

A RAPID EVIDENCE ASSESSMENT ON THE EFFECTIVENESS OF INTRAVENOUS
MEGA-DOSE MULTIVITAMINS ON FIBROMYALGIA, CHRONIC FATIGUE, CANCER,
AND ASTHMA

By

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Abstract

Purpose The focus of this Scholarly Practice Advancement Research project was to examine the evidence regarding the use of intravenous mega-dose vitamins for the specific conditions of interest for this project; fibromyalgia, chronic fatigue, cancer and asthma. These conditions were chosen because they are most frequently advertised by CAM providers as conditions wherein mega-doses of intravenous vitamins could be beneficial. Proponents have also made claims of research supporting intravenous mega-dose vitamin therapy, the Myers' Cocktail and mega-doses of vitamin C and magnesium.

Aims The aims of this project was to (a) conduct a Rapid Evidence Assessment (REA) to identify whether there is quality scientific evidence to support the use of intravenous mega dose m therapy as an effective therapeutic intervention for individuals with fibromyalgia, chronic fatigue, cancer, and asthma; (b) to evaluate the quality of published research available on the use of IVMM therapy for individuals with fibromyalgia, cancer, asthma and chronic fatigue.

Methods A Rapid Evidence Assessment was utilized to explore the quality of scientific evidence available in supporting the use of intravenous mega-dose multivitamin therapy. The databases CINAHL, PubMed Central, Medline, Google Scholar and ClinicalTrials.gov were utilized in gathering studies for this project. Eleven articles were selected for this paper which identified the use of the Myers' Cocktail, mega-doses of intravenous vitamin C, or mega-doses of magnesium.

Results Adverse events were minimal within all studies evaluated, however no patient experienced an objective tumor response, no complete or lasting effect on pain or fatigue and for asthma, conventional therapy was required along with intravenous therapy. Some patient's symptoms also worsened before they became better, and the effect of the interventions were

strongest in subjects with lower baseline levels of the vitamins or in conjunction with conventional treatments.

Conclusion Intravenous mega-doses of multivitamins, vitamin C and magnesium are well tolerated with minimal side effects, however available research fails to provide enough evidence to support the continued use of this complementary therapy. The use of intravenous therapy in conjunction with conventional therapies may have some benefit, however further clinical trials are required.

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Chapter 1: Introduction

With continuous advances in medical treatments available today, alternative and adjunctive therapies are becoming extremely popular. More than 70% of Canadians regularly use complementary and alternative medicine (CAM) therapies, such as vitamins and minerals, to stay healthy and improve their quality of life (Public Health Agency of Canada, 2008). Intravenous mega dose multivitamin (IVMM) therapy, specifically the use of the Myers' Cocktail, a "solution of water-soluble vitamins and minerals" has been one such therapeutic, advocated for the treatment of a number of conditions by CAM providers (Ali et al., 2009, p. 3). Several studies have claimed positive outcomes for patients using IVMM therapy or a modified Myers' Cocktail for a wide range of conditions including fibromyalgia, chronic fatigue, cancer, asthma, headaches, jetlag, Parkinson's disease, depression and also 'detoxification' (Gavura, 2013; Gaby, 2002). Advocates state IVMM is superior to oral dietary intake of vitamins because it avoids issues with food sensitivities and gastrointestinal intolerances related to age and medical conditions (Gavura, 2013). It has also been advertised as a preventative therapy to the general public for strengthening the body and immune system (Gavura, 2013). Proponents support accessing IVMM therapy for people to 'take control' of their health, rather than waiting for a health problem to arise (Ellis, 2016).

In our current healthcare climate, there is significant public interest in exploring 'natural' and alternative methods of treatment over conventional medical treatments. Whereas conventional scientific medicine relies on "methods proven to be safe and effective through carefully designed trials and research," many alternative therapies "lack solid research on which to base sound decisions" (Padayatty et al., 2006; Tabish, 2008).

Current Trends in CAM and IVMM

Provinces in Canada are now granting recognized health professional status to naturopaths alongside other CAM practitioners, “including regulatory reform in Ontario and British Columbia that have expanded their scope of practice of naturopaths to include allergy testing and treatment, as well as new prescribing rights” (Caulfield & Rachul, 2011, p. 1).

