderly

The current recommended dietary allowance (RDA) in the USA and Canada for daily magnesium consumption in adults is 420 mg (~17.3 mmol) for adult males and 320 mg (~13.2 mmol) for adult females\textsuperscript{101}. This contrasts with the actual mean intake of magnesium in the US population based on a 1977-78 nationwide food consumption survey which is only about 70% of the recommended daily intake (actual intake ~300 mg in men over 50 yrs and ~230 mg in women over 50 yrs)\textsuperscript{102}. Intake was even lower in a Swedish population (~210 mg in men and ~170 mg in women)\textsuperscript{103}.

Using the magnesium load method \(\frac{3}{4}\) of 100 elderly patients with congestive heart failure, hypertension or diabetes were shown to have magnesium retentions suggesting deficiency\textsuperscript{104}. This is consistent with a study of 36 healthy older adults receiving 30 mmol of magnesium over 8 hours compared to 53 young adult controls\textsuperscript{98}. In this study the older adults retained 28% of the infusion, compared to only 6% in the young adult controls. There was no evidence of delayed magnesium excretion in the elderly as compared to younger controls when examining 24 hour urines on the second day (hours 24 to 48). In this study the authors concluded that “Magnesium deficiency may be common in asymptomatic elderly”.

Interestingly, pregnant women (who also suffer leg cramps at night) have also been shown by NMR spectroscopy to have low brain and muscle magnesium. Magnesium in these same tissues was even lower if the women were pre-eclamptic (and hence considered at risk for seizure)\textsuperscript{89}.
Putting this in context:

The above told me that the same populations who suffer rest cramps (the elderly and pregnant women) are more likely to be magnesium deficient. This added to the theoretical speculation behind why the therapy might be useful.

1.8.4.4 Commercial Magnesium Supplements

Magnesium is a normal component of a typical diet. Foods which are generally high in magnesium include dark green leafy vegetables (chlorophyll contains magnesium), legumes, nuts, seeds and unrefined grains. Oral magnesium supplements are also widely available without prescription and many of these are actively marketed for cramp prophylaxis. Such supplements are salts of magnesium and typically combine magnesium with citrate, lactate, gluconate, malate, orotate, chloride, oxide, carbonate, hydroxide, sulphate or combinations of these anions. Most are in tablet form but some are available as liquid suspensions or as powders or crystals to be dissolved in water. As a result of the decreasing percentage absorption of magnesium with increasing dose, higher doses of oral magnesium salts can potentially lead to diarrhea (because of osmotic retention of fluid within the colon). Some magnesium salts, such as magnesium sulphate and magnesium hydroxide, are commonly employed as laxatives for that reason. Other than the diarrhea occurring with high doses, oral magnesium supplements are generally considered to be safe and relatively free of adverse effects. Injectable magnesium salts (e.g. magnesium sulphate) are also available and indicated intravenously (IV) in some countries for the acute management of seizures, especially in pregnancy (eclampsia). Excessively rapid IV magnesium infusion can lead to cardiorespiratory suppression and flaccid paralysis of skeletal muscle. Although the IV
preparation can be given intramuscularly (IM), it is associated with discomfort at the injection site.

1.8.4.5  How Magnesium Supplementation Might Have Provided Cramp Prophylaxis

The demonstrated efficacy of IV magnesium to prevent eclamptic seizures\textsuperscript{106}, and the neuromuscular suppression (loss of strength, diminished reflexes) which can manifest when such high parenteral doses of magnesium are used\textsuperscript{107}, both suggested that magnesium could potentially play a role in reducing neuromuscular excitability. Although the mechanism behind skeletal muscle cramps was unclear, if a threshold for depolarization needed to be reached within motor neurons to initiate cramping, anything which conceivably reduced excitability might provide cramp prophylaxis. Hence if magnesium supplementation were to truly suppress excitable tissue, it might also suppress muscle cramps. This would have been consistent with the description of symptoms said to arise from severe magnesium deficiency, which included muscle cramping, though probably as a manifestation of tetany\textsuperscript{108-110}.

1.8.4.6  Review of the Magnesium Literature

*Magnesium Supplementation for the Prophylaxis of Skeletal Muscle Cramps*

*(What was known in the spring of 2006)*

Chapter 3 provides, in detail, the methods and results of a Cochrane Systematic Review of the literature which I performed as the final step in my doctoral research (Fall 2011) to better answer my research question on the efficacy of magnesium to provide cramp prophylaxis. In addition to what was available in 2006, the fall 2011 Review (chapter 3) includes the RCT that I conducted, patient level data that I was able to get from one of the earlier magnesium
trials (Roffe 2002), and the results of two additional trials that were not yet complete in the spring of 2006 (one of which remains unpublished). The number of databases I was able to search in 2011 was greater than 2006 because of access that the Cochrane collaboration granted me but no additional eligible studies for the 2006 or earlier period were identified through those additional databases. The 2006 literature search made use of Medline and Embase and employed essentially the same search algorithm as that provided in chapter 3 for these databases. The three studies available in 2006 were:

1) Dahle 1995

**Design:** This double blind parallel group RCT was the earliest clinical trial of magnesium for skeletal muscle cramps and involved the recruitment of 73 pregnant women (mean 29 wks gestation) who were experiencing rest cramps and had not received any previous cramp treatment. Subjects were recruited out of Swedish prenatal care clinics. The intervention was a chewable tablet containing 122 mg elemental Mg ("primarily as Mg lactate or Mg citrate"), or matched placebo tablet, taken once each morning and twice each evening for 3 weeks. No primary outcome was identified. Instead the study reported a large number of outcomes including change in cramp frequency on a 5 point ordinal scale (daily, every other day, twice a week, once a week, never), time of day cramps occur on a 4 point nominal scale (nighttime only, days and nights, daytime only, free of symptoms), presence of symptoms the day after a night of cramping on a 3 point ordinal scale (always, sometimes, never), global patient assessment of treatment effect on a 5 point ordinal scale (entirely free of symptoms, considerably improved, unchanged, worsened, considerably worsened), cramp intensity on a
visual analog scale, serum Mg and Ca and 24-hr urinary Mg and Ca excretion. The trial was sponsored by the manufacturer of the magnesium tablets used in the study.

**Results:** This study reported a reduction in the frequency of symptoms "from the initial average of every other day, to every 3 days in the placebo group and one to two times a week in the magnesium group (p<0.05)". It also reported benefit in patient evaluation of treatment effect in that "the magnesium group indicated that they had to a significantly greater extent ‘improved considerably’ or ‘become asymptomatic’ compared with the placebo group (p = 0.0002)". Cramp intensity (acute distress at the time of a cramp) on the visual analog scale fell from 68.2 mm to 47.8 mm on placebo (p < 0.05) and 70.4 mm to 30.3 mm on magnesium (p < 0.001) with the difference in distress, magnesium versus placebo, being statistically significant (p< 0.05). At baseline the vast majority (88%) of those suffering cramps did so only at night and this was unchanged by either treatment. The persistence of symptoms the day following a night with cramps (presumed to mean ache or tenderness in the involved muscle) was reduced in the magnesium group - with 50% of placebo patients having persistent symptoms the next day compared to 25% in the magnesium group (p <0.05). None of the laboratory measures were significantly different following the intervention. Adverse effects were not broken down by treatment group but were reported as “infrequent in both groups, consisting primarily of slight or initial nausea”. It was specified that “one patient in the placebo group aborted treatment because of severe, persisting nausea” but adverse events were described in no further detail.
Potential Bias: Limitations of this study include the lack of a description of outcomes as primary and secondary and the outcomes being incompletely described in the methods. I.e. only in results is it evident that before and after comparisons, mean differences and numbers attaining specific cut-offs are used. Hence it is unclear how well outcomes were predefined. The lack of a cramp diary (i.e. instead asking patients to rate their symptoms at the time of an exit interview) is also a limitation as it could magnify any bias that may have occurred if blinding was imperfect.

2) Frusso 1999

Design: This double-blind RCT of cross-over design involved 45 non-pregnant rest cramp sufferers over the age of 18 yrs (mean age 61.6 yrs) who had a normal neurologic exam and at least six leg cramps in a four week placebo run-in. Recruitment was from a single large university-based Argentinean family practice clinic. The intervention was one magnesium citrate 900 mg pill (approximately 100 mg elemental Mg) twice daily or similar tasting and appearing placebo, each for 4 weeks. The trial design included a four week placebo run-in and a 4 week washout between treatments. Number of cramps during the treatment period was the primary endpoint and secondary endpoints included cramp duration by 4 ordinal categories (< 5 minutes, 5-10 minutes, 10-30 minutes, >30 minutes), cramp intensity by analog scale, sleep disturbance on a 0 to 10 scale with 0 = “no sleep disturbance” and 10 = “could not sleep because of the cramps”, and adverse events. The study appears to have been independently funded.
Results: The mean number of cramps was not significantly different with 11.1 ± 7.3 for placebo and 11.8 ± 7.3 for magnesium (p=0.59). Neither was there a significant difference in either cramp intensity on an analog scale (2.07 ± 2 for placebo versus, 2.01 ± 1.73 for magnesium, p = 0.84) or sleep disturbance on a 0 to 10 interval scale (1.47 ± 2.35 for placebo versus 1.89 ± 2.62 for magnesium, p=0.39). Cramp duration was stated to be unchanged but was reported inappropriately as a mean and standard deviation in minutes. A mean was inappropriate as the data was collected in four ordinal categories of greatly varying duration. Multiple attempts to contact the author to clarify this issue were unsuccessful. Side effects were grouped (diarrhea, nausea, vomiting) and similar in placebo (10.1%) versus magnesium (10.7%) arms. A strong period effect was observed in this cross-over trial, with a reduction in the number of cramps in the second period.

Potential Bias: The methods of randomization and treatment allocation were not described. No comments were made as to whether there was a treatment by period interaction (i.e. a potential carryover effect).

3) Roffe 2002

Design: This double blind RCT of cross-over design enrolled 73 non-pregnant rest cramp sufferers (mean age 63 yrs) having at least 2 cramps per week. Recruitment was carried out in a UK population using community advertisement (newspaper ads, billboards). The intervention was 1830 mg of tri-magnesium dicitrate powder (300 mg elemental magnesium) poured from a sachet into a glass of water, or matched placebo powder, taken orally each night for 6 weeks before switching to the alternate therapy. The study employed a 2 week
magnesium free run-in and effectively included a 2 week washout between treatments since only the last 4 weeks of each 6 weeks on treatment was used for outcome assessment. The primary outcome was the number of cramps during the last 4 weeks of each treatment period and secondary outcomes (in the same interval of assessment) included severity of cramps (mild, moderate, severe), duration of cramps (short, medium, long) and self reported assessment of treatment effectiveness (yes, no).

**Results:** This study reported “a trend towards less cramps on magnesium (p = 0.07)” and reported differences for magnesium and placebo starters separately because (presumably) of a strong period effect (p = 0.008). Over the four week evaluation periods, for placebo starters (N = 29) “the median (95% CI) cramps was 9 (6-17) on placebo and 5 (4-8) on magnesium”. For the group starting on magnesium (N = 17) “the median (95% CI) cramps was 9 (5-13) on magnesium and 8 (4-14) on placebo”. Results for severity and duration were only reported as being “not significantly different” without actual numbers being provided. Significantly more subjects on magnesium thought the treatment was effective compared to placebo 36 (78%) versus 25 (54%) respectively (p = 0.03).

**Potential Bias:** The manufacturer provided centralized randomization for the trial in large blocks of 10. Specifics regarding the sequence generation are not given. The resulting allocation was unequal with more subjects included in the analysis receiving magnesium second (29 vs. 17). This is problematic for the computation of an overall difference between treatments because a large difference in treatment effect was also observed depending on the sequence of treatments (i.e. much greater benefit for magnesium is observed if treatment is
received in the order placebo→magnesium). Hence the observed imbalance (more subjects with magnesium second) would favor magnesium. There was also a very high dropout rate (27 of 73 subjects did not complete the study). It is unclear to what extent the difference in observed benefit depending on the sequence of treatment is due to period effect, noncompleters, the potential for carry-over effect or unblinding (as no comments were made as to whether the placebo and magnesium suspensions tasted different). Recruitment was also entirely from advertising which makes it potentially less representative of a family practice population.

_Putting this in context:_

Of the 3 trials available in the spring of 2006 to assess the efficacy of magnesium to provide prophylaxis for skeletal muscle cramps, one parallel RCT in pregnant women showed benefit, one cross-over RCT in older adults showed no benefit, and one cross-over RCT in older adults suggested “a trend to benefit”. Collectively, no conclusion on efficacy could be made.

### 1.8.4.7 The Gap in Knowledge #1

All three of the studies described above were of oral magnesium. Given that magnesium supplements are poorly absorbed, especially in the elderly, it was possible that poor oral bioavailability limited the effectiveness of magnesium in the two trials on older adults. This limitation could be overcome if magnesium were given intravenously, as is the common practice in our health authority when hypomagnesaemia is detected.
There were multiple reasons to undertake a trial of intravenous magnesium for rest
cramp prophylaxis in an older adult population:

1. Serum magnesium does not accurately diagnose magnesium deficiency –
   making unrecognized magnesium deficiency in cramp sufferers possible.
2. The same populations which suffer leg cramps at rest (the elderly and
   pregnant women) had also been shown to have a greater prevalence of
   magnesium deficiency.
3. An RCT of oral magnesium for pregnancy associated leg cramps suggested
   benefit.
4. Although two studies of oral magnesium in older adults failed to show benefit,
   bioavailability may have been more of a problem in that demographic.
5. Intravenous infusion of magnesium should minimize any potential problems
   in bioavailability.
6. A 24-hour urine for magnesium could also be collected to assess for retention
   of magnesium on the first day of infusions. Thus it could be determined if the
   treatment effect varied with the extent of retention of magnesium.
7. The treatment would be very inexpensive if it were durable.
8. While results confirming a beneficial treatment effect would clearly be useful,
   evidence of no benefit would also be useful given oral magnesium is already
   widely marketed over the internet, and in health food stores, for the
   prophylaxis of muscle cramping. Evidence of no benefit for intravenous
   magnesium would imply that benefit for oral magnesium is unlikely and guide
   physicians and patients away from the use of that product.
Thus the first component of my PhD research (Chapter 3) was an RCT of magnesium infusion in non-pregnant rest cramp sufferers intended to better define whether magnesium had efficacy for cramp prophylaxis. Additionally, shortly before completing this body of research, I sought to integrate and update my work with the latest knowledge by performing a Cochrane Systematic Review of the literature (Chapter 3) surrounding the use of magnesium to treat skeletal muscle cramping in any clinical setting (e.g. rest cramps, pregnancy-associated leg cramps, exercise-associated muscle cramps or disease-state associated muscle cramps).

1.9 Cramp Promoting Drugs

The second opportunity that I pursued in my PhD work was to explore whether cramps were occurring in some individuals as a side effect of commonly used medications. A variety of medications had been linked to muscle cramps. Pindolol (an oral beta blocker with partial beta agonism) had randomised controlled trial evidence supporting an increase in muscle cramping over placebo\textsuperscript{111-113}, while atorvastatin had cohort level evidence of an association with symptomatic decline (including the worsening of muscle cramps) when used in Amyotrophic Lateral Sclerosis patients\textsuperscript{114}. However, outside of these studies, the only medication links to cramping I could find were anecdotal (i.e. limited to case reports or expert opinion). Drugs with anecdotal evidence to cramping included diuretics, terbutaline, salmeterol, prednisone, clofibrate and penicillamine\textsuperscript{4, 115-117}. 
1.9.1 The Gap in Knowledge #2

Three of the above medications linked to cramping were (and are) in very common use - these being statins, diuretics and inhaled long-acting beta2-agonists (LABA). Outside of atorvastatin, whose evidence for cramp promotion came from a cohort study in ALS patients, none of these three medication classes had more than anecdotal evidence linking them to cramping. Yet they were each in sufficiently common use that sufferers of frequent nocturnal leg cramps (who are often elderly and on multiple medications) could easily be prescribed one of these medications. If one of these drugs did promote muscle cramping, cramp sufferers who use them would have the opportunity to either reduce their dosage, switch to another agent, or discontinue the medication altogether as a means of lessening their cramp burden. However, in order for physicians to consider such medication alterations, better evidence was required.

Thus another major component of my doctoral research was a pharmacoepidemiologic exploration of the linked British Columbia health care databases in order to determine whether initiation of cramp treatment (as indicated by a new prescription for quinine) increases following the introduction of one of these three potentially cramp promoting medication classes.

1.10 Overall Dissertation Objectives

Objective #1: To assess the efficacy of magnesium supplementation in prophylaxing nocturnal leg cramps by conducting a randomized controlled trial of intravenous magnesium infusion and by determining whether the treatment effect varies with the degree of magnesium retention.
Objective #2: To assess the efficacy of magnesium supplementation in prophylaxing skeletal muscle cramps in any clinical setting (e.g. nocturnal leg cramps, pregnancy-associated leg cramps, exercise-associated leg cramps, disease state-associated leg cramps) by conducting a Cochrane Systematic Review of all randomized trials utilizing magnesium for the prophylaxis of skeletal muscle cramps.

Objective #3: To determine, using linked British Columbia healthcare databases, whether introduction of statins, diuretics or inhaled long-acting beta2-agonists is associated with the initiation of treatment for nocturnal leg cramps (as indicated by new prescriptions for quinine).
Chapter 2: Magnesium Clinical Trial

2.1 Preamble

This was the first research project that I embarked upon. I did so because my original hypothesis was that parenteral magnesium would possess efficacy for the prophylaxis of nocturnal leg cramps. As this chapter will outline, however, we did not find intravenous magnesium to have efficacy for this indication. This work was published in 2011 as: Garrison SR, Birmingham CL, Koehler BE, McCollom RA, Khan KM. The effect of magnesium infusion on rest cramps: randomized controlled trial. The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences 2011 Jun; 66(6):661-6.

2.2 Project Objectives

To assess the efficacy of magnesium supplementation in prophylaxing nocturnal leg cramps by conducting a randomized controlled trial of intravenous magnesium infusion and by determining whether the treatment effect varies with the degree of magnesium retention.

2.3 Hypothesis

Although there might be limited effectiveness of oral magnesium as a cramp prophylactic in older adults because of its limited oral bioavailability, we hypothesized that intravenous (IV) magnesium would provide an effective treatment for rest cramps in older people.
2.4 Methods

Institutional review and approval of the study protocol and written informed consent used in this trial was obtained from the Health Canada Therapeutic Products Directorate and from the University of British Columbia’s Clinical Research Ethics Board.

2.4.1 Participants

Forty six independent community dwelling older adults were recruited by means of waiting room posters and pamphlets in the offices of 21 Richmond BC family physicians, and by community newspaper advertisement within the Greater Vancouver area. All assessed individuals were volunteers who called our contact number inquiring about the study after having learned about it from one of these sources. The only pre-screening consisted of asking, at the time of that initial phone call, if the caller had 2 or more cramps per week, and was free of heart and kidney disease. Anyone answering yes to these questions was given an appointment for assessment. Adult crampers were eligible for the study if they could competently complete a run-in diary showing 8 or more cramps in 30 days. They were excluded if on history, physical exam or screening laboratory evaluation they had estimated glomerular filtration rate (eGFR) <50 ml/min; atrioventricular nodal heart block or heart rate < 54 beats per minute without a pacemaker; previous myocardial infarction; congestive heart failure; digoxin use; significant neurologic disease (e.g. stroke, Multiple Sclerosis, Amyotrophic Lateral Sclerosis, visible fasciculation, upper-motor neuron signs); pregnancy, Addison’s disease; chronic hepatitis; or significant abnormalities of serum calcium, sodium, potassium, chloride, bicarbonate, thyroid-stimulating hormone (TSH), alanine aminotransferase (ALT) or prothrombin time.
Participants had an average age of 69.3 ± 7.7yrs, 70% of them were female and the mean duration of episodic cramping was 16 ± 14yrs. Participants had a normal serum Mg of 0.81 ± 0.09 mmol/L (except for two individuals who were slightly below the normal range), and good renal function overall (eGFR 78.0 ± 16.4ml/min). Quinine was used by 20% of participants and oral Mg by 35% (taken largely as a combined calcium / magnesium supplement intended for bone health rather than for cramp prophylaxis).

2.4.2 Study Design and Intervention

After completing the first 30 days of their cramp diary, subjects were referred to the Richmond Hospital ambulatory care dept where they were randomized to one of two possible sets of 4 hr infusions on five consecutive days (Mon-Fri). The infusions consisted of 250 ml D5W either with (active arm), or without (placebo arm) 20 mmol magnesium sulfate added. The specific magnesium preparation was Health Canada DIN #00602264 Magnesium Sulfate INJ 50% USP 10ml vial = 5g per vial (Sandoz, Boucherville Quebec). Active and Placebo solutions were indistinguishably clear and colorless. Randomization, using a computer generated random allocation sequence without any blocking or stratification was carried out by the hospital pharmacist dispensing the study drugs according to a series of opaque allocation envelopes kept in the pharmacy. All investigators, study nurses and subjects were blinded as to treatment allocation.