However, many of the treatments they support remain scientifically unsupported (Caulfield & Rachul, 2011).

IVMM therapy now represents one of the most promoted services offered by naturopaths in Alberta and British Columbia (Caulfield & Rachul, 2011). These therapies vary, and preparations used are dependent upon the targeted illness, but typically consist of a unique blend of vitamin C, calcium, magnesium and a variety of complementary B vitamins, argued to produce vascular and bronchial smooth muscle relaxation, and to enhance mitochondrial energy production (Erickson, 2003; Foresman, 1984). IVMM therapy is delivered via peripheral intravenous over 10-45 minutes, depending on the provider and therapy concentrations (Ali et al., 2009; Massey, 2007). IVMM infusions are currently not available from publicly funded healthcare providers in Canada, but are available privately. A single private IVMM therapy can cost an individual between \$50 to \$250 (Gavura, 2013). This is significantly higher than the cost of equivalent oral doses of the same vitamins, which have been noted to be approximately \$8 for a month or more of supply (Gavura, 2013).

A major argument for IVMM therapy is that by infusing vitamins intravenously, the gastrointestinal system is bypassed, and vitamins are available for immediate cellular use (Gavura, 2013; Gaby, 2002). However, the mega doses of vitamins infused intravenously could potentially be extremely harmful if an individual were to take the equivalent oral dose (Zoltan,

2012). The literature also suggests that the potential benefits of IVMM vary considerably from person to person, depending on their health status. There may also be significant side effects, such as phlebitis, cardiac arrhythmias, hypotension, or allergic and anaphylactic reactions (Suh et al., 2012).

Current scientific research suggests that unless there is a deficiency that needs replacing, mega doses of vitamins, orally or intravenously, will not prevent an illness (Gavura, 2013). Many studies that support IVMM therapy report that the effects of IVMM on fatigue may last up to 48 hours or more. However, over the next 24 hours, patients will excrete the vast majority of the extra water soluble vitamins and will only retain what the body requires (Ellis, 2016; Gaby, 2002). For the provider, this represents a marketing approach wherein they recommend that clients continue to return for repeat IVMM therapy.

Whilst it has been argued that the public should have access to a wide range of health care practitioners when it comes to their personal health choices, the choice for treatment should be as informed as possible, especially when a treatment choice can make a significant impact on the patients' health and disease process (Caulfield & Rachul, 2011). While advocates of IVMM therapy promise efficacy for many generalized problems, the benefits are vaguely described as boosting energy, improving mood, and strengthening the immune system (Gaby, 2002; Carr, Vissers & Cook, 2014). The value of IVMM therapy in treating symptoms of fibromyalgia, chronic fatigue, cancer, and asthma remains questionable, and an area which needs further investigation. Dr. David Jenkins of University of Toronto urges that the public question why such a therapy that is advertised to treat a variety of ailments, has yet to make its way into the main medical literature and conventional medical treatments (Kirkey, 2015).

Problem Identification

Although multivitamins have been used to treat a variety of condition for decades, the use of IVMM therapy is fairly new, especially with certain health conditions. However, the efficacy and safety of using IVMM therapies, such as the Myers' Cocktail or other mega doses of intravenous vitamins, remains questionable. The lack of information and evidence available for the effect of this therapy is of particular interest as it is not currently offered as part of conventional medical treatment. It is advertised by CAM providers, for a variety of conditions. The specific conditions of interest here are fibromyalgia, chronic fatigue, cancer, and asthma because they are most frequently advertised by CAM providers as conditions wherein IVMM could be beneficial. Proponents have also made several claims of research supporting IVMM therapy, the Myers' Cocktail and mega doses of vitamin C and magnesium (Gavura, 2013). However, there is ambiguity around its safety and effectiveness as a medical therapy for the conditions listed above. Additionally, there is currently no comprehensive review of the literature that assesses the positive effects of IVMM therapy that many advocates are claiming, nor the quality of this evidence.