Recruitment, infusions and all follow-up occurred between January 2007 and October 2008. Subjects were co-located in the ambulatory care unit during treatment (no more than four subjects for any given week) but instructed not to discuss cramps that occurred during the infusion week. They were permitted to use any cramp treatments that were being
employed in the run-in period, however they were requested to stop oral Mg a few days
before and during infusion week, and not to start oral Mg if they had not been on it during the
pre-infusion run-in.

The period of time between reviewing the first 30 days of the diary (to assess
eligibility) and the infusion week was variable (2-4 wks typically) but subjects were
instructed not to stop recording cramps in their diaries. It was the 30 days immediately prior
to infusions that served as the baseline for cramp rate. Subjects were requested to continue
recording cramps for 90 days following completion of infusions. Each cramp was recorded
along with its severity (on a 1-10 pain scale) and duration (broken down into <1 minute, 1-5
minutes or >5 minutes). Only cramps occurring below the waist were recorded.

All subjects received all of their allocated treatments - with the exception of one Mg
subject who felt lightheaded on the evening after the 4th infusion and had her 5th infusion
withheld. The first 30 days of the 90 day post infusion cramp recording were used in
calculating the primary endpoint and all subjects had a complete diary for this period. One
placebo subject stopped recording on day 31 because of a stroke and two subjects (one each
from the Mg and placebo arms) stopped recording short of 90 days (days 62 and 78
respectively). Another subject mistakenly stopped recording her cramps during the interval
between run-in diary and the start of infusions. In this case the 30 day run-in diary was used
as the cramp baseline instead of the 30 days immediately prior to infusions.

2.4.3 Assessment of Magnesium Retention

On days 1 and 5 of the infusion week, concurrent with the start of infusions and after
voiding, a 24-hour urine for Mg collected in plastic bottles and acidified with 5 ml 10%
hydrochloric acid was begun to determine the % Mg retention on the first and last day of infusions respectively. The percent retention of that day’s infused 20mmol Mg load was calculated as 100 x (20mmol – 24-hr urinary excreted Mg) / 20mmol. It was the percent retention of the first day’s infusion that was the main measure of Mg retention. The urines on day 5 were used to assess change in Mg retention over the infusion week, as well as to assess for adequacy of collection on day 1 by comparing the 24-hr urinary creatinine excretion on day 1 and day 5 (day 1 urine creatinine expected to be at least 2/3 of day 5 if adequate collection). To avoid compromising the blind, all subjects underwent urine collection identically and results of urine testing (along with baseline serum Mg) were sequestered from investigators until trial completion. The pharmacist maintaining the study blind communicated directly with the lab courier to indicate which specimens to process for Mg retention and which to discard.

One subject had substantially lower 24-hr creatinine in her day 1 specimen than on day 5 (as well as low urine Mg) and was excluded from assessment of Mg retention because of what was assumed an incomplete catch. All 24 active treatment subjects submitted 24-hr urines for day 1 but three of these subjects did not have a corresponding day 5 urine either because they did not receive the 5th infusion, or the lab did not process their specimens (in one case because it was not properly acidified, in the other because the specimen was discarded by mistake). All three had day 1 urinary creatinine excretions judged appropriate for their body size / gender and were included in the analysis.
2.4.4 Statistical Analysis

The primary objective of the trial was to compare the effectiveness of IV Mg infusions versus IV placebo infusions in reducing the frequency of rest cramps in older adults – with the primary outcome being the change in the frequency of rest cramps per week (active versus placebo arms) over the 30 days immediately pre and post infusions. The secondary objective was to determine the % Mg retention in rest cramp sufferers and to determine if Mg retention correlates with treatment response.

A target sample size of 44 (22 per group) provided 90% power to detect a difference in the mean change in number of cramps per week between groups of one standard deviation magnitude when applying a two sample t-test with a two-tailed significance level of 0.05. In choosing this sample size we were predicting / specifying a baseline of 8 cramps per week, a 20% placebo response, a minimal detectable difference between groups of 50%, and a 4 cramp per week standard deviation for the primary outcome.

Graphical analysis of the primary outcome suggested a normal distribution, and a Welch Modified Two-Sample t-test of the difference between two means of unequal variances was employed to assess the statistical significance of the observed differences. The primary analysis of the change in cramps per week was by intention-to-treat and includes all subjects (n=46).

Sensitivity analyses for confounding of the primary outcome by baseline differences in gender and cramp rate were performed by multiple linear regression using, as independent variables, group allocation and either gender or baseline cramp rate along with an interaction term. Sensitivity analysis for baseline cramp rate was further explored by recalculating the primary endpoint after removing two placebo-assigned high frequency cramp outliers. As
clinicians often think in terms of % reductions, we also analyzed (without exclusions) the % change in cramps between groups.

The effect of Mg retention on treatment response was assessed within Mg recipients using linear regression to search for correlation between % retention of Mg and change in cramp rate. A median split of Mg recipients by degree of Mg retention was also carried out and differences in the change in cramp rate between groups determined by Welch Modified Two-Sample t-test of the difference between two means of unequal variances.
2.5 Results

Baseline demographics are shown in table 2.1. Subjects were well matched for age, eGFR, serum Mg, oral Mg use and quinine use. More men were allocated to placebo (41% versus 21%) and the mean baseline cramp rate was higher in the placebo group (8.6 versus 7.5 cramps / week) due to two outlying crampers (each averaging close to 29 cramps per week) being allocated to placebo.

Table 2.1 Baseline characteristics of rest cramp sufferers

<table>
<thead>
<tr>
<th>Variables</th>
<th>Placebo (n=22)</th>
<th>Magnesium (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>13 (59%)*</td>
<td>19 (79%)</td>
</tr>
<tr>
<td>Mean Age (years)</td>
<td>70.1 (8.7)</td>
<td>68.6 (6.9)</td>
</tr>
<tr>
<td>eGFR (ml/min)†</td>
<td>76.5 (18.1)</td>
<td>79.4 (15.0)</td>
</tr>
<tr>
<td>Serum Mg (mmol/L)‡</td>
<td>0.82 (0.08)</td>
<td>0.81 (0.10)</td>
</tr>
<tr>
<td>Oral Mg use</td>
<td>8 (36%)</td>
<td>8 (33%)</td>
</tr>
<tr>
<td>Quinine use</td>
<td>5 (23%)</td>
<td>4 (17%)</td>
</tr>
<tr>
<td>Median # of yrs cramping</td>
<td>14 (9-28)</td>
<td>10 (6-23)</td>
</tr>
<tr>
<td>Median # cramps / wk</td>
<td>6.2 (3.9–10.5)</td>
<td>5.8 (4.4-8.0)</td>
</tr>
<tr>
<td>Median # cramps / wk lasting &gt; 1 min</td>
<td>2.3 (0.6-4.0)</td>
<td>3.7 (1.2-5.0)</td>
</tr>
<tr>
<td>Mean cramp pain (1-10)</td>
<td>4.1 (1.8)</td>
<td>3.6 (1.8)</td>
</tr>
</tbody>
</table>

* Data are means (SD) or numbers (%) or medians (inter-quartile range)
† eGFR (estimated glomerular filtration rate) - normal >= 60 ml/min
‡ Serum Mg - normal range 0.65 – 0.95 mmol / L
Figure 2.1  Flow of participants through trial

Figure 2.1 shows the flow of subjects through the trial. Of 139 assessed individuals 93 were excluded. Twenty four of those (mostly respondents to newspaper ads) were excluded because they did not have rest cramps. They had exertion or posture (rather than rest) related muscle cramps [8], restless leg syndrome [5], arterial insufficiency [3], neuropathic pain [3], myalgia [2], nocturnal myoclonus [2] and tarsal arthritis. Exclusion for too few cramps (< 8 cramps in 30 days) occurred in 18 potential subjects and 17 declined
enrollment. Concurrent neurologic abnormalities excluded 14 subjects and included diagnoses of spinal stenosis (3), radiculopathy (3), ALS, post-polio syndrome, myelopathy NYD, multiple sclerosis, complex regional pain syndrome, Parkinson’s disease, benign fasciculation syndrome and progressive weakness NYD. A further 20 subjects were excluded by various criteria including eGFR < 50 [7], bradycardia [4], history or ECG evidence of MI [4], heart block [3], hypocalcemia [1] and being unable to satisfactorily complete a baseline diary [1]. This left 46 subjects to be randomized, 24 allocated to the Mg treatment group and 22 to placebo.

The baseline cramp rate averaged 8.0 cramps per week and its distribution was skewed to the right (Fig 2.2) with a median of 5.8 and inter-quartile range 4.4 – 9.0 cramps / week. The mean change in number of cramps per week was normally distributed and, Mg vs. placebo arms, was -2.4 ± 4.4 vs. -1.7 ± 3.3 cramps / week p=0.51 95% CI of the difference [-3.1 to 1.7].

Sensitivity analysis for gender confounding of the primary outcome using multiple linear regression with group, gender and an interaction term as independent variables shows
the gender – treatment group interaction to be not significant (-2.0 cramps / week in treated men p = 0.46 95% CI [-7.3 to 3.35]).

Sensitivity analysis for confounding by differences in baseline cramp rate obtained by excluding the two placebo-assigned high cramp rate outliers provides a mean change in number of cramps per week, Mg vs. placebo arms, of -2.4 vs. -1.6 p=0.47 95% CI of the difference [-3.2 to 1.5] which is virtually identical to the results before the outliers were removed. Regressing the primary outcome against group, baseline cramp rate and an interaction term, however, did show a significant interaction between treatment and baseline cramp rate (-0.53 cramps / week per baseline cramp in treated subjects p = 0.0039 95% CI [-0.88 to – 0.18]). This difference was no longer significant when the two placebo assigned outliers were removed (-0.31 cramps / week per baseline cramp in treated subjects p = 0.19 95% CI [-0.78 to 0.16]).

Percentage change in cramps, Mg vs. placebo, was -26.8% vs. -21.3% p=0.71 95% CI difference [-35.0 to 23.9]. We suggest that the threshold for a clinically meaningful reduction in cramps between groups would be 25%. Using a one sided t-test and assuming a true difference of 25% in favor of the intervention (rather than no difference) as the null hypothesis, we find a p value of 0.09. This means that, if the true difference in treatment effect is a 25% reduction in favor of Mg, the probability of observing a reduction in cramp rate of 5.5% or less (as we have done) is only 9%.

No significant difference was evident in degree of pain, duration of cramps, or cramp rate during either the 5 days of infusions or full 90 day follow-up interval - although the mean change in pain scores during the infusion week trended towards benefit with a non-
significant greater reduction in cramp pain on the 1 to 10 pain scale of -0.64 [-1.31 to 0.03] p = 0.07 from an initial baseline mean pain score of 3.6 in the magnesium group (Table 2.2).

Table 2.2  Change from baseline in the frequency of all cramps, the frequency of cramps lasting more than one minute, and cramp intensity (pain)

<table>
<thead>
<tr>
<th>Outcome Measures</th>
<th>Placebo (n=22)</th>
<th>Magnesium (n=24)</th>
<th>Difference Mg vs Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>During Infusion Week</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in cramp frequency (cramps / wk)</td>
<td>-0.24 (6.65)*</td>
<td>0.79 (6.69)</td>
<td>1.03 [-2.83 to 4.89]</td>
<td>0.60</td>
</tr>
<tr>
<td>Change in mean cramp pain (1-10)</td>
<td>0.02 (1.13)</td>
<td>-0.63 (1.11)</td>
<td>-0.64 [-1.31 to 0.03]</td>
<td>0.07</td>
</tr>
<tr>
<td>Change in # cramps lasting &gt; 1 minute (cramps / wk)</td>
<td>-0.54 (4.96)</td>
<td>-1.03 (2.38)</td>
<td>-0.49 [-2.77 to 1.79]</td>
<td>0.67</td>
</tr>
<tr>
<td><strong>At 30 days</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in cramp frequency (cramps / wk)</td>
<td>-1.69 (3.29)</td>
<td>-2.44 (4.41)</td>
<td>-0.75 [-3.10 to 1.70]</td>
<td>0.51</td>
</tr>
<tr>
<td>Change in mean cramp pain (1-10)</td>
<td>-0.01 (1.05)</td>
<td>-0.38 (1.23)</td>
<td>-0.37 [-1.03 to 0.29]</td>
<td>0.28</td>
</tr>
<tr>
<td>Change in # cramps lasting &gt; 1 minute (cramps / wk)</td>
<td>-1.47 (2.15)</td>
<td>-1.44 (2.92)</td>
<td>0.03 [-1.44 to 1.50]</td>
<td>0.97</td>
</tr>
<tr>
<td><strong>At 90 days</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in cramp frequency (cramps / wk)</td>
<td>-2.20 (3.68)</td>
<td>-3.04 (4.31)</td>
<td>-0.84 [-3.25 to 1.57]</td>
<td>0.49</td>
</tr>
<tr>
<td>Change in mean cramp pain (1-10)</td>
<td>-0.08 (0.50)</td>
<td>-0.11 (0.49)</td>
<td>0.03 [-0.27 to 0.33]</td>
<td>0.84</td>
</tr>
<tr>
<td>Change in cramps lasting &gt; 1 minute (cramps / wk)</td>
<td>-1.71 (2.74)</td>
<td>-1.82 (3.00)</td>
<td>-0.11 [-1.84 to 1.62]</td>
<td>0.90</td>
</tr>
</tbody>
</table>

* Data are means (SD) or differences [95% Confidence Interval]
Mg retention did not predict treatment response, baseline cramp rate or the change in cramp rate during the infusion week (when serum Mg would be highest). Using a median split for Mg retention (median retention = 15%) shows the change in cramp rate for retainers of >15% versus retainers of <15% of the initial Mg load to be -2.4 versus -2.5 cramps / week (p=0.94 (Fig 2.3). No correlation exists between % retention of Mg and change in cramp rate for the Mg treatment group as a whole using linear regression ($R^2 = 0.0087$) – see Fig 2.4. The same is true looking only within the group of >15% Mg retainers.

![Histogram of Change in # Cramps / Week Post Infusions Grouped by degree of Mg retention](image)

**Figure 2.3** Histogram of change in number of cramps per week post infusions (grouped by degree of Mg retention)
Mean 24 hour urinary Mg excretion in Mg recipients at baseline (day 1 of infusions) was 17.5 +/- 3.3 mmol and rose on Day 5 to 20.2 +/- 3.1mmol. A statistically significant positive correlation existed (p=0.03 r=0.46) between urine Mg excretion at baseline and eGFR - which is consistent either with other work suggesting that low intracellular Mg may impair glomerular filtration rate\textsuperscript{94,118}, or with the possibility that lower glomerular filtration of Mg itself leads to lower excretion rates.

Within the Mg treatment group, mean urinary Mg excretion in oral Mg users versus non-users was 18.3 vs. 17.0 mmol/L p=0.36. Non-users of oral Mg trended (non-significantly) towards a greater reduction in cramps / week when given Mg (-3.2 vs. -0.93 cramps / week p=0.13) but this appeared driven solely by the 10 highest rate crampers – none of whom took oral Mg, and who trended non-significantly to a greater response to treatment. Comparing percent reduction in cramp rate instead of change in # cramps per week shows no significant difference between non-users and users of oral Mg (-29.6% vs. -21.6% p=0.64).
The only major adverse event was a stroke on day 31 post infusions in one placebo recipient. Asymptomatic hypotension was reported by the study nurse in 3/24 Mg vs. 0/22 placebo subjects during infusions. Facial flushing was noted in 9/24 Mg and 7/22 placebo recipients but was generally not complained of by subjects. Two Mg recipients noted transient lightheadedness several hours after the infusions on day 3 and day 4 and more Mg recipients noted burning of the IV site (12/24 vs. 0/22) with 5/24 Mg subjects receiving some piggybacked extra dilution of the IV solution with normal saline to improve tolerability.

Subjects had been told that IV site discomfort was possible with both placebo and Mg infusions. While generally it was considered that blinding was reasonable, the sensation of burning at the IV site, coupled with the additional saline dilution in some Mg subjects, could have compromised the blind to some extent (presumably favoring the intervention).
2.6 Discussion

I observed a 2.4 cramp per week (-26.8%) reduction in the Mg treatment group compared to a 1.7 (-21.3%) cramp per week reduction in placebo recipients. The difference of 0.7 cramps per week (5.5% reduction) between groups is not statistically significant, nor would it be clinically significant if it were the true difference. I would consider a 25% reduction in cramp rate between groups to be at the lower end of clinical significance for this therapy. If the true difference between therapies is a 25% reduction in favor of Mg, the chance of observing a difference in favor of Mg of 5.5% or less (as we have found) is only 9%. Hence it is unlikely that Mg provides a clinically significant benefit in this population of cramp sufferers.

There was no relationship between the degree of Mg retention at baseline and the change in cramp rate following Mg therapy. This is important since the degree of retention of infused Mg is believed to reflect Mg status 73, 78, 91, 93, and has been shown to correlate very strongly with the extent of intracellular Mg increase following a series of Mg infusions (assessed via skeletal muscle biopsy) 90. On its own, the observation that there was no greater reduction in cramps following Mg infusion in retainers of Mg argues strongly against a therapeutic value for Mg in cramp prophylaxis.

Two previous published RCTs (N=42 and N=46 included in analysis) have assessed oral Mg in older adult rest crampers 64, 65. Both employed a crossover design. The first found no difference between oral Mg and placebo 64, the second suggested a trend to benefit (p=0.07) 65. Both studies used magnesium citrate. However the study finding no benefit gave it in pill form, while the study suggesting benefit gave it as a powder dissolved in water. In this second study the placebo powder (provided by the manufacturer and sponsor of the trial)
consisted of vehicle / flavoring without Mg citrate added. Bias in this cross-over trial may have been introduced both by unsuccessful blinding and by a very high (37%) drop-out rate.

My results differ from those of the single study (N=73 parallel design) that reported a benefit from oral Mg in the rest cramps of pregnancy\textsuperscript{66}. This population is metabolically very distinct from the older adults we studied and it would not be surprising if the rest cramps of aging and pregnancy prove to have different underlying etiologies.

Subjects for my clinical trial were recruited roughly equally from participating Richmond family practices and from self-referral following newspaper advertisement in the Vancouver area. Ad responders were much more likely to have leg complaints which were not truly cramps, and to have associated neurologic conditions that disqualified them. I was very careful in screening out anyone who did not appear to have typical rest cramps and I believe my results can be generalized to both a primary care and referral geriatric population.

Conceivably, I could have missed a meaningful reduction in cramps because of the slow equilibration of Mg within different tissue compartments\textsuperscript{77} preventing adequate Mg replacement during the 5 days of infusions. However, the mean urinary Mg excretion rose from 17.5 mmol on day 1 to 20.2 mmol on day 5 with the percentage of those with >15% retention falling from 48% (11/23) day 1 to 10% (2 / 21) day 5 – which is consistent with adequate replacement. Additionally, both human studies of experimental Mg deficiency and case reports of muscle cramping in established Mg deficiency have all shown resolution of cramps following infusions of substantially less Mg than the 100 mmol total Mg infused in this study\textsuperscript{108-110}.

I also observed a non-significant trend to a greater reduction in cramp pain during the infusion week. This was a post-hoc analysis and may be a spurious finding, however there is
evidence that magnesium infusions can lessen pain in post-herpetic neuralgia patients during a 30 minute magnesium infusion\textsuperscript{119} (presumably by it’s role as an NMDA receptor antagonist) so this potential effect of magnesium deserves further consideration.

It is possible that a clinically distinct subset of crampers (e.g. non-users of oral Mg with very high cramp rates) can be defined that might still benefit from Mg, but studies with larger numbers of those subsets would be needed to determine benefit. If a true reduction in rest cramp frequency can be attributed to Mg supplementation in an older adult population, it would appear to be restricted either to a minority subgroup or, if the majority benefit, to a relatively small magnitude of effect.

2.7 Conclusion

Although oral Mg has demonstrated efficacy only in the setting of pregnancy associated rest cramps, it is marketed over-the-counter worldwide to the elderly - who constitute the majority of rest cramp sufferers. I have found no benefit to Mg therapy in older adults despite a highly reliable (intravenous) delivery method, and have additionally shown that treatment response does not vary with the degree of Mg retention. Collectively, these findings suggest that Mg therapy is unlikely to be beneficial for cramp prophylaxis in a geriatric population.
Chapter 3: Cochrane Systematic Review: Magnesium for Muscle Cramps

3.1 Preamble

Having demonstrated that parenteral magnesium lacked efficacy in preventing nocturnal leg cramps in older adults, I then asked the question of whether magnesium possessed efficacy in preventing skeletal muscle cramps in any clinical setting. A Cochrane Systematic review of leg cramps in pregnancy concluded that magnesium had the best evidence for cramp prophylaxis, however the evidence for that statement came from a single study. Additionally, this Cochrane review was out of date, having initially been published in 1996 and last updated on Oct 30, 2001. According to the Cochrane Collaboration website they were “looking for new authors to update this review”.

Instead of looking to update this particular review I proposed to the Cochrane Neuromuscular Diseases Group to do a new review of “Magnesium for Skeletal Muscle Cramps” intended to synthesize all randomized trial evidence relevant to the use of magnesium in providing prophylaxis for skeletal muscle cramps in any clinical setting (including pregnancy). The following chapter provides the content of this review. The protocol has already been published as: Garrison SR, Allan GM, Sekhon RK, Musini VM, Khan KM. Magnesium for skeletal muscle cramps (Protocol). Cochrane Database of Systematic Reviews. 11. 2011. At the time of submitting this dissertation the full review was complete and under editorial review by the Cochrane Neuromuscular Diseases Working Group.
3.2 Project Objectives

To review systematically randomized controlled trials (RCTs) comparing magnesium supplementation to no treatment, placebo control or other cramp therapies in participants with symptomatic skeletal muscle cramps.

3.3 Hypothesis

Magnesium supplements do not possess efficacy for the prophylaxis of skeletal muscle cramps despite widespread marketing for that purpose.

3.4 Methods

3.4.1 Criteria for Considering Studies for This Review

Types of studies

Open label, single blind or double blind RCTs (including parallel group or cross-over trials).

Types of participants

People in any age group with all forms of skeletal muscle cramp, whether idiopathic or disease-associated, and in any body part. Participants potentially included (but were not limited to) those with nocturnal leg cramps, pregnancy-associated leg cramps, exercise-associated cramps and disease state-associated cramps such as those associated with amyotrophic lateral sclerosis (ALS), haemodialysis or liver failure.
**Types of interventions**

Magnesium salts and combinations of salts (e.g. magnesium citrate, lactate, gluconate, malate, orotate, chloride, oxide, carbonate, hydroxide or sulphate) administered orally or parenterally (IM or IV) at any dose. I excluded trials if the intervention combined magnesium salts with other active ingredients unless the same intervention was given to both groups. Valid comparators included placebo, no treatment or other cramp therapies (e.g. prophylactic stretching, quinine, calcium channel blockers, sodium channel blockers, electrolyte supplements or supplemental hydration).

**Types of outcome measures**

**Primary outcomes**

The primary outcome measure was the *percentage reduction from baseline in the number of muscle cramps per week at four weeks*. I also reported the same measure at 12 weeks as a secondary outcome.

I chose percent reduction from baseline as the primary outcome because I believe it to be the most clinically relevant outcome measure and because the effect of cramp treatments in general is more likely to be proportional to baseline cramp rate than to be additive (i.e. a patient with 20 cramps per week and a patient with two cramps per week who receive benefit from a therapy are more likely to see a similar percentage reduction in cramps than to share a similar absolute reduction in the number of cramps per week).
Secondary outcomes

1) *Percentage of subjects with at least a 25% reduction from baseline in the number of muscle cramps per week at four weeks and 12 weeks.*

   This was chosen as a secondary outcome since most therapies only work in a subset of individuals. It is hence useful to know how many people receive what I believe to be the minimally important clinical difference (a 25% reduction in cramp rate).

2) *Number of cramps per week at four weeks and 12 weeks.*

   I chose this as a secondary outcome to improve the ability to pool results if studies did not report baseline cramp rates. I also chose this measure because percentage change in cramp rate (the primary outcome) can have low power when the correlation between baseline and post-treatment measures is low (i.e. Pearson correlation coefficient less than 0.5) and in this low range of correlation the difference between treatment groups at the end of treatment offers better power than either percentage change or absolute change from baseline\textsuperscript{120}. In the RCT of magnesium infusion I had just finished conducting (Chapter 2) the correlation coefficient between baseline and post-treatment cramps was approximately 0.5.

3) *Cramp intensity (pain) on a three-point scale at four weeks and 12 weeks.*

   The mean of all cramp intensities (if cramps were individually rated) or the global assessment of cramp pain while on treatment were translated into a three-point scale representing cramp intensity, where 1 = mild, 2 = moderate, 3 = severe. I analysed cramp intensity by looking at mean values and also by looking at the number of individuals rating
their cramps as moderate or severe (i.e. a score of at least two on the three-point intensity scale).

4) **Cramp duration on a three-point scale at four weeks and 12 weeks.**

I translated the mean of all cramp durations (if cramps were individually rated) or the global assessment of cramp duration while on treatment into a three-point scale representing cramp duration where one is equal to less than one minute; two is equal to one to five minutes; and three is equal to more than five minutes. I analysed cramp duration by looking at the number of individuals rating their cramps as lasting more than one minute (i.e. a score of at least two on the three-point duration scale).

5) **Treatment withdrawals due to adverse events.**

6) **Number of subjects reporting minor adverse events** (minor adverse events being symptoms not requiring medical treatment, e.g. diarrhea).

7) **Number of subjects reporting major adverse events** (major adverse events being death, hospitalization and or symptoms requiring medical treatment).
3.4.2 Search Methods for Identification of Studies

Electronic searches


I used the following terms: muscle cramp(s); muscle spasm(s); muscle contraction(s); charlie horse(s); charley horse(s); EAMC(s); Magnesium; Mg2. EAMC is a commonly used sports medicine acronym for "exercise associated muscle cramp" and charlie (or charley) horse is a lay term for muscle cramps.

The detailed search strategies are in the appendices: CENTRAL (Appendix A.1), MEDLINE (Appendix A.2), EMBASE (Appendix A.3), LILACS (Appendix A.4), CINAHL Plus (Appendix A.5), AMED (Appendix A.6) and SPORTDiscus (Appendix A.7).

Searching other resources

I checked all references in the identified trials and contacted the authors to identify any additional published or unpublished data. I contacted relevant pharmaceutical manufacturers to request any unpublished trials that might be in their possession. I also searched the International Clinical Trials Registry Platform (WHO-ICTRP) in an attempt to uncover unpublished trials, searched ISI Web of Science for papers citing the studies included in this review, and contacted the FDA to ask if they had any related clinical trial information in their possession.
3.4.3 Data Collection and Analysis

Selection of studies

Two review authors independently examined the titles and abstracts of all articles identified by the search algorithm, obtained the full text of all potentially relevant studies and determined which studies met the inclusion criteria. A third author was available to adjudicate any disagreements regarding study inclusion.

Data extraction and management

Two authors independently rated the risk of bias of each study and extracted data onto specially designed forms.

3.4.4 Assessment of Risk of Bias in Included Studies

Two authors assessed the risk of bias in the included studies according to The Cochrane Collaboration's recommended tool. Risk of bias within each study was documented according to seven domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, use of a cramp diary and 'other sources of bias'. Each domain was rated as at high, low or unclear risk of bias. Use of a cramp diary was included as a dimension for bias in this review since patient recollection at the time of an exit interview is open to more bias, especially if blinding is poor. Two authors of this review (Dr. Khan and I) were co-authors of one of the included trials (Chapter 2). Neither Dr. Khan nor I participated in the bias rating of our own trial.
3.4.5 Measures of Treatment Effect

Diary recording of individual cramps, along with their intensity and duration, was the preferred measure of cramps, but I accepted any means of recording cramp data (e.g. subject recollection at the time of reassessment) from which the number of cramps per week could be calculated. In order to combine results, the number of cramps per week needed to be reported and calculable on a continuous scale. I did not use cramp frequency data for meta-analysis if it was reported in category ranges such as 'less than two cramps per week' or 'more than seven cramps per week'.

For duration and intensity of cramps, either an average of the duration and intensity of each cramp over the treatment period, or a global assessment by each subject regarding duration and intensity was acceptable so long as it could be meaningfully translated into the three-point scales for intensity and duration outlined above.

For each included study the unit of analysis and the unit of randomisation (expected to be the patient) needed to match to prevent the introduction of bias.

3.4.6 Dealing with Missing Data

I requested any missing data from the study authors. Where studies measured cramp rate, intensity or duration in categories that did not allow us to meaningfully convert cramp rate into a continuous number of cramps per week (or intensity and duration into our three-point scales), I described and discussed these studies but did not include them in the meta-analysis.
3.4.7 Data Synthesis

My inclusion criteria encompassed a wide range of diagnoses (e.g. cramps associated with exercise, pregnancy, aging or disease states such as ALS) for which a variation in treatment effect was certainly possible. However, combining such disparate patient populations using a random-effects model and producing an overall treatment effect for magnesium across all populations could have been misleading and not properly address the clinical question, which should clearly account for the patients' clinical setting. Accordingly, I undertook a fixed-effect analysis within each of the clearly defined clinical settings for which data was available (these being pregnancy and age associated leg cramps) and did not provide meta-analysis across all patient groups. Any across group comparison was descriptive (qualitative) in nature. For meta-analysis within each clinical setting the fixed-effect statistic $I^2$ was calculated to assess for heterogeneity and, if it exceeded 25%, a sensitivity analysis was conducted. An $I^2$ threshold of greater than 25% was selected since it conservatively excluded heterogeneity which the Cochrane Handbook considers “might not be important”\textsuperscript{121}.

Trial data identified for inclusion in this review were combined using the Cochrane statistical package, Review Manager (RevMan). Continuous outcomes were combined using the generic inverse variance method (GIV) which allowed paired data from cross-over trials (in which subjects serve as their own controls) to be combined with two-group parallel studies. Standard error estimates for included studies were obtained from intervention and control group means and standard deviations when unpaired t-tests were applied (parallel group trials), and from the mean difference between groups and p-value for the difference when paired t-tests were used (cross-over trials).
Assessment of reporting biases: I planned to use a funnel plot to assess publication bias but there were too few studies for this to be meaningful.

Subgroup analysis: An insufficient number of studies were available to permit meaningful subgroup analysis at this time.

Sensitivity analysis: Heterogeneity existed in the trials of magnesium versus placebo for the prophylaxis of pregnancy induced leg cramps (2 studies). Neither of these trials had reported outcomes in a way that permitted data pooling. Differences in study design that could have led to their discrepant results were discussed qualitatively.

3.5 Results

3.5.1 Description of Studies

Results of the search

Search results from MEDLINE, EMBASE, CENTRAL, CINAHL Plus, SPORTDiscus, Cochrane NMD Group Register, AMED and LILACS revealed 82, 57, 16, 14, 14, 4, 1 and 1 papers respectively. Thirty three titles were relevant to the topic and the abstracts of these were analysed. The full texts of 11 studies were reviewed. Five were excluded (see the table Characteristics of Excluded Studies) leaving 6 studies that met our inclusion criteria. Additionally, one unpublished eligible RCT was uncovered by a search of the International Clinical Trials Registry Platform (WHO-ICTRP), bringing the total of included studies to 7. Contacting the FDA, Health Canada and relevant manufacturers revealed no further studies. Nor did searching ISI Web of Science for papers citing the studies included in this review. Examining reference lists of all included papers and relevant reviews revealed two studies whose full papers were obtained but which were excluded. See tables 3.1 to 3.7 for
characteristics of the included trials. All included trials are in English but no exclusions were made based on language.

**Included studies**

Magnesium was generally compared to placebo (six trials)\(^{64-66, 122-124}\) although one trial (Sohrabvand 2006)\(^{125}\) with four parallel treatment arms compared no treatment to magnesium, calcium carbonate and a combined supplement of vitamins B1 and B6.

Magnesium was given orally in all but one trial, where it was administered as a series of intravenous infusions (Garrison 2011)\(^{122}\). Oral magnesium was given either once at night (Roffe 2002)\(^{65}\) or twice daily (Dahle 1995; Frusso 1999; Sohrabvand 2006; Nygaard 2008; Rosenbaum 2011)\(^{64, 66, 123-125}\), with larger doses at night in two studies (Dahle 1995; Nygaard 2008)\(^{66, 123}\).

The amount of elemental magnesium administered daily through the various oral protocols included 366 mg from "primarily magnesium lactate and magnesium citrate" tablets (Dahle 1995; Nygaard 2008)\(^{66, 123}\), 200 mg from magnesium citrate tablets (Frusso 1999)\(^{64}\), 300 mg from tri-magnesium dicitrate powder dissolved in water (Roffe 2002)\(^{65}\), 336 mg from magnesium lactate as slow release tablets (Rosenbaum 2011)\(^{124}\), and 364 mg from magnesium aspartate (Sohrabvand 2006)\(^{125}\) (unclear if tablet or powder). The durations of treatment for oral magnesium ranged from 14 to 42 days, with total oral doses of elemental magnesium over the entire treatment period ranging from 5,096 mg to 12,600 mg. The study (Garrison 2011)\(^{122}\) providing magnesium intravenously (i.e. my study) gave 20 mmol of magnesium sulfate (486 mg of elemental magnesium) as an infusion over 4 hours on 5
consecutive days. This provided a total treatment dose of 2,430 mg of elemental magnesium, although with presumably different (higher) bioavailability.

This (my) trial recorded cramps for 90 days post infusions but all other trials recorded cramps over 2-4 weeks. Five of the studies were parallel in design and two were cross-over. Three studies involved treatment of pregnancy-associated leg cramps (Dahle 1995; Sohrabvand 2006; Nygaard 2008) and the remaining four involved the treatment of idiopathic cramps in older adults (most of whom are presumed to have been suffering nocturnal leg cramps). One of the trials was unpublished (Rosenbaum 2011) but some patient level data was made available to us. Two other studies (Roffe 2002; Garrison 2011) also made patient level data available, although the data from Roffe did not include noncompleters. No studies investigating exercise or disease state associated cramps were found.

A total of 406 unique participants were enrolled in these trials. Of these, 118 were cross-over subjects and additionally formed their own controls. All trials were small, varying from 40 to 84 participants. All subjects were community dwelling. Most were outpatients recruited from primary care or maternity clinics, although some were recruited by newspaper or radio advertisement. Subjects in the idiopathic cramp trials were 64.8 years of age on average and 62.8% female. Only one of the three pregnancy trials provided data on mean age (30.9 years).

One of the cross-over trials (Frusso 1999) used a 28 day washout. The other (Roffe 2002) did not have a formal washout period but evaluated outcomes only in the last four weeks of each of two sequential six week treatment periods. This effectively gave a two week washout to those who started on magnesium and an extra two weeks of magnesium
therapy (while on magnesium) prior to each evaluation period. The author of this trial kindly provided me patient level data to permit data pooling. It is my opinion that this cross-over trial demonstrated a large difference in treatment effect depending on the sequence of treatments. Of 17 subjects receiving the sequence magnesium → placebo, eight favour magnesium, seven favour placebo and two are unchanged. In contrast, of 29 subjects receiving the sequence placebo → magnesium, 21 favour magnesium, five favour placebo and 3 are unchanged. It is unclear how much of this difference was due to the period effect and how much was due either to the high rate of noncompleters (27 of 73 subjects did not complete the trial), the potential for carry-over or the potential for unblinding. As a result of this sequence order effect I chose to minimize these potential sources of bias by using only data from the first period of this study.
Tables 3.1 to 3.7 Characteristics of included studies

Table 3.1 Study characteristics for Dahle 1995

<table>
<thead>
<tr>
<th>Dahle 1995</th>
<th>66</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Double-blind, parallel group RCT</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>73 pregnant women (mean 29 wks gestation) with rest cramps and no previous cramp treatment. Recruitment from Swedish prenatal care clinics.</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Either a chewable tablet containing 122 mg elemental Mg (&quot;primarily as Mg lactate or Mg citrate&quot;), or matched placebo tablet, taken once each morning and twice each evening for 3 weeks</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Primary outcome unclear. Change in cramp frequency on a 5 point ordinal scale. Time of day cramps occur on a 4 point nominal scale. Presence of symptoms the day after a night of cramping on a 3 point ordinal scale. Global patient assessment of treatment effect on a 5 point ordinal scale. Cramp Intensity on a visual analog scale. Serum Mg and Ca and 24-hr urinary Mg and Ca excretion</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>Published. Manufacturer sponsored. Did lab tests at only one of the two centres</td>
</tr>
</tbody>
</table>

Table 3.2 Study characteristics for Frusso 1999

<table>
<thead>
<tr>
<th>Frusso 1999</th>
<th>64</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Double-blind RCT of cross-over design</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>45 non-pregnant rest cramp sufferers &gt; 18 yrs (mean age 61.6 yrs) having a normal neurologic exam and at least 6 leg cramps in a 4 week placebo run-in. Recruitment from a single large university-based Argentinean family practice clinic.</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Magnesium citrate 900 mg pill (approx 100 mg elemental Mg) twice daily or similar tasting and appearing placebo, each for 4 weeks. Four week placebo run-in and 4 week washout between treatments.</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Primary: Number of cramps in treatment period. Secondary: Cramp duration by 4 ordinal categories (&lt; 5 minutes, 5-10 minutes, 10-30 minutes, &gt;30 minutes). Cramp intensity by “analog scale”. Sleep disturbance on a 0 to 10 scale with 0 = “no sleep disturbance” and 10 = “could not sleep because of the cramps”. Adverse events.</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>Published. Independent funding. The 4 week placebo run-in was pre-randomization. Unclear what the range for the analog scale of intensity is (assumed 0 -10). Cramp duration is recorded by ordinal category but reported with a mean and standard deviation in minutes.</td>
</tr>
</tbody>
</table>
### Table 3.3 Study characteristics for Garrison 2011

<table>
<thead>
<tr>
<th></th>
<th>Garrison 2011</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Double-blind, parallel group RCT</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>46 non-pregnant rest cramp sufferers (mean age 69.3 yrs) with at least 8 cramps in a 30 day baseline diary. Recruitment from posters and pamphlets in 21 Canadian (Richmond BC) family practitioner offices and also by newspaper advertisement</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>5 days consecutive 4 hour intravenous infusions of 250 ml D5W either with (treatment group) or without (control group) 20 mmol of magnesium sulfate added (20 mmol = 486 mg elemente Mg).</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Primary: Change in the number of cramps per week from baseline at 30 days. Secondary: Change in the number of cramps per week from baseline at 90 days. Percentage change in cramps / wk. Cramp pain (1 to 10 interval scale). Cramp duration on a 3 point ordinal scale (1 = &lt; 1 minute, 2 = 1-5 minutes, 3 = &gt; 5 minutes). 24 hr urine magnesium on days 1 and 5 to determine % retention of infused magnesium.</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>Published. Independent funding.</td>
</tr>
</tbody>
</table>

### Table 3.4 Study characteristics for Nygaard 2008

<table>
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<th></th>
<th>Nygaard 2008</th>
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<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Double-blind, parallel group RCT</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>45 pregnant women with rest cramps and no previous cramp treatment. Recruitment by pamphlets provided to pregnant Norwegian women undergoing 18 week ultrasound</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Either a chewable tablet containing 122 mg elemente Mg (&quot;primarily as Mg lactate and Mg citrate&quot;), or a matched placebo tablet, taken once each morning and twice each evening for 2 weeks</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Number of days or nights in which cramps occur over 2 weeks. Degree of cramp pain on a 5 point ordinal scale. Side effects. Serum Mg and Ca and 24-hour urinary Mg on days 1 and 15</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>Published. Source of funding not provided.</td>
</tr>
</tbody>
</table>
### Table 3.5 Study characteristics for Roffe 2002

<table>
<thead>
<tr>
<th>Methods</th>
<th>Double blind RCT of cross-over design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>73 non-pregnant rest cramp sufferers (mean age 63 yrs), having at least 2 cramps per week. Recruitment by community advertisement in a UK population</td>
</tr>
<tr>
<td>Interventions</td>
<td>Either 1830 mg of tri-magnesium dicitrate powder (300 mg elemental magnesium) poured from a sachet into a glass of water, or matched placebo powder, taken orally each night for 6 weeks before switching to the alternate therapy. 2 week magnesium free run-in and effectively a 2 week washout between treatments since only the last 4 weeks of each 6 weeks on treatment was used for outcome assessment</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Number of cramps during the last 4 weeks of each treatment period. Severity of cramps (mild, moderate, severe). Duration of cramps (short, medium, long). Self reported assessment of treatment effectiveness (yes, no)</td>
</tr>
<tr>
<td>Notes</td>
<td>Published. Manufacturer sponsored. Only data from the first period is used in this review because large differences in treatment effect are seen depending on the sequence in which treatment is given. Patient level data provided by the principle investigator.</td>
</tr>
</tbody>
</table>

### Table 3.6 Study characteristics for Rosenbaum 2011

<table>
<thead>
<tr>
<th>Methods</th>
<th>Double blind, parallel group RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>40 non-pregnant rest cramp sufferers (45 to 80 yrs of age) with normal renal function having at least 2 cramps per week that were rated 5 or more on a 0-10 pain scale. Recruitment by radio advertisement in an American (State of Michigan) population.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Either 168 mg elemental magnesium from slow release magnesium lactate tablets (MagTabSR) or matching placebo tablets taken orally twice daily for 30 days.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Frequency, duration and severity of leg cramps captured daily x 1 wk pre-intervention and daily during the 30 days of intervention (via diary recording of cramps and sleep disturbance). Pittsburgh Sleep Quality questionnaire also administered pre and post intervention.</td>
</tr>
<tr>
<td>Notes</td>
<td>Unpublished. Sponsorship not provided. Incomplete results reporting. Patient level data for cramp frequency was kindly provided by study statistician.</td>
</tr>
<tr>
<td><strong>Table 3.7 Study characteristics for Sohrabvand 2006</strong></td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Methods</strong></td>
<td></td>
</tr>
<tr>
<td>Open label randomized controlled trial with 4 parallel treatment groups</td>
<td></td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td></td>
</tr>
<tr>
<td>84 pregnant women. Recruitment method (Iranian women) not provided.</td>
<td></td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td></td>
</tr>
<tr>
<td>Group 1: 500mg calcium carbonate tablet once daily</td>
<td></td>
</tr>
<tr>
<td>Group 2: 7.5 mmol magnesium aspartate (182 mg elemental Mg) twice daily</td>
<td></td>
</tr>
<tr>
<td>Group 3: 100 mg of thiamine (vitamin B1) plus 40 mg of pyridoxine (vitamin B6) once daily</td>
<td></td>
</tr>
<tr>
<td>Group 4: No treatment</td>
<td></td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td></td>
</tr>
<tr>
<td>&quot;Change in muscle spasms&quot; on a 3 point ordinal scale (no change, &quot;relative improvement&quot;, or &quot;absolute improvement&quot;)</td>
<td></td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td></td>
</tr>
<tr>
<td>Unusual design. Each treatment is given over two weeks but efficacy is assessed at 4 weeks. Published as a &quot;brief communication&quot; (letter) only. Funding source not provided. No definition of relative and absolute improvement was given in the manuscript but this was confirmed with the author to mean partial and complete resolution of the overall cramp burden (which presumably takes into account both intensity and frequency).</td>
<td></td>
</tr>
</tbody>
</table>
Excluded studies

Excluded trials were either uncontrolled, did not have a magnesium treatment arm, or did not measure outcomes relevant to cramping (Table 3.8).