Purpose

The aims of this paper are to:

- (a) conduct a Rapid Evidence Assessment (REA) to identify whether there is quality scientific evidence to support the use of IVMM therapy as an effective therapeutic intervention for individuals with fibromyalgia, chronic fatigue, cancer, and asthma.
- (b) to evaluate the quality of published research available on the use of IVMM therapy for individuals with fibromyalgia, cancer, asthma and chronic fatigue.

The findings and recommendations from this work will inform the work of clinicians and ensure that the public is provided with accurate information regarding therapeutic choices and the value of IVMM therapy for the conditions considered in this REA in particular.

Research Question

The United Kingdom Government Social Research Service (GSRS) developed a Rapid Evidence Assessment Toolkit (REA) outlining standards for carrying out a REA. The GSRS (2009) recommend that researchers determine whether the research question is an impact or non-impact question and to facilitate this process, the toolkit provides a PICO format. PICO represents: Population of interest, Intervention, Comparison, and Outcome and not all four aspects need to be covered in a question (GSRS, 2009). The PICO format assists the researchers in breaking down the concepts in a question and to consider different aspects of the information the researcher is interested in (GSRS, 2009). The research question for my REA is an impact questions, as I aim to explore the impact of a specific therapeutic intervention (IVMM therapy) on fibromyalgia, chronic fatigue, cancer and asthma. My research question is as follows:

1. What is the scientific evidence that intravenous mega dose multivitamin therapy is an effective treatment for fibromyalgia, chronic fatigue, cancer and asthma?
2. What is the quality of the published research in the last 30 years on the value of intravenous mega dose multivitamin therapy as an effective therapy for individuals with fibromyalgia, cancer, asthma and chronic fatigue?

Chapter 2: Background

There are a number of implementations of IVMM that have been developed and are being advertised by CAM providers. The few that are being examined for this REA are high doses of IV vitamin C, IV magnesium (IVMg) and the use of Myers' Cocktail. Discussing intravenous vitamin C (IVVC) for this REA is beneficial as vitamin C is a part of the Myers' Cocktail and the theories and efficacy of the Myers' Cocktail are similar and have been informed by the theory and research on IVVC. Therefore, broadening the search to include IVVC and IVMg allowed for the inclusion of a greater number of studies in this review.

Historical Context

High-dose intravenous Vitamin C

High-doses of IVVC have been used by some physicians for over 60 years as a therapeutic agent, since its introduction by the American biochemist and two-time Nobel Prize winner, Linus Pauling (Padayatty et al., 2010). In 1968, Pauling argued that a person's individual need for vitamins and nutrients varied and that in order to maintain good health, people needed significantly more Vitamin C than the daily recommended intake of 60mg/day (Barrett, 1995; Government of Canada, 2016). Pauling further suggested that mega doses of vitamins and minerals might be beneficial and termed this approach "orthomolecular," meaning "right molecule" (Barrett, 1995). He shared these ideas with the public and expanded the list of conditions that could be treated with mega doses of vitamin therapy.

The use of high-dose IV vitamin C, especially for treating cancer, was highlighted by Pauling. He stated that "many species can produce their own vitamin C" however, humans lack this ability and lead people to believe that some diseases may be directly linked to vitamin C deficiency (Gauvura, 2013; World Health Organization, 2004). However, in 1976, Pauling conducted a clinical trial with Dr. Ewan Cameron (a Scottish physician), in which he claimed

efficacy of treating cancer with vitamin C. Subsequent reviews of this trial by other researchers established that no real conclusion could be drawn as the trial was flawed and the patient groups were incomparable (Gauvura, 2013; Barrett, 1995). There was no standardization, no matching for age or stage of cancer controls, and a high selection bias (Cameron and Pauling, 1976).