Table 3.8 Excluded studies

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aagaard 2005 126</td>
<td>This RCT looked at muscle strength, muscle mass and muscle magnesium content. It did not look at measures of muscle cramping.</td>
</tr>
<tr>
<td>Hammar 1987 129</td>
<td>No magnesium treatment arm.</td>
</tr>
<tr>
<td>Haringer 1981 130</td>
<td>No control group. Article in German. Abstract and Methods translated.</td>
</tr>
<tr>
<td>Riss 1983 131</td>
<td>Uncontrolled. Article in German with English abstract.</td>
</tr>
<tr>
<td>Weller 1998 132</td>
<td>This RCT looked at exercise performance and magnesium concentration in various tissues. It did not look at measures of muscle cramping.</td>
</tr>
</tbody>
</table>
Risk of bias in included studies

The risk of bias assessment was carried out as outlined in methods and summarized in Figure 3.1. There was considerable variability in the quality of included trials.

**Allocation (selection bias)**

The risk of selection bias (randomization or allocation) was unclear (though likely adequate) in six of seven trials, largely because of inadequate description of methods in the manuscripts and our inability to obtain responses from some authors. In one cross-over trial (Roffe 2002) the manufacturer provided randomization in large blocks which were either unbalanced initially or became unbalanced because of noncompleters (17 subjects were randomized to placebo → magnesium and 29 to magnesium → placebo). Since the treatment effect in this trial varied depending on the sequence order of treatment this imbalance in sequence allocation was an important potential source of bias and only the first treatment period was used for data pooling.
**Blinding (performance bias and detection bias)**

Blinding was low risk in four of seven trials. In one trial (Garrison 2011)\(^{122}\) it was unclear because of a greater likelihood of magnesium recipients experiencing a burning sensation at the IV site during intravenous infusion. In one cross-over trial (Roffe 2002)\(^{65}\) it was unclear because no description was given as to whether magnesium and placebo solutions could be distinguished by taste. The risk of bias was high in one trial (Sohrabvand 2006)\(^{125}\) because blinding was not possible (open label).

**Incomplete outcome data (attrition bias)**

Attrition bias was low risk in five of the seven studies. It was unclear in one study (Nygaard 2008)\(^{123}\) with a 15.6% dropout rate and high risk in one study (Roffe 2002)\(^{65}\) with a 37% dropout rate.

**Selective reporting (reporting bias)**

In three of the seven studies reporting bias was considered to be low. This included two studies (Roffe 2002; Garrison 2011)\(^{65, 122}\) whose manuscripts did report selectively (i.e. both reported that some secondary outcomes were not statistically significant without providing actual numbers) but whose authors provided us the patient level data to allow for the calculation of these outcomes. Studies with greater than low risk included two studies (Sohrabvand 2006; Frusso 1999)\(^{125}\) whose risk was unclear because of inconsistencies in reporting, one unpublished study (Rosenbaum 2011)\(^{124}\) whose risk was high because only a subset of outcomes was available and one study (Dahle 1995)\(^{66}\) whose risk was high because it was unclear how well the outcomes were predefined (i.e. there was no description of
outcomes by primary and secondary and the outcomes were incompletely described in the methods).

**Other potential sources of bias**

Two of the three trials in pregnant women (Dahle 1995; Sohrabvand 2006)\(^{66,125}\) were viewed as having high risk of bias for not using cramp diaries (instead recalling cramp frequency at the time of exit interviews) and one trial was also felt to be at high risk of bias for being extremely under reported (Sohrabvand 2006)\(^{125}\). Most studies also had one or more additional sources of bias but nothing which was in common with other trials or viewed as a fatal flaw.
<table>
<thead>
<tr>
<th>Bias</th>
<th>Author’s judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Not described (&quot;The patients were then randomly allocated to either magnesium or placebo&quot;)</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not described. See above for only quote</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>Low risk</td>
<td>Quote: “A magnesium-placebo tablet batch of 90 numbered bottles was prepared by ACO Lakemedel...” Comment: Probably satisfactory, although pills were not described</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>4 / 73 subjects dropped out of the study and were excluded from the analysis. Reasons for dropout were well described but treatment group was not identified. One placebo patient withdrew from treatment but appears (unclear) to have been included in the analysis. Comment: Probably adequate as total number of dropouts was small.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>No description of outcomes by primary and secondary and outcomes were incompletely described in methods. I.e. only in results is it evident that before and after comparisons, mean differences and numbers attaining specific cutoffs are used. Unclear how well outcomes were predefined. Inadequate reporting: no actual numbers for many p values. This study also reported a reduction in cramp frequency &quot;from the initial average of every other day, to every 3 days in the placebo group and one to two times a week in the magnesium group (p &lt; 0.05)&quot;. However, &quot;every 3 days&quot; and &quot;one to two times a week&quot; do not belong to the 5-point ordinal scale used to measure this outcome (daily, every other day, twice a week, once a week, never).</td>
</tr>
<tr>
<td>Cramp Diary (recall Bias)</td>
<td>High risk</td>
<td>No diary used</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Subjects treated differently at each site (one used lab testing, the other did not).</td>
</tr>
</tbody>
</table>
Table 3.10 Frusso 1999 rationale for risk of bias assessment

<table>
<thead>
<tr>
<th>Bias</th>
<th>Author’s judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
</table>
| Random sequence generation (selection bias)    | Unclear risk       | Quote: “Patients randomly received magnesium or placebo...”  
Comment: Unclear how randomization was performed |
| Allocation concealment (selection bias)        | Unclear risk       | Quote: “The codes were inside a sealed envelope opened at the end of the analysis.”  
Comment: Unclear who allocated subjects and maintained the blind |
| Blinding (performance bias and detection bias) | Low risk           | Quote: “Each pill contained 900 mg of magnesium citrate or matched placebo (same appearance and taste).”  
Comment: Satisfactory blinding |
| Incomplete outcome data (attrition bias)       | Low risk           | 3 / 45 subjects withdrew with reasons given. It is not stated which intervention they were receiving at the time or how their data was dealt with.  
Comment: Probably satisfactory as the number of dropouts is small. |
<p>| Selective reporting (reporting bias)           | Low risk           | No indication of selective reporting for clinical endpoints (although urine for Mg was collected and not reported). Duration of cramps is measured on a 4 point ordinal scale but results were reported as mean durations and standard deviations in minutes as though it were a continuous variable. |
| Cramp Diary (recall Bias)                      | Low risk           | Diary Used                                                                                                                                           |
| Other bias                                     | Low risk           | No obvious other bias                                                                                                                                  |</p>
<table>
<thead>
<tr>
<th>Bias</th>
<th>Author’s judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
</table>
| Random sequence generation (selection bias)  | Low risk           | Quote: "Randomization, using a computer generated random allocation sequence without any blocking or stratification was carried out by the hospital pharmacist dispensing the study drugs according to a series of opaque allocation envelopes kept in the pharmacy."  
Comment: Satisfactory randomization                                                                 |
| Allocation concealment (selection bias)      | Low risk           | Quote: "All investigators, study nurses and subjects were blinded as to treatment allocation."  
Comment: Satisfactory allocation concealment                                                                 |
<p>| Blinding (performance bias and detection bias)| Unclear risk       | Quote: 1) &quot;Active and Placebo solutions were indistinguishably clear and colorless.&quot; 2) &quot;Subjects had been told that IV site discomfort was possible with both placebo and Mg infusions. While generally it was considered that blinding was reasonable, the sensation of burning at the IV site, coupled with the additional saline dilution in some Mg subjects, could have compromised the blind to some extent (presumably favouring the intervention).&quot; |
| Incomplete outcome data (attrition bias)      | Low risk           | No drop-outs or losses to follow-up. Analysis was intention to treat.                                                                                   |
| Selective reporting (reporting bias)          | Low risk           | Did not process urine samples for magnesium on those getting placebo (although did a reasonable job collecting urine samples from all patients to make sure the blinding was not broken). Severity and duration of cramps were described only as not being different (i.e. no numbers given), however this data was made available by the authors. |
| Cramp Diary (recall Bias)                     | Low risk           | Diary used                                                                                                                                              |
| Other bias                                   | Low risk           | No obvious other bias                                                                                                                                    |</p>
<table>
<thead>
<tr>
<th>Bias</th>
<th>Author’s judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: “The randomization program was provided by Medstat Research AS.” Comment: Probably adequate</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No description of allocation method given</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>Low risk</td>
<td>Quote: “Both groups received a plastic container with the trial medication, 42 chewable tablets...”, containing either magnesium or placebo, both provided by the manufacturer Comment: Probably adequate</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>7 / 45 women (15.6%) dropped out (2 from the treatment arm and 5 from control). Reasons were given and most were unrelated to potential drug effects. None of the 7 were included in the analysis because of a lack of data.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Primary outcome assumed to be the number of days and nights with cramping but not explicitly stated. All outcomes reported.</td>
</tr>
<tr>
<td>Cramp Diary (recall Bias)</td>
<td>Low risk</td>
<td>Diary used</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Frequency of cramping at baseline was not assessed, making it impossible to tell if the groups were imbalanced in this important baseline characteristic</td>
</tr>
</tbody>
</table>
### Table 3.13 Roffe 2002 rationale for risk of bias assessment

<table>
<thead>
<tr>
<th>Bias</th>
<th>Author’s judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Random sequence generation</strong></td>
<td>Unclear risk</td>
<td>The manufacturer provided centralized randomization for the trial in large blocks of 10. Specifics regarding the sequence generation were not given. The resulting allocation was unequal with more subjects included in the analysis receiving magnesium second (29 vs. 17).</td>
</tr>
</tbody>
</table>
| **Allocation concealment**        | Low risk           | Quote: "The randomisation code was not known to the investigators who gave out the sachets. The code remained concealed from everyone except the pharmacist who prepared the sachets..."  
Comment: Satisfactory concealment |
<p>| <strong>Blinding</strong>                      | Unclear risk       | No description of whether the magnesium and placebo suspensions tasted different                                                                       |
| <strong>Incomplete outcome data</strong>       | High risk          | Reasons for dropout documented, but 27 of 73 subjects (37%) did not complete the study                                                                  |
| <strong>Selective reporting</strong>           | Low risk           | Severity and duration of cramps were described only as not being different (i.e. no numbers given), however these data were provided to us by the authors. |
| <strong>Cramp Diary</strong>                   | Low risk           | Diary used                                                                                                                                            |
| <strong>Other bias</strong>                    | Unclear risk       | Manufacturer played an active role in the trial. There was a large difference in treatment effect depending on the sequence of treatments (much greater benefit if treatment was received in the order placebo→magnesium). Unclear if this difference was due entirely to period effect or if noncompleters, the potential for carry-over or unblinding contributed. This difference in benefit resulting from treatment order was important since the randomization was unbalanced (many more subjects receiving the placebo→magnesium sequence). |</p>
<table>
<thead>
<tr>
<th>Bias</th>
<th>Author’s judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Stated as randomized but details not provided.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No details provided.</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;Masking: Double Blind (Subject, Investigator, Outcomes Assessor)&quot;. No details provided. Probably adequate.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>Small number of dropouts, two from magnesium and one from placebo. Reasons not provided.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>Patient level data were provided to us but were only available for a subset of the outcomes.</td>
</tr>
<tr>
<td>Cramp Diary (recall Bias)</td>
<td>Low risk</td>
<td>Diary used</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>No obvious other bias</td>
</tr>
<tr>
<td>Bias</td>
<td>Author’s judgement</td>
<td>Support for judgement</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>--------------------</td>
<td>----------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>No description</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No description</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>High risk</td>
<td>Open label trial</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>No details regarding flow of patients in the manuscript but author communication suggests no dropouts.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Primary outcome not identified (though only one outcome reported). Table 2 showed statistical significance in total improvement for group 2 and 3 compared to group 4 but in the text it stated groups 1 and 3 (which is supported by the CI results).</td>
</tr>
<tr>
<td>Cramp Diary (recall Bias)</td>
<td>High risk</td>
<td>Specifics were not given but there appeared to have only been a qualitative assessment of the change in cramps upon study completion</td>
</tr>
<tr>
<td>Other bias</td>
<td>High risk</td>
<td>Baseline characteristics were said to be not significantly different but they were not provided. Unclear who rated the degree of improvement (patient or physician). Trial was very under reported. Outcomes are grouped in an unpractical way</td>
</tr>
</tbody>
</table>
### 3.5.2 Effects of Interventions

Table 3.16 Summary of findings for idiopathic rest cramps

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Assumed risk</strong></td>
<td><strong>Corresponding risk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>Magnesium</td>
<td>-3.9% (-21.1, 13.3)</td>
<td>83 (2 studies)</td>
<td>⊕⊕⊕⊝ moderate</td>
<td>This difference was neither clinically nor statistically significant. The 95% confidence interval excludes a 25% reduction beyond placebo.</td>
</tr>
<tr>
<td><strong>Percentage change in cramp frequency from baseline at 4 weeks</strong></td>
<td>The mean percentage change in cramp frequency in the control groups was -27.8% (i.e. a 27.8% reduction)</td>
<td>-8% (-28%, 12%)</td>
<td>83 (2 studies)</td>
<td>⊕⊕⊕⊝ moderate</td>
<td>This difference was neither clinically nor statistically significant.</td>
</tr>
<tr>
<td><strong>Percentage of participants with a ≥25% reduction in their cramp frequency at 4 weeks</strong></td>
<td>The mean percentage of placebo recipients achieving a 25% or better reduction in the frequency of their cramps was 65.9%</td>
<td>0.01 cramps per week (-0.52, 0.55)</td>
<td>213 (4 studies)</td>
<td>⊕⊕⊕⊝ moderate</td>
<td>This difference was not clinically or statistically significant. The 95% confidence interval excludes a 1 cramp per week reduction.</td>
</tr>
<tr>
<td><strong>Number of cramps per week at 4 weeks</strong></td>
<td>The mean number of cramps per week in the placebo groups while on treatment was 4.35</td>
<td>0.01 cramps per week (-0.52, 0.55)</td>
<td>213 (4 studies)</td>
<td>⊕⊕⊕⊝ moderate</td>
<td></td>
</tr>
</tbody>
</table>
Table 3.16 (Continued)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo</strong></td>
<td><strong>Magnesium</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Percentage of participants rating their cramps as moderate or severe (i.e. mean cramp intensity &gt;= 2 on the 3 point intensity scale) at 4 weeks</strong></td>
<td>The mean percentage of placebo recipients rating their cramps as moderate or severe was 30%</td>
<td>The mean percentage of magnesium recipients rating their cramps as moderate or severe was 9% greater</td>
<td>9% (-7%, 25%)</td>
<td>91 (2 studies)</td>
<td>⊕⊕⊕⊝ moderate</td>
</tr>
<tr>
<td><strong>Percentage of participants with the majority of cramp durations ≥ 1 minute at 4 weeks</strong></td>
<td>The mean percentage of placebo recipients with the majority of cramp durations ≥ 1 minute was 22.7%</td>
<td>The mean percentage of magnesium recipients with the majority of cramp durations ≥ 1 minute was 19% greater</td>
<td>19% (-7%, 45%)</td>
<td>43 (1 study)</td>
<td>⊕⊕⊝ low</td>
</tr>
<tr>
<td><strong>Number of participants with major adverse events</strong></td>
<td>1 out of 22</td>
<td>0 out of 24</td>
<td>-50 per 1000 [-160 to 70]</td>
<td>⊕⊕⊕⊕ very low</td>
<td>This difference was neither clinically nor statistically significant.</td>
</tr>
<tr>
<td><strong>Number of participants with minor adverse events</strong></td>
<td>Adverse events were not reported in a way that permitted the number of participants with minor adverse events to be determined. Each study of oral magnesium inferred that side effects were similar in frequency to placebo. Intravenous magnesium was associated with asymptomatic hypotension (3/24 magnesium versus 0/22 placebo recipients), transient light-headedness (2/24 magnesium versus 0/22 placebo) and burning of the IV site (12/24 magnesium versus 0/22 placebo).</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3.5.2.1 Measures of Cramp Frequency

While all studies attempted to measure the cramp frequency, or change in cramp frequency, the three trials in pregnant women all used frequency measures which prevented data pooling and only one (Nygaard 2008) used a cramp diary. Cramp frequency measures that could not be pooled included cramp frequency on a five point ordinal scale (Dahle), cramp frequency on a three point ordinal scale (Sohrabvand 2006), and number of days and nights in which cramps occurred (Nygaard 2008). In contrast, all four idiopathic rest cramp trials used cramp diaries and recorded the occurrence of each cramp, permitting analysis of cramp frequency as a continuous variable. The resulting pooled estimates of cramp frequency measures include data from two trials rated as having a high risk of bias, either due to a high dropout rate (Roffe 2002) or selective reporting (Rosenbaum 2011).

A) Percentage reduction from baseline in the number of muscle cramps per week at four weeks (the primary outcome) and at 12 weeks (a secondary outcome)

Magnesium versus placebo

Pregnancy-associated cramps

None of the pregnancy trials determined the baseline cramp rate needed to calculate a percentage change.
Idiopathic rest cramps

At four weeks

Two of the four idiopathic rest cramp trials measured the baseline cramp rate, either over 30 days pre-treatment (Garrison 2011)\textsuperscript{122} or seven days pre-treatment (Rosenbaum 2011)\textsuperscript{124}. Pooling these two studies provides a statistically nonsignificant -3.93\% [-21.12, 13.26] difference in the percentage change in cramp rate, magnesium versus placebo (Figure 3.2). There was no evidence of heterogeneity ($I^2 = 0\%$) and the resulting 95\% confidence interval excludes a 25\% reduction in cramp rate over placebo.

At 12 weeks

Only one study (Garrison 2011)\textsuperscript{122} had data to 12 weeks and found a nonsignificant mean difference, magnesium versus placebo of -12.09\% [-40.22, 16.04].

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{forest_plot.png}
\caption{Forest plot of comparison: Idiopathic Rest Cramps, Magnesium versus placebo, outcome: \%Change in cramp frequency from baseline at 4 week}
\end{figure}
B) Percentage of participants with ≥ 25% reduction in cramp frequency at 4 weeks and at 12 weeks

Magnesium versus placebo

*Pregnancy-associated cramps*

None of the pregnancy trials determined the baseline cramp rate needed to calculate a percentage change.

*Idiopathic rest cramps*

At four weeks

Pooling results from the only two trials with baseline measures (Garrison 2011; Rosenbaum 2011)\textsuperscript{122, 124} shows 65.9% of participants in the placebo group to have achieved a 25% or better reduction in cramp frequency, with the magnesium group being a nonsignificant 8% lower [-28%, 12%] (Figure 3.3). There was no evidence of heterogeneity ($I^2 = 0\%$).

At 12 weeks

The single (Garrison 2011)\textsuperscript{122} study to 12 weeks found the percentage of subjects achieving a 25% or better reduction in the frequency of their cramps to be a nonsignificant 11% higher [-19%, 41%] in the magnesium group.
C) Number of cramps per week at 4 weeks and at 12 weeks

**Magnesium versus placebo**

*Pregnancy-associated cramps*

At four weeks

There were two trials evaluating the frequency of leg cramps, magnesium versus placebo, in pregnant women. The earliest (Dahle 1995) was the first published RCT of magnesium in cramping (in any setting) and the only trial to show statistically significant benefit for reducing the frequency of cramps. It measured cramp frequency on a 5 point ordinal scale (daily, every other day, twice a week, once a week, never) and also measured patient evaluation of treatment effect on a 5 point ordinal scale (entirely free of symptoms, considerably improved, unchanged, worsened, considerably worsened). This study reported a reduction in the frequency of symptoms "from the initial average of every other day, to every 3 days in the placebo group and one to two times a week in the magnesium group (p<0.05)."

The way in which this result is reported is problematic in that "every 3 days" and "one to two times a week" do not belong to the 5 point ordinal scale used to measure this outcome. Dahle 1995 also reported benefit in patient evaluation of treatment effect in that "the magnesium group indicated that they had to a significantly greater extent "improved considerably" or
"become asymptomatic" compared with the placebo group \((p = 0.0002)\) (17/34 magnesium and 11/35 placebo recipients improving considerably, and 10/34 magnesium and 3/35 placebo recipients becoming asymptomatic). In contrast, the subsequent trial (Nygaard 2008)\(^1\) measured the mean number of days and nights with leg cramps present and found no significant benefit with \(7.7 \pm 4.7\) (SD) days and nights of cramping over 2 weeks in the placebo group and \(9.5 \pm 5.1\) in the magnesium group \((p = 0.27)\).

At 12 weeks

There are no trials in pregnant women longer than 3 weeks duration.

**Idiopathic rest cramps**

At four weeks

Cramps per week on treatment was available as an outcome for all four of the idiopathic rest cramp trials and provided a nonsignificant pooled estimate \((N = 216)\) for the mean difference in the number of cramps per week of \(0.01\) cramps / week \([-0.52, 0.55]\) (Figure 3.4). There was no evidence of heterogeneity \((I^2 = 0)\) and the confidence interval excludes a one cramp per week reduction. As mentioned under Included Studies, only the first period of Roffe 2002\(^6\) was used because of an unbalanced randomisation and a difference in benefit depending on treatment order.

At 12 weeks

The single study (Garrison 2011)\(^1\) to 12 weeks found a nonsignificant mean difference in the number of cramps per week of \(-0.84\) \([-3.23, 1.55]\).
Figure 3.4 Forest plot of comparison: Idiopathic Rest Cramps, Magnesium versus placebo, outcome: Number of cramps per week at 4 weeks.

No treatment versus magnesium, calcium carbonate and a combination vitamin B1 / B6 supplement

Pregnancy-associated cramps

At four weeks

The single study in any clinical setting (Sohrabvand 2006)\textsuperscript{125} to use a comparator other than placebo used four parallel treatment arms to compare no treatment with either 182 mg elemental magnesium twice daily (from magnesium aspartate), 500 mg of calcium carbonate once daily or 100mg of thiamine (vitamin B1) combined with 40mg of pyridoxine (vitamin B6) once daily in a group of pregnant Iranian women. This trial had an unusual design with the intervention being given over 2 weeks but outcomes assessed over 4 weeks. The outcome for this study was "change in muscle spasms" on a 3 point ordinal scale with "no change", "relative improvement", and "absolute improvement" clarified with the authors to mean no improvement, partial resolution and complete resolution of cramping. A multinomial regression test was applied to each of the three possible response categories to see if any of the active treatment arms differed from no treatment. Significantly more women reported absolute improvement in both the B vitamin and calcium arms, but not in the magnesium
arm. Neither was there a difference in relative improvement between no treatment and the magnesium arm. Comparisons between the active intervention arms were not made.

3.5.2.2 Measures of Cramp Intensity (Pain)

A) Cramp Intensity (pain) on a 3 point scale (1=mild, 2=moderate, 3=severe) at 4 weeks and at 12 weeks

Magnesium versus placebo

Pregnancy-associated cramps

Although two of the three trials in pregnant women recorded cramp severity on scales which could potentially have been transformed into our 3 point scale, neither reported results in a manner that allowed us to do so. In Dahle66 cramp intensity was recorded on a 0 to 100 mm visual analog scale but mean scores were reported without standard deviations along with p-value thresholds for the difference in change from baseline within and between groups. These results were reported as follows: "Subjectively experienced distress according to the visual analog scale was reduced from 68.2 mm before to 47.8 mm after treatment (p < 0.05) in the placebo group and from 70.4 mm to 30.3 mm (p <0.001) in the magnesium group. The reduction of distress in the magnesium group was significantly greater (p < 0.05) than in the placebo group." In Nygaard123 the intensity of cramping during each nighttime and each daytime were recorded on a 0 to 4 intensity scale (0 = no pain, 1 = light pain, 2 = medium pain, 4 = severe pain) and added together over the 2 week assessment period. The mean of each patients summed intensity scores was 11.4 ± 8.5 for placebo and 13.2 ± 6.5 for magnesium with a nonsignificant p-value for the difference (p = 0.46).
**Idiopathic rest cramps**

At four weeks

Pooling results from the three trials with available data (Frusso 1999; first period of Roffe 2002; Garrison 2011)\(^6^4, 6^5, 1^2^2\) shows a statistically nonsignificant mean difference of -0.04 [-0.21, 0.13] on a 3 point intensity scale. \((I^2 = 5\%)\).

At 12 weeks

The single study with 12 week data (Garrison 2011)\(^1^2^2\) showed a statistically nonsignificant mean difference of -0.18 [-0.55, 0.19] on a 3 point intensity scale.

**B) Percentage of subjects rating their cramps as moderate to severe (i.e. with mean cramp intensity >= 2 on the 3 point intensity scale) at 4 weeks and at 12 weeks**

**Magnesium versus placebo**

**Pregnancy-associated cramps**

None of the studies in pregnant women reported results in this way and patient level data was unavailable.

**Idiopathic rest cramps**

At four weeks

Results were not reported in this manner but patient level data was available from 2 studies (first period of Roffe 2002; Garrison 2011)\(^6^5, 1^2^2\) to allow this statistic to be calculated. Pooled results show the mean percentage of placebo recipients rating their cramps as moderate or severe (i.e. 2 or 3 on the 3 point scale) to be 30%, with the mean percentage of
magnesium recipients rating their cramps as moderate or severe being a nonsignificant 9% greater (-7%, 25%) ($I^2 = 79\%$) Figure 3.5. Heterogeneity could have been high in this analysis because of what appear to be very different patient populations. Only 3 of 46 patients (6.5%) in Garrison rated their cramps as moderate to severe compared to 25 of 45 (56%) in Roffe. This difference in patient population might be accounted for by differences in recruitment methods since Roffe recruited 100% of patients from community advertising while Garrison recruited half from advertising and half from GP referral. The higher dropout rate in Roffe (37% versus 0%) might also have contributed if participants who would have rated their cramps as less severe were more likely to drop out of the trial.

At 12 weeks

The single study with 12 week data (Garrison 2011)$^{122}$ found that 10% of placebo recipients rated their cramps as moderate or severe, with the magnesium group being a nonsignificant 6% lower (-21%, 10%).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Magnesium</th>
<th>Placebo</th>
<th>Risk Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Garrison 2011</td>
<td>24</td>
<td>2</td>
<td>22</td>
</tr>
<tr>
<td>Roffe 2002</td>
<td>12</td>
<td>17</td>
<td>26</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>41</strong></td>
<td><strong>50</strong></td>
<td><strong>100.0%</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi$^2 = 4.88, df = 1 (P = 0.03); I$^2 = 79\%$

Test for overall effect: Z = 1.14 (P = 0.26)

---

Figure 3.5 Forest plot of comparison: Idiopathic Rest Cramps, Magnesium versus placebo, outcome: Proportion of subjects rating their cramps as moderate or severe (i.e. >=2 on a 3 point scale) at 4 weeks
3.5.2.3 Measures of Cramp Duration

Number of subjects with majority of cramp durations $\geq$ 1 min at 4 wks and at 12 wks

Magnesium versus placebo

Pregnancy-associated cramps

None of the studies in pregnant women recorded the duration of cramps.

Idiopathic rest cramps

At four weeks

Three idiopathic cramp trials measured cramp duration. Frusso$^{64}$ used a 4 point ordinal scale divided into $<$ 5 min, 5-10 min, 10-30 min and $>$ 30 min. Garrison$^{122}$ used a 3 point ordinal scale divided into $<$ 1 min, 1-5 min and $>$5 min. And Roffe$^{65}$ used a 3 point ordinal scale divided into short, medium and long. All three studies reported no statistically significant difference in duration. The single study (Garrison 2011)$^{122}$ that recorded duration using a 1 minute cut-off found the mean percentage of placebo recipients having the majority of cramp durations $\geq$ 1 minute to be 22.7%. The mean percentage of magnesium recipients having the majority of their cramp durations $\geq$ 1 minute was a nonsignificant 19% greater (-7%, 45%).

At 12 weeks

The single study with 12 week data (Garrison 2011)$^{122}$ found the placebo group to have 25% of participants reporting the majority of their cramps as lasting one minute or more, with the magnesium group being a nonsignificant 14% greater (-13%, 42%).
3.5.2.4 Measures of Safety and Tolerability

A) Treatment withdrawals due to adverse events

Magnesium versus placebo

Most studies had omissions or inconsistencies which made the determination of the number of withdrawals due to adverse effects difficult. Because we believed that the difference in withdrawals due to adverse events and the difference in total withdrawals between groups would be estimating the same parameter, we used total withdrawals for each group whenever it was unclear how many patients withdrew due to adverse effects. Neither of the cross-over studies (Frusso\(^6^4\); Roffe\(^6^5\)) could be used to estimate withdrawals due to adverse effects since information on patient experience in each period was not available (i.e. would patients withdrawing in one period also have withdrawn in the other?). Although we had patient level data for Roffe\(^6^5\), we could not use data from the first period to estimate withdrawals since the data provided to us only included patients completing both study periods. Determined in this way, and using only parallel studies, the percentage difference in withdrawals across all studies (which we presume to be due to adverse events) is, magnesium versus placebo, -3% (95% CI -10% to 3%) (Figure 3.6).
Figure 3.6 Forest plot of comparison: Idiopathic Rest Cramps, Magnesium versus placebo, outcome: Withdrawals due to adverse effects

B) Number of subjects reporting minor adverse events

**Magnesium versus placebo**

Adverse events were reported in most studies but usually not in a way which allowed us to determine the number of subjects reporting minor adverse events.

**Pregnancy-associated cramps**

In Nygaard\textsuperscript{123}, 6/23 patients (26.1\%) in the magnesium arm and 6/22 patients (27.3\%) in the placebo arm reported adverse events which were lumped together as gastrointestinal in nature (nausea, flatulence, diarrhea, intestinal air). Dahle\textsuperscript{66} only noted adverse events as being infrequent (without specifying placebo versus magnesium) and consisting of "primarily slight or initial nausea".
Idiopathic rest cramps

Frusso\textsuperscript{64} reported diarrhea, nausea or vomiting as occurring in 10.7% of magnesium recipients and 10.1% of placebo recipients. Roffe\textsuperscript{65} and Garrison\textsuperscript{122} reported the number of patients with different specific side effects but not the number of subjects with any side effect (i.e. the same subjects may be counted more than once). In Roffe\textsuperscript{65} diarrhea occurred in 30% on magnesium and 17% on placebo. Constipation occurred in 13% on magnesium and 24% on placebo. Nausea, indigestion or flatulence occurred in 2 magnesium and 4 placebo subjects. Other side effects included skin peeling (one on magnesium), bruising (one on placebo) and headaches (one on placebo). Garrison\textsuperscript{122} was different in that it was a study of magnesium given intravenously. Side effects included asymptomatic hypotension (reported by the study nurse) in 3/24 magnesium versus 0/22 placebo participants and facial flushing being noted in 9/24 magnesium and 7/22 placebo recipients but not generally complained of by participants. Two magnesium recipients noted transient light-headedness several hours after the infusions on day 3 and day 4 and more magnesium recipients noted burning of the IV site (12/24 vs. 0/22) with 5/24 magnesium participants receiving some piggybacked extra dilution of the IV solution to improve tolerability.

C) Number of subjects reporting major adverse effects

Magnesium versus placebo

Pregnancy-associated cramps

Nygaard\textsuperscript{123} reports no major adverse events during the study. The other studies do not state it explicitly.
Idiopathic rest cramps

Garrison\textsuperscript{122} and Roffe\textsuperscript{65} both reported one stroke that occurred in the placebo arms but reported no other major adverse events. This data was not available from Rosenbaum\textsuperscript{124}, and Frusso\textsuperscript{64} did not explicitly state whether major adverse events occurred. Being a cross-over trial without data on all patients for both periods, Roffe\textsuperscript{65} could not be combined with Garrison\textsuperscript{122} to improve the estimate of major adverse event rates.

3.6 Discussion

3.6.1 Magnesium Versus Placebo

3.6.1.1 Idiopathic Rest Cramps

There is moderate evidence that magnesium supplementation does not offer a clinically important benefit over placebo in the prophylaxis of idiopathic cramps in older adults (most of whom are presumed to have been experiencing nocturnal leg cramps). The difference in percentage change in cramps per week from baseline at 4 weeks was small and nonsignificant (-3.93%, 95% CI -21.12 to 13.26) and the confidence interval excludes a 25% reduction (the difference we predefined as being clinically important). As well, while medications are often only effective in a subset of patients, the percentage of patients obtaining a 25% or greater reduction from baseline in the number of cramps per week at 4 weeks did not even trend in favor of magnesium (-8%, 95% CI -28% to 12%). This makes it less likely that a meaningful subset of patients receiving a > 25% benefit is being missed by averaging their results in with nonresponders. Cramp frequency was also measured looking at the number of cramps per week on treatment at 4 weeks. This measure allowed pooling of
the largest number of studies (four studies, N = 216) and similarly found no significant reduction in the change in cramps per week on treatment (0.01 cramps / week, 95% CI -0.52 to 0.55) with a confidence interval that excludes a one cramp per week reduction.

Similarly, the mean difference in cramp intensity on a 3 point scale at 4 weeks was no different (-0.04, 95% CI -0.21 to 0.13), nor was the mean percentage of patients rating their cramps as moderate or severe - which was a nonsignificant 9% greater (95% CI -7% to 25%) in the magnesium group. Only one study reported cramp duration in a format that allowed us to determine the number of subjects with the majority of cramp durations > 1 min. In this study the mean percentage of participants having the majority of their cramp durations >= 1 minute was a nonsignificant 19% greater (95% CI -7% to 45%) in the magnesium group.

Two other studies reported cramp duration in different formats and in neither was there a significant difference. All the above outcomes were also sought at 12 weeks but only one study had 12 week data. The results of this single study at 12 weeks were not materially different than the 4 week results above.

Adverse events and withdrawals due to adverse events were poorly reported in most trials. Supplementing the number of withdrawals due to adverse events with total withdrawals, we found a nonsignificant difference for the number of withdrawals due to adverse events of -3% (95% CI -10% to 3%). Two major adverse events (strokes) occurred in the placebo groups and none in the magnesium group. The number of patients with minor adverse events could not be meaningfully estimated. Qualitatively it appears that the frequency of side effects from oral magnesium are low and minimally different from placebo (with the possible exception of diarrhea). Intravenous magnesium appeared to cause a
burning sensation at the IV site in half of patients (compared to none in the placebo group) and a small subset of patients had either asymptomatic hypotension or light-headedness.

3.6.1.2 Pregnancy Associated Cramps

It is unclear whether magnesium supplementation can provide an advantage over placebo in the prophylaxis of pregnancy associated cramps since the only two relevant studies were discordant and did not report results in a way that enabled us to pool their data. Dahle reported a reduction in cramp frequency on a 5-point ordinal scale, a reduction in cramp intensity on a VAS, and a more favorable global assessment of treatment effect also on a 5-point ordinal scale. In contrast, the subsequent trial (Nygaard) measured the mean number of days and nights with leg cramps present and found no significant benefit (7.7 ± 4.7 (SD) days and nights of cramping over two weeks in the placebo group and 9.5 ± 5.1 in the magnesium group, P = 0.27). Cramp intensity (5-point ordinal scale) was also not significantly different. Neither of these studies reported the duration of cramps. Nygaard reported the number of subjects with minor adverse events to be the same (6 subjects) in placebo and magnesium arms and noted no major adverse events. Dahle reported only that side effects were infrequent and that one patient withdrew from the placebo group because of nausea.

Both of these trials were parallel double blind RCTs in Scandinavian maternity clinic patients and both used the same intervention, a chewable tablet containing 122 mg elemental Mg "primarily as Mg lactate or Mg citrate" taken once each morning and twice each evening (366mg daily). And yet despite these similarities they were discrepant. Factors which might have prevented Nygaard from showing benefit include less power (although there was not
even a trend to benefit) due to fewer subjects (45 versus 73), a shorter period of therapy (two weeks versus three) and the lack of baseline measures of cramp frequency. The lack of baseline measures is particularly important since the outcome was the number of cramps during the treatment period and it is not known if the mean baseline cramp rates were equal. Conversely, the trial design of Dahle\textsuperscript{66} might have biased towards benefit in that outcomes were not well defined (in particular no primary outcome was identified), randomization and allocation concealment were not described and no cramp diary was used.

### 3.6.2 Magnesium Versus Other Therapies (No Treatment)

**Pregnancy associated cramps**

The single study (Sohrabvand 2006)\textsuperscript{125} to use a comparator other than placebo randomized pregnant Iranian women to four parallel treatment arms comparing no treatment with either oral magnesium, calcium carbonate or a combined vitamin B1 / B6 supplement. The outcome for this study was the patients reporting of either no improvement, partial resolution or complete resolution of cramping. A multinomial regression test was applied to each of the three possible response categories to see if any of the active treatment arms differed from no treatment. Significantly more women reported absolute improvement in the B vitamin and calcium arms, but not in the magnesium arm. Neither was there a significant difference in relative improvement between no treatment and the magnesium arm. Comparisons between the active intervention arms were not made. It would not be unusual for placebo to show benefit from baseline in cramp trials. One might speculate that the same "placebo effect" benefit might be seen for any active intervention over no treatment, which makes the benefit seen for B vitamins and calcium over no treatment in this trial unreliable. However
magnesium was certainly no better than calcium or vitamin B supplements and was alone in not reaching significance for benefit against no treatment. Collectively, these results do not support a clinically important benefit for magnesium over no treatment.

3.6.3 Effect of Dose, Duration and Route of Administration

Serum magnesium levels are known to correlate poorly with tissue magnesium, making it difficult to detect patients with magnesium deficiency in the clinic. In theory, if magnesium deficiency played a role in skeletal muscle cramping, either the duration of therapy or the total dose provided over the course of the trial might be an important variable (since a deficit might be better replaced in longer duration, higher total dose trials). However, the differences in dosing and duration for the oral magnesium trials is not that great, with the idiopathic rest cramp trials using 200mg to 336mg of elemental magnesium daily over 4 to 6 weeks and the pregnancy associated cramp trials using either 364 or 366 mg daily over two to three weeks. No obvious pattern is present, but the oral trials are too few and too close in dose / duration to be able to detect any meaningful pattern. However one trial (Garrison 2011)\textsuperscript{122} used a series of slow intravenous infusions of magnesium to improve delivery and simultaneously measured 24 hour urinary magnesium excretion to determine the extent to which patients were retaining magnesium. Measuring the percentage retention of the infused magnesium was felt to be important because it had been used as a tool to predict total body Mg deficiency (retention of magnesium suggesting the presence of deficiency)\textsuperscript{73, 78, 90, 91, 93,} and because there is a strong positive correlation between the total amount of intravenous magnesium retained during replacement therapy and the rise in intracellular magnesium on skeletal muscle biopsy\textsuperscript{90}. In this trial of intravenous magnesium, no correlation was found
between percent retention of magnesium on day one of infusions and the reduction in the number of cramps per week from baseline. On its own, this finding argues against a therapeutic benefit to magnesium in providing cramp prophylaxis.

### 3.6.4 Potential Biases in the Review Process

Data was available from all relevant RCTs identified for inclusion in this trial. This includes patient level data for three of the four ideopathic (older adult) cramp trials, including one cross-over trial (Roffe 2002\textsuperscript{65}) where this patient level data was used (by looking at the first period only) to reduce potential bias from an unbalanced randomisation and a strong treatment order effect. Although we were able to identify one relatively recent (2011) unpublished trial using a clinical trial registry, we could be missing other unpublished RCTs that predate trial registration. However we would expect such missing trials to be less likely to have demonstrated a significant benefit because of publication bias. All of the included trials were fairly small, ranging from 40 to 73 subjects, and all had some degree of methodological limitations (Figure 3.1). However heterogeneity was low for all but one analysis (percentage of subjects rating their cramps as moderate or severe) where a difference in pain scores may have resulted from differences in the method of recruitment.
3.7 Conclusions

Implications for practice
It is unlikely that magnesium supplementation provides clinically meaningful cramp prophylaxis to older adults experiencing skeletal muscle cramps. In contrast, for those suffering pregnancy associated rest cramps the literature is conflicting and unclear. No randomized controlled trials evaluating magnesium for exercise associated muscle cramps or disease state associated muscle cramps have been conducted.