Conventional medical and nutritional practice has not shared Pauling's views on the efficacy of IV Vitamin C in large doses, and there has been limited clinical uptake (Barrett, 1995). Overall, the results obtained in clinical studies to date suggest that the clinical benefits of IV Vitamin C are yet to be confirmed by controlled clinical trials and the "notion that high-dose vitamin C was selectively toxic to cancer cells was biologically implausible" (Padayatty et al., 2006, p. 937). Also, there has been a lack of good quality randomized or placebo controlled studies, therefore, IV vitamin C treatment for cancer has not been accepted by the scientific community at large (Ohno, S., Ohno, O., Suzuki, Som, & Inoue, 2009). IVVC has also been linked to reducing fatigue, however published studies have yielded inconsistent results on the efficacy of IVVC and reducing fatigue due to the studies having varying routes of delivery and not solely studying the effects of only IVVC, and included oral routes as well (Suh et al., 2012). However, for this REA, only intravenous studies were included. While searching for literature for this REA, one study by Suh et al., 2012 set out to do a randomized, double-blind, controlled clinical trial, and the results showed a decrease in fatigue for only one day, therefore, maintenance treatment is required (Suh et al., 2012).

Intravenous Magnesium

Similar to IVVC and the Myers' Cocktail, the mechanism of exactly how IVMg benefits patients with asthma is still unknown. However, researchers state that the effects may come from the ability of magnesium to inhibit cellular uptake of calcium across the smooth muscle

membranes, leading to bronchial smooth muscle relaxation (Kokotajlo, Degnan, Meyers, Siu and Robinson, 2014). The first study exploring the use of IVMg was published in 1987 by Okayama and colleagues. They studied the effects that magnesium had on 10 adults with asthma, after administering 250mg of IVMg and measuring their lung function (Okayama et al., 1987). Their study revealed that when IVMg was administered, it caused bronchodilation quickly in both mild and severe asthma. One of the biggest safety concerns when administering IVMg is hypotension (Kokotailo et al., 2014). Overall, using IVMg for asthma appears to be safe and effective for severe acute asthma and a possible benefit for moderate to severe asthma along with the standard bronchodilators, however there are insufficient RCT's to verify whether IVMg does in fact have clinical benefit compared to traditional treatment methods (Guerrera, Volpe and Mao, 2009).

Myers' Cocktail

The pioneer for introducing the use of high dose intravenous vitamins and minerals in a combined application was a physician from Baltimore, Maryland: Dr. John Myers (Gaby, 2002; Foresman, 1984). Building on Linus Pauling's work, the Myers' Cocktail (as it became known) was introduced in the late 1950's. Dr. Myers' studied diet and nutrition and noted that only minimal amounts of nutrients were being absorbed into the blood stream through meals (Foresman, 2012). Therefore, the initial idea behind the introduction of IV vitamin therapy was to aid individuals with illnesses associated with digestive disturbances, such as Crohn's Disease, ulcerative colitis or irritable bowel syndrome, based on the theory that these individuals might not be capable of absorbing many of the nutrients we normally digest orally to maintain good health (Gavura, 2013; Mary, 2014).

The introduction of this IVMM therapy was essentially designed to achieve high serum concentrations of specific vitamins and minerals unobtainable through oral or intramuscular

administration (Gaby, 2002). It was employed to treat a variety of conditions including: fibromyalgia, chronic fatigue, cancer, asthma, acute migraines, upper respiratory tract infections, allergies and many more (Gaby, 2002; Mary, 2014). The Myers' Cocktail has been popular in treating fibromyalgia among CAM providers for many years, since its etiology is poorly understood, forcing individuals to seek out alternative methods to control their symptoms (Ali et al., 2009). Fibromyalgia is a condition with an unknown etiology that is described by individuals experiencing “widespread pain and muscle tenderness” accompanied by “chronic fatigue, sleep disturbances and depressed mood” (Ali et al., 2009).

Some of the conditions that IVMM therapy is advertised for also cause the body to use nutrients at a much faster rate, or require higher amounts of vitamins, such as infections and inflammations, in order for the individual to heal (Mary, 2014). Therefore, IVMM therapy is argued to be effective because it is administered directly into the bloodstream, bypassing the digestive system (Gavura, 2013; Mary 2014). This may provide individuals a ‘nutritional boost’ for a short period of time, causing individuals to seek regular maintenance IV therapy, which can be an expensive intervention compared to the conventional way of getting vitamins and minerals through diet (Gavura, 2013; Ellis, 2016). However, the literature suggests that the effects of IVMM therapy differ person to person, as do the number of IVMM therapy sessions required to boost nutritional status.