Implications for research
Given the low probability of benefit in older adult cramp sufferers, investigators may be less inclined to pursue the evaluation of magnesium for other cramp indications. However there is conflicting evidence surrounding the benefit of magnesium for pregnancy associated leg cramps and it is conceivable that magnesium could have differing efficacies in metabolically distinct populations. To resolve the uncertainty surrounding the role of magnesium in pregnant women we need more parallel randomized placebo controlled trials of magnesium in that population. Trialists should measure cramp rates as a continuous variable (e.g. number of cramps on treatment or change from baseline) to permit pooling of data. If not using change from baseline, they should also consider stratifying the study randomization by baseline cramp rate to help ensure an unequal distribution of cramp frequencies does not invalidate their findings.
Chapter 4: Quinine Pharmacoepidemiologic Analysis

4.1 Preamble

Since magnesium no longer held much promise for rest cramp prophylaxis I decided to investigate another therapeutic avenue. From reading the cramp literature, I was aware of anecdotal reports linking some commonly used medications to the development of muscle cramps\textsuperscript{4,111-117}. I knew that the elderly were prone to both cramping and polypharmacy and I reasoned that there might be a substantial number of crampers unknowingly taking cramp-promoting drugs. In these individuals, reduction or discontinuation of those drugs might be an effective therapeutic maneuver.

I sought population level evidence to inform whether the cramp implicated medications in commonest use (long-acting beta2-agonists, diuretics and statins) were associated with cramp treatment. To do this I approached and partnered with a group of researchers who had access to the linked British Columbia Healthcare databases\textsuperscript{134,135}. My primary objective was to determine whether treatment for muscle cramps increased in the year following introduction of one of these three common drug classes. Because quinine use is still common in Canada, and almost exclusive to the treatment of rest cramps, I was able to apply the novel method of \textit{prescription sequence symmetry analysis}\textsuperscript{136} to detect any changes in cramp treatment associated with these drugs.

The following chapter will outline the methods and findings of this work, which has recently been published as: Garrison SR, Dormuth CR, Morrow RL, Carney GA, Khan KM. Nocturnal Leg Cramps and Prescription Use That Precedes Them: A Sequence Symmetry Analysis. \textit{Archives of Internal Medicine}. 2012 Jan 23;172(2):120-6. Epub 2011 Dec 12.
4.2 Project Objectives

**Primary:** To determine, using linked British Columbia healthcare databases, whether introduction of a statin, diuretic or inhaled long-acting beta2-agonist is associated with the initiation of treatment for nocturnal leg cramps (as indicated by a new prescription for quinine).

**Secondary:** To explore for heterogeneity of effect across the 3 main subclasses of diuretic (loop, thiazide-like and potassium-sparing) and the two main formulations of inhaled LABA (LABA alone and LABA-steroid combination).

4.3 Hypothesis

Statins, diuretics and inhaled long-acting beta2 agonists promote the development of nocturnal leg cramps

4.4 Methods

4.4.1 Study Design

An important innovation in this study was the use of sequence symmetry design\textsuperscript{136} to analyze individuals starting, within a year of each other (in either order), prescriptions for both quinine and one of three index drug classes we are studying for cramp association (‘index drugs’). Sequence symmetry exploits the fact that, if no relationship exists between two drugs, recipients of both should be equally likely to receive them in either order. In contrast, if one drug causes a symptom that the other treats, the causal drug will more often be prescribed first. Sequence order is largely independent of patient characteristics and hence a
sequence symmetry design helps control for many potential confounders (e.g. age, sex, co-morbidity, polypharmacy). Importantly, this technique helps control for unrecognized yet important patient characteristics which might unknowingly unbalance cohorts constructed to answer the same question.

I compared the number of individuals in whom quinine followed the index drug (i.e. the potentially causal sequence) with the number of individuals in whom quinine preceded it (the non-causal sequence). This was done by dividing the number of pairs with “quinine following” by the number which had “quinine preceding” to create the crude sequence ratio. If prescribing rates are constant and if there is no relationship between the drugs we expect a crude sequence ratio = 1; if there is a causal relationship we expect a ratio > 1.

As prescribing rates can vary with time, fluctuations in population prescribing also need to be considered. For instance, a drug increasing in its use would be expected to occur second more often simply because prescriptions for it are more frequent in the later period. Sequence symmetry accounts for this by calculating the null ratio, the expected crude sequence ratio if there is no relationship, based on the overall prescribing of both drugs in the population at large. The crude sequence ratio is then divided by the null ratio to create the adjusted sequence ratio (ASR) which accounts for fluctuations in population prescribing.

\[
Adjusted \, Sequence \, Ratio = \frac{Crude \, Sequence \, Ratio}{Null \, Ratio}
\]

The null ratio is created by examining the date of each quinine start among all eligible index-quinine recipients and calculating the probability, on that day, of an index prescription coming first. This probability is determined from the number of population index prescriptions observed in the year before, compared to the number in the year after, the date of that quinine start. Each participant has their index first probability calculated in this
manner and the index first probabilities of all eligible participants are averaged to create the “null probability” – which is the mean probability that a prescription pair within the data set would be index first if no causal relationship exists. The null ratio, the expected ratio of index first to index second pairs in the event of no relationship then becomes:

$$\text{null ratio} = \frac{\text{null probability}}{1-\text{null probability}}.$$  

Although the null ratio usually utilizes all prescriptions in the database, I stratified it by year of birth – i.e. the index first probability of each participant was calculated using only those in the population at large who were the same age. I did this because most drugs have more than one indication and the relative use for those indications can vary with age - e.g. older adults, compared to those in middle age, may receive relatively more LABA for COPD (relative to asthma) and more potassium-sparing diuretic for CHF (relative to hypertension).

The sequence ratio is best conceptualized as the rate of events in exposed individuals compared to what would be expected for a similar unexposed population (i.e. the same individuals in the year before the exposure). This is essentially a relative risk, and I have been able to show that the two measures approximate each other under certain conditions (see appendix B).

### 4.4.2 Setting

Pharmacists in British Columbia (BC) are required to enter all prescriptions dispensed, independent of payer, into the PharmaNet database. This makes available province-wide drug utilization data with minimal underreporting and misclassification\textsuperscript{134,135}. The BC Ministry of Health Services also maintains linkable data on all physician services and hospitalizations for all individuals in its publically funded health care system. These two databases, along with
Medical Services Plan registration data and vital statistics data on date of death, were linked for the period January 1 1996 to June 23 2009 and comprised the source data for our study. I did not have permission to use data from the 4% of the population who are federally insured (military personnel, aboriginals and prisoners). The source population consisted of the roughly 4.2 million residents of the province of BC.

On Nov 30 2000 quinine ceased to be available without a physician’s prescription in British Columbia. To ensure new Pharmanet prescriptions were true starts and not renewals of “over-the-counter” (previously unrecorded) quinine, we limited our analysis to new quinine prescriptions dispensed at least one year after the date of quinine’s mandatory prescription status. Thus the earliest eligible quinine prescription was on Dec 1 2001.

To avoid the possibility of seasonal bias, I analyzed data in multiples of 1 year so that all months of the year were equally represented. Because I required 2 yrs of index data following the last eligible quinine start (1yr to see if the index drug was prescribed and another year to see if it was renewed) the last date for eligible quinine starts was Nov 30 2006.

**4.4.3 Population**

Study Size: The number of eligible cases within the database determined the study size.

Inclusion Criteria:

1. Age ≥ 50 yrs (nocturnal leg cramps are uncommon in younger adults and young crampers may have a higher proportion of neurodegenerative disorders)
3. Receipt of first ever prescription of one of the three classes of index drugs within 1 year of (before or after) the start of quinine.

4. Renewal of the index drug within 1 yr of its start date (to help ensure the prescription was used).

5. Evidence within the PharmaNet or Ministry of Health Services databases of the patient receiving prescriptions or medical services over a period at least 2 years prior to, and at least 2 years following, the quinine start date.

Evidence of at least 2 years of prescriptions or medical services prior to the quinine start date was required to ensure that new residents, or transients through the province, were not filling renewal prescriptions which falsely appeared to be new starts (since they were new to the province). The two year data period after the quinine start date ensured full opportunity for index drug prescription and renewal. I used services rendered, rather than registration data, to determine whether patients were resident in the province since individuals beginning to live abroad might not immediately cancel their provincial medical plan coverage.

Exclusion Criteria:

1. Physician diagnostic coding or procedural billing indicating malaria, dialysis or amyotrophic lateral sclerosis at any point in the data record (i.e. eliminating potential quinine users who did not have nocturnal leg cramps)
Switching within a drug class:

Patients at times switch between different drugs within a class (e.g., switching between statins if there were side effects). I counted only the first renewed prescription within a class for the purpose of our analysis. Hence if an individual started on pravastatin (with renewal), and then changed to atorvastatin, the atorvastatin prescription was not considered a new start and thus not included in our analysis. Similarly, any loop diuretic prescription after a renewed thiazide prescription was excluded. Only the first renewed diuretic start was eligible. I did not consider salbutamol (albuterol) to be a long-acting beta-agonist and preceding prescriptions for salbutamol did not exclude subsequent LABA starts. Cerivastatin was withdrawn from the Canadian market in Aug 2001 due to an association with rhabdomyolysis. Since the first eligible quinine prescription was Dec 1 2001, we excluded anyone from the statin analysis if their first renewed statin was cerivastatin.

Combination Products:

Many drugs are available as combination products. For each analysis I excluded all combination products, and combination first users. The exception to this was potassium-sparing diuretics, the majority of which are prescribed in Canada in combination with a thiazide. Thus the sub-category of potassium-sparing diuretics in our analysis includes potassium-sparing diuretics with or without a combined thiazide. The breakdown of specific index drugs included in the analysis is provided in table 4.1.
### Table 4.1 Breakdown of index drugs used in symmetry analysis

<table>
<thead>
<tr>
<th>Diuretics</th>
<th>Long-Acting Beta-Agonists</th>
<th>Statins</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 1,590)</td>
<td>(n = 576)</td>
</tr>
<tr>
<td><strong>Loop 407 (25.6%)</strong></td>
<td><strong>LABA Alone 137 (23.8%)</strong></td>
<td>Atorvastatin 876 (66.1%)</td>
</tr>
<tr>
<td>Furosemide 406 (99.8%)†</td>
<td>Salmeterol 65 (47.5%)</td>
<td>Simvastatin 258 (19.5%)</td>
</tr>
<tr>
<td>Ethacrynate 1 (0.2%)</td>
<td>Terbutaline 39 (28.5%)</td>
<td>Rosuvastatin 142 (10.7%)</td>
</tr>
<tr>
<td></td>
<td>Formoterol 32 (23.4%)</td>
<td>Pravastatin 38 (2.9%)</td>
</tr>
<tr>
<td><strong>Thiazide-Like 977(61.5%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCTZ 971 (99.4%)‡</td>
<td>Fenoterol 1 (0.7%)</td>
<td>Lovastatin 6 (0.5%)</td>
</tr>
<tr>
<td>Indapamide 6 (0.6%)</td>
<td><strong>LABA-Steroid 439 (76.2%)</strong></td>
<td>Fluvastatin 6 (0.5%)</td>
</tr>
<tr>
<td></td>
<td>Salmeterol-Fluticasone 291 (66.3%)</td>
<td></td>
</tr>
<tr>
<td><strong>K⁺- Sparing 206 (13.0%)</strong></td>
<td>Formoterol-Budesonide 148 (33.7%)</td>
<td></td>
</tr>
<tr>
<td>Triamterene-HCTZ 119 (57.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spironolactone 46 (22.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiloride-HCTZ 34 (16.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spironolactone-HCTZ 7 (3.4%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Values are the number of quinine-index recipients used in analysis (as percentage of index class)
† Values are the number of quinine-index recipients used in analysis (as percentage of index sub-class)
‡ HCTZ = Hydrochlorothiazide

### 4.4.4 Bias

Confounders in a sequence symmetry analysis are prescribing influences which either vary over time, or link prescribing order in ways other than those hypothesized\(^{136}\). I have corrected for trends in prescribing that vary with time, age and aging (over the 2 year window of observation surrounding the quinine start date) using the birth year stratified null ratio.
Additionally, quinine shares no common indications or contraindications with the index drugs that should affect prescribing order (i.e. no first-line drugs preceding second-line or avoidance of one drug because another is in use).

However, it is conceivable that the indication for an index drug (e.g. leg edema as an indication for diuretics) might also be an unrecognized trigger for cramps. If patients are consistently quicker to seek treatment for one of these indications (e.g. faster to treat edema than cramps) then an association (in either direction) could be produced. As well, if one of the two drugs is more likely to lead to follow-up visits then increased physician contact following initiation of that drug could give greater opportunity for discussion and prescribing of the other study drug. Although this could occur in either direction, drugs with a greater expectation of planned follow-up such as statins and antihypertensives (e.g. diuretics) might be expected to have an increase in subsequent quinine prescribing because of greater prescriber contact.

4.4.5 Statistical Methods

The primary outcome measure of this study was the sequence order of quinine – index starts and the primary statistic of interest was the adjusted sequence ratio. I calculated sequence ratios for the three main index drug classes (LABAs, diuretics, and statins), the three main subtypes of diuretic (loop, thiazide-like and potassium-sparing) and the two main formulations of inhaled LABA (LABA-alone and LABA-corticosteroid combination).

Confidence intervals were created using bootstrap resampling methods\textsuperscript{137}. Specifically, 10,000 iterations of ASR were created by 1) bootstrapping (resampling with replacement) all observed index-quinine pairs to produce 10,000 crude sequence ratios and 2)
bootstrapping all in-range (i.e. within one year of the quinine prescription being matched) same-age population index starts to produce 10,000 null sequence ratios. Each bootstrapped iteration of the crude and null sequence ratios were then divided to produce each iterative ASR value. For all drug classes and subclasses the distribution of ASR iterations was smooth, approximately symmetric and centred on the observed values for ASR. As such, percentile based bootstrap confidence intervals were appropriate and 95% confidence intervals for ASR were determined from the 2.5 and 97.5 percentiles of ASR iteration.

Approximate p-values for each drug class and subclass were created using the normal approximation to the binomial distribution to determine the probability of observing a number of index-first prescriptions as extreme as that observed if the true probability were the null probability.

4.4.6 Secondary Analysis

To confirm my findings I performed sequence symmetry on medications for which a null effect was postulated ("negative controls"), these being betablockers and the inhaled anticholinergics Ipratropium and Tiotropium (which share a first line indication with LABA for the treatment of COPD). Betablockers were chosen because their mechanism of action is opposite to that of LABA and because they are often prescribed in settings similar to diuretics and statins (i.e. hypertension, post MI, CHF).

As a further check, I also performed a Cox proportional hazards analysis comparing time to quinine start in new users of either inhaled LABA (case) or inhaled anticholinergic (control) who first filled (and renewed within 1 year) their medication between Dec 1 2001 and Nov 30 2006 (details in appendix C).
4.5 Results

4.5.1 Descriptive Data

Excluding those with malaria, ALS or dialysis, but before applying any age or index drug exclusions, the cohort of all provincial quinine starters (which we assume to be rest cramp sufferers) between Dec 1 2001 and Nov 30 2006 was 62.5% female with median age 69 yrs (inter-quartile range 58 to 80 yrs, mode 73 yrs). Family physicians provided 88% of these quinine prescriptions and over a 5 year period 50% of recipients renewed their quinine.

Subgroup demographics and a breakdown of exclusions are shown (Fig 4.1). Of 24,417 eligible quinine starters there were 1,590 diuretic, 1,326 statin and 576 LABA starters upon which a symmetry analysis could be performed.

Figure 4.1 Flow diagram for selecting symmetry populations
4.5.2 Main Results

Quinine prescriptions were significantly more likely to follow, rather than precede, prescriptions from all three main index classes (Table 4.2). The association was greater for long-acting beta2-agonists than it was for statins and did not differ whether LABAs were combined with steroids, or were used alone. Thiazide-like diuretics and, in particular, potassium-sparing diuretics were also more strongly associated with cramp treatment than were statins. Loop diuretics and statins had small magnitudes of association. Neither of the negative control drug classes (inhaled anticholinergics and betablockers) associated with cramp treatment.

Of all quinine recipients, 77.5% filled a prescription for LABA, diuretic or statin over 13 years of available data. Medications with the greatest association to cramp treatment (LABAs, potassium-sparing diuretics and thiazide-like diuretics) were filled by 60.3% of quinine recipients. If we assume the potential cramp promoting effect of these drugs extends to renewals, up to 13.6% of quinine starts could be attributable to their use (appendix D). Unfortunately our data cannot produce a meaningful estimate of absolute risk increase since only a small fraction of those with a greater cramp burden can be detected using new quinine starts (i.e. our analysis excludes anyone with prior quinine use and cannot detect altered cramp rate in non-quinine users).

Histograms of the distribution of time intervals between index prescribing and quinine receipt are shown (Figs 4.2 and 4.3). Quinine prescriptions rose sharply within a month of introducing beta2-agonists or diuretics. The small rise in quinine prescribing following statin starts took 3 months to manifest.
Table 4.2 Prescribing order in recipients of both quinine and select index drugs

<table>
<thead>
<tr>
<th>Index Drug Class</th>
<th># pairs index-first&lt;sup&gt;a&lt;/sup&gt;</th>
<th># pairs index-after&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Null Probability&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Adjusted Sequence Ratio&lt;sup&gt;d&lt;/sup&gt;</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Statins</td>
<td>716</td>
<td>610</td>
<td>0.50</td>
<td>1.16 (1.04 to 1.29)</td>
<td>.004</td>
</tr>
<tr>
<td>All LABAs</td>
<td>397</td>
<td>179</td>
<td>0.48</td>
<td>2.42 (2.02 to 2.89)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>B2A alone</td>
<td>100</td>
<td>37</td>
<td>0.56</td>
<td>2.17 (1.56 to 3.02)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>B2A-steroid</td>
<td>297</td>
<td>142</td>
<td>0.45</td>
<td>2.55 (2.06 to 3.12)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>All Diuretics</td>
<td>956</td>
<td>634</td>
<td>0.51</td>
<td>1.47 (1.33 to 1.63)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Loop</td>
<td>226</td>
<td>181</td>
<td>0.51</td>
<td>1.20 (1.00 to 1.44)</td>
<td>.07&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Thiazide-like</td>
<td>586</td>
<td>391</td>
<td>0.50</td>
<td>1.48 (1.29 to 1.68)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Potassium-sparing</td>
<td>144</td>
<td>62</td>
<td>0.53</td>
<td>2.12 (1.61 to 2.78)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Negative Controls

<table>
<thead>
<tr>
<th></th>
<th># pairs index-first&lt;sup&gt;a&lt;/sup&gt;</th>
<th># pairs index-after&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Null Probability&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Adjusted Sequence Ratio&lt;sup&gt;d&lt;/sup&gt;</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Betablockers</td>
<td>450</td>
<td>447</td>
<td>0.51</td>
<td>0.97 (0.85 to 1.11)</td>
<td>.62</td>
</tr>
<tr>
<td>All Inhaled</td>
<td>170</td>
<td>166</td>
<td>0.49</td>
<td>1.07 (0.84 to 1.36)</td>
<td>.56</td>
</tr>
</tbody>
</table>

<sup>a</sup> The potentially causal sequence; index drug precedes cramp treatment

<sup>b</sup> The non-causal sequence; index drug follows cramp treatment

<sup>c</sup> Probability of index drug coming first based on age-matched population index prescribing

<sup>d</sup> Ratio of the crude sequence ratio (# potentially causal sequences / # non-causal sequences) to the null ratio (expected crude sequence ratio based on age matched population prescribing); ASR (95% Confidence Interval)

<sup>e</sup> The confidence interval and p-value are created using different methods, hence the Loop CI can sit on the border of significance while the approximated p-value is not exactly = 0.05. The CI determined significance.

Histograms of the distribution of time intervals between index prescribing and quinine receipt are shown in figures 4.2-4.4. Quinine prescriptions rose sharply within a month of introducing beta2-agonists or diuretics. The small rise in quinine prescribing following statin starts took 3 months to manifest.
Figure 4.2  Frequency of quinine starts in the months before and after initiating either a statin, diuretic or LABA
Figure 4.3  Frequency of quinine starts in the months before and after initiating either a loop, potassium-sparing or thiazide-like diuretic.
4.5.3 Secondary Analysis

Consistent with the LABA symmetry results, Cox proportional hazards analysis comparing starters of LABA to starters of inhaled anticholinergic yielded a hazard ratio of 2.37 (p < .0001 CI 1.73 to 3.23) for a quinine start in the following year (this analysis is provided in detail in appendix C).

Figure 4.4 Frequency of quinine starts in the months before and after initiating either LABA alone or a LABA-steroid combination.
4.5.4 Quinine Seasonality

Quinine starts were highly seasonal (more prescribing in summer months), with peak to trough differences in the rate of new starts being approximately 2/3 of the mean value (Fig 4.5). The distribution of age, gender, prescriber specialty type, and local health authority (i.e. geographic location) showed no seasonal variability and quinine starts had a similar renewal rate regardless of the month in which they were received.

LABA and diuretic starts were also seasonal with furosemide, the most seasonal diuretic, having peak to trough differences in the rate of prescribing (summer higher) approximately 40% of the mean value. The degree of LABA seasonality was similar to furosemide but peaked in winter (presumably due to respiratory infections). Statin starts were not seasonal. Excluding users of diuretics and beta-agonists showed no change to the degree of seasonality in quinine starts, suggesting use of these medications was not the cause of quinine seasonality.
Figure 4.5  Number of monthly quinine starts in British Columbia residents
Figure 4.6 New starts, refills and total quinine prescriptions per month

The transient fall in quinine use is co-incident with Vancouver Sun and CBC radio stories (Nov 16th and Nov 22nd 2007) which warn about the risk of quinine.
Fig 4.7 Percentage of new quinine Rx which will ultimately be refilled versus month of prescription receipt.
Average Age at Time of Initial Quinine Rx

No seasonal variation in the age of quinine starters

Fig 4.8 Average age at time of initial quinine prescription versus month of receipt – demonstrates no seasonal variation
Fig 4.9 Percentage of new quinine starts which are male – demonstrates no seasonal variation
Fig 4.10 Percentage of quinine starts from family physicians – demonstrates no seasonal variation
4.6 Discussion

These population-wide observational data suggest that inhaled long-acting beta2-agonists, diuretics and statins promote muscle cramping in older adults. The association is particularly strong for long-acting beta2-agonists (ASR 2.42) and potassium-sparing diuretics (ASR 2.12); moderate for thiazide-like diuretics (ASR 1.48); and weak for both loop diuretics (ASR 1.20) and statins (ASR 1.16). A strong circannual variation in quinine starts, with more prescribing in summer months, was also observed. With the exception of aboriginals, whose prescriptions were not available to me, my results are drawn from the large multi-ethnic population of British Columbia and should generalize well to similar populations.

My analytic design controls for patient attributes (including polypharmacy and comorbidity) and corrects for trends in prescribing that vary with time, age and aging using the birth year stratified null ratio. Although the sudden change in quinine starts following LABA, potassium-sparing or thiazide-like diuretic starts (Figs 2-3) supports the hypothesized effect of cramp promotion, the same observation could also be explained by quinine use lessening the likelihood of a subsequent index prescription. This could occur if quinine had a biologic effect (such as blood pressure lowering) that lessened the indication for index drug use, or if physicians already avoid these index drugs in cramp sufferers. Additionally, if follow-up is more frequent following index drugs than quinine, then greater opportunity for cramp discussion and prescribing could arise. Conceivably, the relatively small statin and loop diuretic associations might be explained by either greater physician contact and prescribing in the follow-up period or avoidance of these drugs in cramp sufferers.

By use of province-wide administrative pharmacoepidemiology data, my results substantially extend and support the limited evidence linking LABAs and diuretics to muscle
cramping. In contrast, I have found the statin association to be only minor. However, although statins are widely known to cause muscle symptoms, the description of statin myopathy does not include muscle cramps. The only literature linking statins to cramping is a single study of ALS patients. Randomized controlled trials have not implicated any of the medications we studied as causing cramp (possibly because the elderly are poorly represented in most clinical trials).

My sequence ratios provide the rate of cramp treatment in the year following index drug introduction, compared to the expected rate in the same population. Viewed in this way, thiazide-like diuretics, potassium-sparing diuretics and inhaled long-acting beta2-agonists (prescribed to 60.3% of quinine recipients over a 13 year span) have sequence ratios suggesting a 48% (thiazide) to 142% (LABA) increase in the indication for cramp treatment. If discontinuing these drugs, or switching to other therapeutic options, provided an equivalent reduction in the need for cramp treatment, such a maneuver would result in a number needed to treat (NNT) of 1.7 (LABA) to 3.1 (Thiazide).

Clinicians may be surprised that potassium-sparing diuretics have a stronger link to cramp treatment than loop diuretics, yet hyperkalemia facilitates neuronal excitation and hypokalemia suppresses motor neuron activity. Beta2-agonists are also known to have a stimulatory effect on motoneurons and beta2 receptors are found on peripheral nerves. Irrespective of the mechanisms explaining the phenomenon, clinicians should be aware of the epidemiological association between cramp treatment and the use of LABAs, potassium-sparing diuretics, and thiazides.

My study also raises questions about why cramp treatment shows such strong seasonal fluctuation. Seasonal variations in factors such as heat, physical activity, sweating,
hydration, vitamin D and diet are all possible explanations, as is circannual variation in
neuromuscular function\textsuperscript{145,146}. Given the large effect size necessary for the degree of
seasonality observed, uncovering the cause of this phenomenon may have significant utility
in coming to understand, and treat, nocturnal leg cramps.
Chapter 5: Conclusions

5.1 The Limited Role for Magnesium Supplements in Cramp Prophylaxis

5.1.1 Nocturnal Leg Cramps

Although magnesium supplements are marketed worldwide to the elderly for the prevention of skeletal muscle cramps, I have provided multiple lines of evidence suggesting that magnesium supplements are unlikely to provide clinically meaningful cramp prophylaxis in a geriatric population. This evidence includes:

1. A randomized controlled trial of magnesium provided by a highly reliable delivery method (intravenous infusion) that showed a clinically and statistically nonsignificant -0.7 cramps per week (-5.5%) difference in cramp rate compared to placebo. There is only a 9% chance of obtaining the observed difference of 5.5% or less if the true difference between therapies was a 25% reduction in favor of magnesium (what I consider to be at the lower end of clinical significance for this therapy).

2. The demonstration within this same RCT that there is no relationship between the change in cramp rate following magnesium therapy and the degree of magnesium retention on the first day of infusions. This was important since magnesium retention has been shown to correlate strongly with the rise in intracellular magnesium on skeletal muscle biopsy and since magnesium retention has been used to assess for total body magnesium deficiency. On its own, the observation of no greater reduction in cramp rate in retainers of magnesium argues against a therapeutic value for magnesium in cramp prophylaxis.
3. A Cochrane Systematic Review of the literature which combines both my RCT, and an unpublished RCT, with the two trials of oral magnesium in older adults that were available when I began this research project. Meta-analysis performed in this review (magnesium versus placebo) shows a clinically and statistically nonsignificant -3.9% (95% CI -21.1 to 13.3) difference in the change in cramp rate from baseline at four weeks, with a confidence interval that excludes a 25% reduction. It also shows the mean percentage of magnesium recipients achieving a 25% or better reduction in the frequency of their cramps to be a nonsignificant 8% lower in the magnesium group (95% CI -28% to 12%). The mean difference in the number of cramps per week on treatment at 4 weeks was also a nonsignificant 0.01 cramps per week higher in the magnesium group and there were no statistically significant differences in either cramp intensity or cramp duration.

5.1.2 Pregnancy-Associated Leg Cramps

Although I did not include pregnant women in my RCT, I did search for information on this population in the Cochrane Review on Magnesium for Skeletal Muscle Cramps. At the time I began my PhD work there was a single study in pregnant women which showed statistically significant benefit for reducing cramp frequency and intensity. The currently existing Cochrane review specific to the leg cramps of pregnancy has not been updated and still shows only this single magnesium trial suggesting benefit. My review identified another more recent RCT that refutes these findings. Both trials had a very similar design but used differing ordinal and composite endpoints to measure cramp frequency that prevented meta-analysis. It is certainly conceivable that magnesium supplements could work in one
metabolically distinct population (e.g. pregnancy) and not another (e.g. older adults) but this new contradictory study, and the apparent lack of benefit in older adults, begins to shed doubt. More research is needed to determine whether pregnant women truly benefit from receiving magnesium for cramp prophylaxis.

5.1.3 Other Clinical Settings Associated with Cramping
My systematic review of the literature found no randomized controlled trials that evaluate magnesium for skeletal muscle cramps in any clinical setting other than pregnancy or idiopathic cramping (largely in older adults). Specifically, there are no studies evaluating magnesium for exercise associated muscle cramps or disease state associated muscle cramps.

5.2 The Importance of Avoiding Cramp Promoting Drugs
At the start of my PhD work the link between muscle cramps and long-acting beta2-agonists, diuretics and statins was largely anecdotal. Using sequence symmetry methods I was able to provide province wide pharmacoepidemiologic evidence to evaluate the link between the use of these medications and the subsequent prescribing of quinine (i.e. subsequent treatment for muscle cramps). The statistic of interest, the adjusted sequence ratio (ASR), provided what is best conceptualized as the rate of cramp treatment in exposed individuals relative to what would be expected for a similar population (i.e. it is analogous to a relative risk).

5.2.1 Inhaled Long-Acting Beta2-Agonists
There was a strong relationship between the use of inhaled long-acting beta2-agonists and cramp treatment with an ASR of 2.42 (95% CI 2.02 to 2.89). This result was similar for all
LABAs whether or not they were combined with steroids. In contrast the commonest therapeutic alternative to LABA for the treatment of COPD, inhaled anticholinergics, had no relationship to cramp treatment with an ASR of 1.07 (95% CI 0.84 to 1.36). Although the mechanism by which Beta2-agonism could promote muscle cramps cannot be well elucidated since the mechanism behind muscle cramping itself is unclear, Beta2 agonists are known to have a stimulatory effect on motor neurons and Beta2 receptors are found on peripheral nerves (where cramps are believed to arise). Presumably, if the depolarization of peripheral nerves is an integral part of the mechanism by which cramps occur, beta2 agonists (and anything which facilitates peripheral nerve depolarization) may facilitate muscle cramping for this reason.

5.2.2 Diuretics

Diuretics as a whole had a significant relationship to cramp treatment but this varied importantly by the subclass of diuretic. The strongest diuretic, furosemide, had a very weak association which bordered on significance (ASR 1.20, 95% CI 1.00 to 1.44). In contrast potassium-sparing diuretics had a strong association (ASR 2.12, 95% CI 1.61 to 2.78) and thiazide-like diuretics had a moderate association (ASR 1.48, 95% CI 1.29 to 1.68). It is interesting that the most potent diuretic had the least association to cramping and raises the question of whether serum potassium (typically lowered by loop diuretics and raised by potassium sparing diuretics) might modulate a cramp threshold in some way. This would be supported by the fact that potassium concentrations are the primary ionic determinant of the resting membrane potential of neurons, and that hyperkalemia has been demonstrated to
facilitate neuronal excitation while hypokalemia has separately been shown to suppress motor neuron activity\textsuperscript{140, 141}.

### 5.2.3 Statins

The statin association is remarkable in that it is weak (ASR 1.16, 95\% CI 1.04 to 1.29). This is important in that it is my clinical impression that clinicians generalize their knowledge of statin myopathy to include muscle cramps – even though the literature does not support this generalization. The only link between statins and muscle cramps comes from a single cohort study of amyotrophic lateral sclerosis patients.

### 5.3 The Seasonality of Nocturnal Leg Cramps

I also observed, quite unexpectedly, that quinine starts were highly seasonal (more prescribing in summer months), with peak to trough differences in the rate of new starts being approximately 2/3 of the mean value. This seasonal prescribing pattern was unrelated to age, gender, prescriber specialty type, local health authority (i.e. geographic location) or the use of diuretics or LABAs (both of which also have some degree of seasonality to their use). Cramp seasonality can also be demonstrated using the Google Trends search engine – in this case showing that search volume for the term “leg cramps” in the United States had a similar sinusoidal variation with more searches in summer months (Fig 5.1).
Seasonal variations in factors such as heat, physical activity, sweating, hydration, vitamin D and diet are all possible explanations for cramp seasonality, as is circannual variation in neuromuscular function. Many mammals vary metabolic parameters in advance of the seasons (e.g. body weight, fur thickness, estrus). Conceivably humans may also undergo seasonal variations in parameters such as the resting membrane potential (perhaps to deal with thermogenesis), variations in the rate of axonal regeneration, or variations in fluid and electrolyte balance that might seasonally modulate a threshold for muscle cramping.

Cramp seasonality may also explain why, during my magnesium infusion RCT, the placebo group was observed to have a 21.6% reduction in the number of cramps per week from baseline. It may be that, rather than placebo working through a particular (unknown) physiologic mechanism to reduce cramp rate, the strong seasonal (cyclic) nature of symptoms in cramp sufferers may magnify the influence of regression to the mean on the primary outcome (i.e. subjects enroll during times of higher cramp rate and then move closer to their mean, lower rate, during the course of the trial).
5.4 Strengths and Limitations of the Research Findings

5.4.1 RCT of Intravenous Magnesium

The magnesium treatment trial is strong in being a randomized controlled trial that employed, for the first time, a delivery method (IV infusion) which avoided the theoretical limitation inherent in the poor oral bioavailability of magnesium supplements. It is also strong in looking at outcomes according to the extent to which infused magnesium was retained on the first day of infusions (since this is a recommended method of assessing for magnesium deficiency and since this measure correlates with the change in intracellular magnesium on skeletal muscle biopsy post magnesium replacement therapy).

The limitations of this trial include its relatively small size (46 participants), the fact that half of its recruitment came from community advertising and the fact that 12/24 patients experienced burning of the IV site (compared to 0/22 placebo patients). Small size is a problem for any clinical trial in that important patient characteristics may not have been distributed evenly. In particular, in this trial two participants with extremely high cramp rates (both averaging about four cramps per day) were both randomized to placebo. However sensitivity analysis conducted by excluding these two placebo outliers provided virtually the same result.

Having half of recruitment coming from community advertisement is problematic in that the patients may not be representative of the family practice patients to whom I would like to generalize the findings. For instance, Ad responders were much more likely to have symptoms which were not truly muscle cramps and to have neurologic conditions which would exclude them. However, I was very careful to exclude anyone without typical rest
cramps and I do believe the results generalize well to both family practice and referral geriatric populations.

The fact that half of the magnesium recipients described burning of the IV site (compared to none of the placebo recipients) is limiting in that it may have compromised the blind to some extent (although all subjects were advised that burning could occur with both placebo and magnesium solutions). However a compromise of the blind would presumably have favored the intervention, and this study failed to find benefit – which suggests that any effect of unblinding would have been small.

Conceivably, I could also have missed a meaningful reduction in cramps because of the slow equilibration of Mg within different tissue compartments preventing adequate Mg replacement during the 5 days of infusions. However, the mean urinary Mg excretion rose from 17.5 mmol on day 1 to 20.2 mmol on day 5 with the percentage of those with >15% retention falling from 48% (11/23) day 1 to 10% (2 / 21) day 5 – which is consistent with adequate replacement. Additionally, both human studies of experimental Mg deficiency and case reports of muscle cramping in established Mg deficiency have all shown resolution of cramps following infusions of substantially less Mg than the 100 mmol total Mg infused in this study.

5.4.2 Cochrane Systematic Review

This study is strong because of the rigorous method inherent in all Cochrane Systematic Reviews and because of the fact that I was able to obtain both unpublished (one trial) and patient level data (three trials) from some authors. For at least one measure of cramp frequency in older adults (number of cramps per week on treatment at four weeks) I was able
to pool the results from four trials (N=213). Additionally, this review was strong because confidence intervals for multiple outcomes were able to exclude clinically meaningful differences.

Weaknesses of this review include the lack of studies for cramp syndromes other than age and pregnancy associated cramping, the small number of studies in general, and the fact that two of the trials (both in pregnant women) created either ordinal or composite variables for cramp frequency which prevented the pooling of their data. As a result, meta-analysis of the trials in pregnant women (both of which came to different conclusions) was not possible.

5.4.3 Quinine Sequence Symmetry Analysis

This pharmacoepidemiologic study is strong because it utilizes province wide health information on the roughly 4.2 million residents of British Columbia (except for 4% of residents who are federally insured). It also employs a means of detecting escalating cramp burden (i.e. new quinine prescriptions) that would not be possible using physician diagnostic coding (since few physicians provide ICD9 codes specific enough to pick out nocturnal leg cramps). It is also strengthened by an analytic design (sequence symmetry) that controls for time invariant patient attributes such as polypharmacy use and comorbidity. Importantly this analytic method simultaneously helps to control for unrecognized but important patient characteristics that might unknowingly unbalance cohorts constructed to answer the same question.

Although strong in controlling for time-invariant patient characteristics, a sequence symmetry analysis can be confounded by prescribing influences that vary over time or link prescribing order in ways other than those hypothesized. I corrected for trends in prescribing
that vary with time, age and aging using the birth year-stratified null ratio and quinine shares no common indications or contraindications with the index drugs that should affect prescribing order (i.e. no first-line drugs preceding second-line drugs or avoidance of one drug because another is in use). However, it is conceivable that the indication for an index drug (e.g., leg edema as an indication for diuretics) might also be an unrecognized trigger for cramps. If patients are consistently quicker to seek treatment for one of these indications (e.g., faster to treat edema than cramps), then an association (in either direction) could be produced. As well, if one of two drugs is more likely to lead to follow-up visits, then increased physician contact following initiation of that drug could give greater opportunity for discussion and prescription of the other study drug. Although this could occur in either direction, drugs with a greater expectation of planned follow-up visits, such as statins and antihypertensives (e.g., diuretics), might be expected to have an increase in subsequent quinine prescribing because of greater prescriber contact. In addition, although the sudden change in quinine starts following LABA, potassium-sparing diuretic, or thiazidelike diuretic starts supports the hypothesized effect of cramp promotion, the same observation could also be explained by the use of quinine lessening the likelihood of a subsequent index prescription. This could occur if quinine had a biologic effect (e.g., blood pressure lowering) that lessened the indication for index drug use or if physicians already avoid these index drugs among individuals with cramp. Conceivably, the small statin and loop diuretic associations might be explained either by greater physician contact and prescription in the follow-up period or by avoidance of these drugs among individuals with cramp.

To help check the results of this study I also performed sequence symmetry on two meaningful negative controls (inhaled anticholinergics and beta-blockers) and conducted a
more conventional Cox proportional hazards survival analysis of time to quinine start in individuals newly starting either LABA (the case cohort) or inhaled anticholinergic (the control cohort). Both of the negative controls demonstrated no relationship to quinine use and the Cox proportional hazards survival analysis provided an association between LABA and quinine starts almost identical in magnitude to our symmetry findings. While confounding can never be ruled out in observational studies these secondary analyses all help to support the potential causality of the associations found.

5.5 Utility of the Research Findings

5.5.1 Magnesium’s Lack of Efficacy
Supplements of magnesium are already widely marketed both over the internet and in health food stores for the prophylaxis of skeletal muscle cramps. At the inception of this body of work there were three studies of magnesium for cramp prophylaxis - one showing benefit in pregnant women, one showing no benefit in older adults and one showing a “trend to benefit” in older adults. At the time there was no clarity on whether this therapy was effective, especially since the effectiveness of oral supplements may have been limited by poor oral bioavailability. Collectively the RCT and Cochrane Systematic Review that I have conducted help to resolve the uncertainty as to whether magnesium is effective for cramp prophylaxis (at least for older adults) and will hopefully help steer physicians and patients towards other therapies which might hold more benefit.

5.5.2 Cramp Promoting Effects of LABA, K-Sparing Diuretics and Thiazides
Although LABAs, potassium-sparing diuretics and thiazides likely account for only a minority of new quinine prescriptions, 60.3% of quinine recipients (cramp sufferers) received
a prescription for one of these common yet potentially cramp promoting medications over a
13 year span. This underscores the importance of physicians becoming aware that these
medications may have the potential for cramp promotion. It also opens up a very useful
opportunity for cramp sufferers who already take these drugs to potentially lessen the burden
of their cramping by altering the use of their medication.

LABAs, potassium-sparing diuretics and thiazides have sequence ratios suggesting a
48% (thiazide) to 142% (LABA) increase in the indication for cramp treatment. If
discontinuing these drugs, or switching to other therapeutic options, provided an equivalent
reduction in the need for cramp treatment, such a maneuver would result in a number needed
to treat (NNT) of 1.7 (LABA) to 3.1 (thiazide). This is a degree of benefit that most
physicians would consider worth pursuing. Given there are many alternatives to diuretics for
blood pressure control, and given I have shown the main alternatives to LABA for the
management of COPD (inhaled anticholinergics) do not associate with cramp treatment,
there should be ample opportunity to either perform a therapeutic substitution, lower the dose
of the drug involved, or attempt a “drug holiday” to determine both whether the medication is
still needed for its original purpose and whether a reduction in cramp frequency is obtained
following discontinuation.

5.6 Future Research
My quinine work raises questions about why cramp treatment would show such a strong
seasonal fluctuation. Given the large effect size necessary for the degree of seasonality
observed, uncovering the cause of this phenomenon may have significant utility in coming to
understand not only nocturnal leg cramps but also other conditions believed to arise from
abnormal excitability of peripheral nerves. One example of this would be peripheral neuropathy. Using the Google Trends database I have recently found common lay descriptions of peripheral neuropathy ("tingling feet" OR "burning feet") to have a similar, summer higher, seasonality in search volume (Fig 5.2).

![Google Trends graph showing seasonal variation in search volume for "tingling feet" OR "burning feet" in the USA](image)

**Fig 5.2 Internet search volume for the phrases “tingling feet” OR “burning feet” in the USA**

To follow-up on this observation I am attempting to get BC Ministry of Health database access to see if drugs used to treat peripheral neuropathy in diabetics have a similar seasonality to that we have observed for cramp treatment. I have also initiated a collaboration with an Australian researcher who has access to data from the BEACH study, which is an ongoing assessment of general practice activity in Australia. This database may be able to show whether a similar (but reversed) seasonal association in complaints of leg cramps and neuropathy occur in Australia. Determining whether vitamin D worsens nocturnal leg cramps (since cramping is worse in summer) would also be useful but an RCT of large doses of vitamin D for the prophylaxis of muscle cramps is already ongoing and should answer this question.

Given my diuretic findings it is also possible that serum potassium might modulate a threshold for cramping. As it is conceivable that electrolyte concentrations and fluid balance...
might vary with the seasons (it is common for patients to complain to me of leg swelling in the summer), I am currently pursuing efforts to obtain aggregate data from Lifelabs on the mean monthly serum potassium for the population of British Columbia and look for seasonal fluctuation – which might also explain the seasonal fluctuation in cramp treatment. Further sequence symmetry work looking at other drugs which affect potassium metabolism (e.g. ACEI inhibitors) might also be useful.
References


135. Williams JI, Young W. Inventory of Studies on the Accuracy of Canadian Health Administrative Databases. Toronto, ON: Institute for Clinical Evaluative Sciences; 1996.


Appendices

Appendix A - Database Search Strategies for Cochrane Systematic Review

A.1 CENTRAL Search Strategy

#1"muscle cramp*" or "muscle spasm*" or "muscle contraction*"
#2"charley horse*" or "charlie horse*"
#3eamc
#4"exercise associated muscle cramp*"
#5(#1 OR #2 OR #3 OR #4)
#6magnesium or mg2
#7(#5 AND #6)

A.2 MEDLINE (OvidSP) Search Strategy

1 randomized controlled trial.pt. (319110)
2 controlled clinical trial.pt. (83678)
3 randomized.ab. (224381)
4 placebo.ab. (129163)
5 drug therapy.fs. (1505532)
6 randomly.ab. (161540)
7 trial.ab. (232182)
8 groups.ab. (1070965)
9 or/1-8 (2788051)
10 exp animals/ not humans.sh. (3698786)
11 9 not 10 (2365479)
12 Muscle Cramp$.mp. (2287)
13 muscle spasm$.mp. (1208)
14 Muscle Contraction$.mp. (90622)
15 (charley horse$ or charlie horse$).mp. (3)
16 eamc.mp. (13)
17 exercise associated muscle cramp$.mp. (14)
18 or/12-17 (93884)
19 (magnesium or mg2).mp. (96848)
20 11 and 18 and 19 (84)
21 remove duplicates from 20 (82)

A.3 **EMBASE (OvidSP ) Search Strategy**

1 crossover-procedure/ (30907)
2 double-blind procedure/ (100996)
3 randomized controlled trial/ (290224)
4 single-blind procedure/ (14260)
5 (random$ or factorial$ or crossover$ or cross over$ or cross-over$ or placebo$ or (doubl$ adj blind$) or (singl$ adj blind$) or assign$ or allocat$ or volunteer$).tw. (1024327)
6 or/1-5 (1094729)
7 exp animals/ (1655604)
8 exp humans/ (12628304)
9 7 not (7 and 8) (1260032)
10 6 not 9 (1058983)
11 limit 10 to embase (858133)
12 (muscle cramp$ or muscle spasm$ or muscle contraction$).mp. (84647)
13 (charley horse$ or charlie horse$).mp. (3)
14 eamc.mp. (17)
15 exercise associated muscle cramp$.mp. (20)
16 or/12-15 (84654)
17 (magnesium or mg2).mp. (124341)
18 11 and 16 and 17 (57)
19 remove duplicates from 18 (57)

A.4 LILACS Search Strategy

muscle cramp$ or muscle spasm$ or muscle contraction$ or charley horse$ or charlie horse$
or eamc or exercise associated muscle cramp$ [Words] and magnesium or mg2
[Words] and ((Pt randomized controlled trial OR Pt controlled clinical trial OR Mh
randomized controlled trials OR Mh random allocation OR Mh double-blind method OR Mh
single-blind method) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Pt
clinical trial OR Ex E05.318.760.535$ OR (Tw clin$ AND (Tw trial$ OR Tw ensa$ OR Tw
estud$ OR Tw experim$ OR Tw investiga$)) OR ((Tw singl$ OR Tw simple$ OR Tw
doub$ OR Tw doble$ OR Tw duplo$ OR Tw trebl$ OR Tw trip$) AND (Tw blind$ OR Tw
ciego$ OR Tw ciego$ OR Tw mask$ OR Tw mascar$)) OR Mh placebos OR Tw placebo$
OR (Tw random$ OR Tw randon$ OR Tw casual$ OR Tw acaso$ OR Tw azar OR Tw
aleator$) OR Mh research design) AND NOT (Ct animal AND NOT (Ct human and Ct
animal)) OR (Ct comparative study OR Ex E05.337$ OR Mh follow-up studies OR Mh prospective studies OR Tw control$ OR Tw prospectiv$ OR Tw volunt$ OR Tw volunteer$) AND NOT (Ct animal AND NOT (Ct human and Ct animal))) [Words]

A.5 CINAHL Plus (EBSCOhost) Search Strategy

S24 S18 and S22 and S23
S23 magnesium or mg2
S22 s19 or s20 or s21
S21 eamc or exercise associated muscle cramp*
S20 charley horse* or charlie horse*
S19 muscle cramp* or muscle spasm* or muscle contraction*
S18 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17
S17 ABAB design*
S16 TI random* or AB random*
S15 ( TI (cross?over or placebo* or control* or factorial or sham? or dummy) ) or ( AB (cross?over or placebo* or control* or factorial or sham? or dummy) )
S14 ( TI (clin* or intervention* or compar* or experiment* or preventive or therapeutic) or AB (clin* or intervention* or compar* or experiment* or preventive or therapeutic) ) and ( TI (trial*) or AB (trial*) )
S13 ( TI (meta?analys* or systematic review*) ) or ( AB (meta?analys* or systematic review*) )
S12 ( TI (single* or doubl* or tripl* or trebl*) or AB (single* or doubl* or tripl* or trebl*) )
and ( TI (blind* or mask*) or AB (blind* or mask*) )
S11 PT ("clinical trial" or "systematic review")
S10 (MH "Factorial Design")
S9 (MH "Concurrent Prospective Studies") or (MH "Prospective Studies")
S8 (MH "Meta Analysis")
S7 (MH "Solomon Four-Group Design") or (MH "Static Group Comparison")
S6 (MH "Quasi-Experimental Studies")
S5 (MH "Placebos")
S4 (MH "Double-Blind Studies") or (MH "Triple-Blind Studies")
S3 (MH "Clinical Trials+")
S2 (MH "Crossover Design")
S1 (MH "Random Assignment") or (MH "Random Sample") or (MH "Simple Random Sample") or (MH "Stratified Random Sample") or (MH "Systematic Random Sample")

A.6 AMED (OvidSP) Search Strategy
1 Randomized controlled trials/ (1462)
2 Random allocation/ (299)
3 Double blind method/ (424)
4 Single-Blind Method/ (21)
5 exp Clinical Trials/ (3109)
6 (clin$ adj25 trial$).tw. (5273)
7 ((singl$ or doubl$ or treb$ or trip$) adj25 (blind$ or mask$ or dummy)).tw. (2166)
8 placebos/ (514)
9 placebo$.tw. (2448)
10 random$.tw. (12220)
11 research design/ (1663)
12 Prospective Studies/ (396)
13 meta analysis/ (106)
14 (meta?analys$ or systematic review$).tw. (1668)
15 control$.tw. (26563)
16 (multicenter or multicentre).tw. (701)
17 ((study or studies or design$) adj25 (factorial or prospective or intervention or crossover or cross-over or quasi-experiment$)).tw. (9356)
18 or/1-17 (40966)
19 (cramp$ or spasm$ or contraction$).mp. (5288)
20 (charley horse$ or charlie horse$).mp. (0)
21 eamc.mp. (1)
22 exercise associated muscle cramp$.mp. (3)
23 or/19-22 (5288)
24 (magnesium or mg2).mp. (229)
25 18 and 23 and 24 (1)

A.7 SPORTDiscus (EBSCOHost) Search Strategy
S11 S5 and S9 and S10
S10 magnesium or mg2
S9 S6 or S7 or S8
S8 eamc
S7 charley horse* or charlie horse*
S6 cramp* or spasm* or contraction*
S5 S1 or S2 or S3 or S4
S4 cross?over or placebo* or control* or factorial or sham? or dummy
S3 (single* or doubl* or tripl* or trebl*) and (blind* or mask*)
S2 clinical trial*
S1 randomi*
Appendix B - The Relationship Between Relative Risk and Sequence Ratio

Let’s assume that you want to compare the effect of two drugs (Drug A and a control drug, Drug B) in causing a particular outcome. The outcome could be anything – an event or, in the case of our analysis, the subsequent prescribing of another drug such as quinine. You could potentially perform two separate sequence symmetry analyses, one for each of Drug A and Drug B, and compare results. Or you could perform a survival analysis using cohorts of Drug A and Drug B recipients and look at the relative risk of Drug A recipients having the outcome compared to those receiving Drug B. We can mathematically describe both the relative risk (RR), and the sequence ratio (SR), and easily combine these equations to show how the relative risk and sequence ratio relate to each other.

Assuming: 1) Negligible censoring (e.g. using a risk interval and selecting only subjects who were present in the database throughout the follow-up period).
2) Equivalent time intervals for analysis (i.e. the symmetry analysis looks both forward, and then backward, a period of time equivalent to the follow-up period in the survival analysis).
3) Use of the same subjects (and hence the same outcomes).

Let: \( T_A = \) the total time recipients of Drug A are in the survival analysis
\( T_B = \) the total time recipients of Drug B are in the survival analysis
\( O_A = \) # of outcomes that follow receipt of Drug A
\( O_B = \) # of outcomes that follow receipt of Drug B
\( P_A = \) # of outcomes that precede receipt of Drug A

\[
RR = \frac{O_A / T_A}{P_A / T_B}
\]
\[
SR = \frac{O_A / T_A}{O_B / T_B}
\]

We can mathematically describe both the relative risk (RR), and the sequence ratio (SR), and easily combine these equations to show how the relative risk and sequence ratio relate to each other.
\( P_B = \# \) of outcomes that precede receipt of Drug B

\( SR_A = \) the sequence ratio of the outcome surrounding initiation of Drug A

\( SR_B = \) the sequence ratio of the outcome surrounding initiation of Drug B

\( RR_{A/B} = \) relative risk of the outcome in recipients of Drug A compared to Drug B

Given:

\[
RR_{A/B} = \frac{O_A/T_A}{O_B/T_B}
\]  

And:

\[
SR_A = \frac{O_A}{P_A} \quad \& \quad SR_B = \frac{O_B}{P_B}
\]

(which can also be written \( O_A = SR_A \times P_A \) and \( O_B = SR_B \times P_B \) )

Then substituting (2) into (1) gives:

\[
RR_{A/B} = \frac{O_A/T_A}{O_B/T_B} = \frac{SR_A \times P_A/T_A}{SR_B \times P_B/T_B}
\]

Or:

\[
RR_{A/B} = \frac{SR_A}{SR_B} \times \frac{P_A/T_A}{P_B/T_B}
\]

But, since we assume little or no censoring, both \( T_A \) and \( T_B \) are roughly equal to the number of individuals recruited into each cohort multiplied by the duration of follow-up.

\[# \text{i.e. } T_A = N_A \times t \quad \& \quad T_B = N_B \times t \]

Where \( t = \) the duration of the follow-up window (e.g. 1 year)
NA, NB = the number of subjects recruited for survival analysis in each arm

Substituting equations (5) into equation (4) and cancelling out t we find:

\[ RR_{A/B} = \frac{SR_A}{SR_B} \times \frac{P_{A/N_A}}{P_{B/N_B}} \]  \hspace{1cm} (6)

But \( P_{A/N_A} \) and \( P_{B/N_B} \) are the proportion of subjects with outcomes in an interval of time \( t \) before the study drugs are given. If the populations are chosen to have equivalent risk, outside of that incurred by the administration of Drug A or B, then these proportions are identical and cancel out. Hence we are left with:

\[ RR_{A/B} = \frac{SR_A}{SR_B} \]  \hspace{1cm} (7)

But if Drug B has no association to the outcome \( SR_B = 1 \)

Hence \( \text{Relative Risk}_{A/B} = \text{Sequence Ratio}_A \) \hspace{1cm} (8)

When

1) Receipt of Drug B is not correlated with occurrence of the outcome.

2) There is no loss to follow-up.

3) The survival analysis follow-up period matches the symmetry window (i.e. if the survival interval is \( t \) then the symmetry analysis looks forward \( t \) and backward \( t \) surrounding receipt of Drug A).
4) The baseline risk of the outcome is the same in both cohorts before drugs A and B are received.
Appendix C - Cox Proportional Hazards Analysis

I performed a Cox proportional hazards analysis comparing time to quinine start in new users of either inhaled LABA (exposed cohort) or inhaled anticholinergic (unexposed cohort) who first filled (and renewed within 1 year) their medication between Dec 1 2001 and Nov 30 2006. Subjects were excluded if they had prior renewed use of either cohort defining drug or a previous prescription for quinine. Censoring occurred upon addition of the other cohort defining medication (i.e a LABA cohort subject receiving inhaled anticholinergic, or vice-versa), after one year of follow-up and on Nov 30 2006. Subjects were excluded if they were less than 50 years old at the time they received their treatment and if they did not have evidence of medical services within the database for one year following, and two years preceding, receipt of the cohort defining medication.

I fit a model including all potential confounders of the exposure / outcome relationship. Increasing age, female gender and a number of diagnoses are known to be associated with cramps (including peripheral vascular disease, coronary artery disease, chronic kidney disease, dialysis, motor neuron disease, cirrhosis, radiculopathy / myelopathy and hypothyroidism). The number of patient visits to a family physician in the prior year and the number of distinct medication types received in the prior year were included as we thought this might indicate patients with more physician contact and a greater receptiveness to medication use. New starts of potassium-sparing and thiazide-like diuretics received within the prior year were also added as covariates based on our symmetry findings. Although not previously shown to be associated with cramps we included as covariates a diagnosis of either asthma or COPD in the prior 5 years, and use of salbutamol or inhaled steroids in the immediately prior year, in case these identified categories of LABA or
anticholinergic users that were differentially susceptible to cramps. I also included a prior diagnosis of malaria since this is an alternate use for quinine.

Results of my Cox analysis are given in Table 3. The hazard ratio for LABA starters as compared to anticholinergic starters (HR 2.37 p <.0001 95%CI 1.73 to 3.23) is consistent with our symmetry results. Thiazide and potassium-sparing diuretic starts were not numerous enough for significance but had hazard ratios in a similar range to the ASR values calculated using symmetry. If only renewed diuretic starts are considered, the HR for potassium sparing diuretics becomes significant (HR 5.35 p = 0.0009 95%CI 1.99 to 14.39), though this required searching for renewals during the risk interval. There was no significant interaction between LABA and potassium sparing diuretic starts. Cases of malaria and motor neuron disease were too few in number to include as covariates in the final model.

Table A.1  Cox proportional hazards analysis of time to quinine start in new users of LABA compared to new users of inhaled anticholinergic

<table>
<thead>
<tr>
<th>Cohort</th>
<th># of Subjects</th>
<th># of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>LABA</td>
<td>15,423</td>
<td>196</td>
</tr>
<tr>
<td>Anticholinergic</td>
<td>8,307</td>
<td>58</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>------------</td>
</tr>
<tr>
<td>LABA</td>
</tr>
<tr>
<td>Age (per year)</td>
</tr>
<tr>
<td>Female Gender</td>
</tr>
<tr>
<td># Distinct Drugs Used in Prior Yr</td>
</tr>
</tbody>
</table>
Table A.1 (Continued)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td># Primary Care Visits in Prior Yr</td>
<td>1.00&lt;sup&gt;b&lt;/sup&gt;</td>
<td>(0.98 to 1.01)</td>
<td>.576</td>
</tr>
<tr>
<td>Peripheral Vascular Disease</td>
<td>1.64</td>
<td>(1.11 to 2.43)</td>
<td>.013</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td>2.22</td>
<td>(1.30 to 3.81)</td>
<td>.004</td>
</tr>
<tr>
<td>Dialysis</td>
<td>1.40</td>
<td>(0.18 to 10.71)</td>
<td>.746</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>1.62</td>
<td>(0.60 to 4.37)</td>
<td>.341</td>
</tr>
<tr>
<td>Radiculopathy / myelopathy</td>
<td>2.19</td>
<td>(1.03 to 4.67)</td>
<td>.042</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>1.67</td>
<td>(1.15 to 2.42)</td>
<td>.007</td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
<td>1.08</td>
<td>(0.81 to 1.42)</td>
<td>.614</td>
</tr>
<tr>
<td>Thiazide Diuretic Start In Prior Yr</td>
<td>1.50</td>
<td>(0.82 to 2.76)</td>
<td>.186</td>
</tr>
<tr>
<td>K-Sparing Diuretic Start in Prior Yr</td>
<td>2.47</td>
<td>(0.79 to 7.73)</td>
<td>.120</td>
</tr>
<tr>
<td>Asthma</td>
<td>1.05</td>
<td>(0.80 to 1.38)</td>
<td>.739</td>
</tr>
<tr>
<td>COPD</td>
<td>1.12</td>
<td>(0.71 to 1.76)</td>
<td>.626</td>
</tr>
<tr>
<td>Salbutamol Use In Prior Yr</td>
<td>0.76</td>
<td>(0.55 to 1.05)</td>
<td>.096</td>
</tr>
<tr>
<td>Inhaled Steroid Use In Prior Yr</td>
<td>1.28</td>
<td>(0.92 to 1.77)</td>
<td>.144</td>
</tr>
</tbody>
</table>

<sup>a</sup> Hazard ratio per distinct drug used in prior year.

<sup>b</sup> Hazard ratio per patient visit to a general practitioner in prior year.
Appendix D - Attributable Proportions

a) Determining the proportion of quinine starters receiving an index start in the prior year that can be attributed to that index drug:

Using \( \text{Attributable Proportion} = \frac{\text{ASR} \times \text{baseline rate} - \text{baseline rate}}{\text{ASR} \times \text{baseline rate}} \)

Or \( \text{Attributable Proportion} = \frac{\text{ASR} - 1}{\text{ASR}} = 1 - \frac{1}{\text{ASR}} \)

Then the proportion of quinine starts in the year following the start of an index drug that are attributable to that index drug are:

For thiazides \( = 1 - \frac{1}{1.48} = 0.324 = 32\% \)

For k-sparing diuretics \( = 1 - \frac{1}{2.12} = 0.528 = 53\% \)

For LABA \( = 1 - \frac{1}{2.42} = 0.587 = 59\% \)

b) Estimating the proportion of all quinine starts attributable to these three index drugs: To make this estimation I examined all BC residents over the age of 50 on Dec 1 2001 who received a new Rx for quinine between Dec 1 2001 and Nov 30 2006 (i.e. our study period). I then looked at the year before each quinine start to see if our index drugs were prescribed. Since an examination of figure 2 suggested that the increase in quinine prescribing following thiazides and potassium sparing diuretics was sustained, I considered that whether prescriptions were starts or not, diuretic use had a similar influence on cramp promotion. This did not seem a reasonable assumption with LABA as the risk appeared to be lower (though still present) 6 to 12 months after the LABA start. In the case of LABA we
considered starts and renewals separately. If a LABA was prescribed in the year before quinine but was not a new start we used an ASR calculated using only the latter 6 months of prescribing seen in Figure 2 (producing ASR = 1.48). Determining how many quinine starters had received each of these index drugs in the year prior, and using the ASR for those drugs to estimate the number of attributable quinine prescriptions, I was able to estimate the proportion of all quinine starts collectively attributable to the three index drugs. To be conservative I assumed that users of more than one of these drugs had a cramp promoting effect only from the drug with the greater ASR (e.g. if both a potassium-sparing and thiazide diuretic were received in the year prior to starting quinine we assumed only the potassium-sparing diuretic contributed to cramp promotion – hence in the calculation below that individual was counted as having a potassium-sparing diuretic in the year before but the thiazide was not counted).

The proportion of all quinine starts attributable to the three index drugs was estimated by:

\[
\frac{\text{Attributable Proportion}_{\text{all quinine starts}}}{\# \text{ quinine starts}} = \frac{\left(1 - \frac{1}{\text{ASR}_L}\right) \times S_L + \left(1 - \frac{1}{\text{ASR}_K}\right) \times (C_L - S_L) + \left(1 - \frac{1}{\text{ASR}_T}\right) \times C_T}{S_L + \left(1 - \frac{1}{\text{ASR}_L}\right) \times S_T + \left(1 - \frac{1}{\text{ASR}_K}\right) \times C_K + \left(1 - \frac{1}{\text{ASR}_T}\right) \times C_T}
\]

Where \(\text{ASR}_L = \) Adjusted Sequence Ratio for LABA = 2.42

\(\text{ASR}_{L*} = \) ASR for LABA use that is not a new start = 1.48

\(\text{ASR}_K = \) Adjusted Sequence Ratio for K-Sparing Diuretics = 2.12

\(\text{ASR}_T = \) Adjusted Sequence Ratio for Thiazides = 1.48

\(S_L = \) Number of LABA starts prior to starting quinine = 596
\( C_L = \text{Total number receiving LABA prior to starting quinine} = 1,731 \)

\( C_T = \text{Total number receiving Thiazide prior to starting quinine} = 4,459 \)

\( C_K = \text{Total number receiving K-Sparing prior to starting quinine} = 2,352 \)

\# quinine starts = 25,129

Using these numbers in the above formula gives an \textbf{Attributable Proportion} = 13.6\%