Composition of the Myers' Cocktail

The original ‘cocktail’ contents remain unknown because Dr. Myers died in 1984, and no published or written material on the treatment were available. The current version in clinical use is, therefore, a modified Myers' cocktail, and was produced by Dr. Alan Gaby, who inherited Dr. Myers' practice after he passed away (Gaby, 2002, p. 389).

The current modified cocktail contains the following nutrients (Ali et al., 2009; Gaby, 2002):

Table 1: Nutrients in the current modified Myers' Cocktail

Volume	Nutrients	Normal adult RDA
5 mL	Magnesium chloride hexahydrate (20%)	535mg/day
3 mL	Calcium gluconate (10%)	1000mg/day
1 mL	Hydroxocobalamin (Vitamin B12) (1,000 ug/mL)	2ug/day
1 mL	Pyridoxine hydrochloride (Vitamin B6) (100mg/mL)	1.8mg/day
1 mL	Dexpanthenol (Vitamin B5) (250 mg/mL)	1-7mg/day
1 mL	B-complex 100 containing:	
	100 mg of thiamine HCl	1.3mg/day
	2 mg of riboflavin	1.6mg/day
	2 mg of pyridoxine HCl (Vitamin B6)	1.8mg/day
	2 mg of panthenol (Vitamin B5)	1-7mg/day
	100 mg of niacinamide	16-18mg/day
	2% benzyl alcohol	5mg/kg
5 mL	Vitamin C (500mg/mL)	60mg/day
20 mL	Sterile water	

*RDA – recommended daily allowance

Although the nutrients listed above are considered to be the fundamental components of the hypertonic Myers' Cocktail solution, the concentrations used for each of the nutrients may differ depending on the condition being treated, and the age and health status of the client (Ali et al., 2009; Erickson, 2003; Gaby, 2002). This may make comparisons of efficacy of the intervention in clinical studies more difficult.

Clinical Use and Evidence

High dose intravenous Vitamin C

The Canadian Food Inspection Agency recommends a daily oral Vitamin C (also referred to as L-ascorbic acid or ascorbate) intake of 60mg/day for persons 2 years of age or older, which is best consumed in portions throughout the day (Government of Canada, 2016). Examining the pharmacokinetics of Vitamin C reveals that when oral doses exceed 200 mg, “absorption decreases, urine excretion increases and ascorbate bioavailability is reduced” (Ohno et al., 2009, p. 810). However, if vitamin C is administered intravenously, and bypasses the intestinal

absorption system, high plasma concentration levels can be created (Ohno et al., 2009). In return, the urine concentrations are also 140-fold higher than those from oral vitamin C intake as well, causing the extra vitamin C to be excreted within a few hours (Ohno et al., 2009).

While IVVC is being used for a wide variety of conditions, such as cancer, fatigue, asthma, and Crohns disease, to treat nausea and vomiting, and to improve quality of life and emotional status, more interest lies in its potential use in prolonging or treating cancer (Mikirova, Casciari, Riordan and Hunninghake, 2013). It is said that IVVC works in two ways to prolong cancer progression, the production of H_2O_2 and the pro-oxidant effect. The production of H_2O_2 (hydrogen peroxide) occurs when “vitamin C in blood is oxidized to dehydroascorbate acid” which flows freely through the cell membranes through the glucose transport (Agus, Vera and Golde, 1999). Therefore, when dehydroascorbate acid enters cancer cells, glutathione turns the dehydroascorbate back into vitamin C, which then cannot be moved out of the cancer cells. This vitamin C is then converted to dehydroascorbate again and produces H_2O_2 , which destroys cancer cells (Agus et al., 1999; Ohno et al., 2009). It is said that once plasma concentrations of vitamin C reached 33.7mM, cancer cell death occurs (Yeom, Jung and Song, 2007). Another mechanism of action of IVVC is the increase in collagen, which inhibits cancer cell growth and promotes necrosis in cancer cells (Yeom et al., 2007). Lastly, Yeom et al., (2007) stated that vitamin C influences amino acid levels in our body and can deplete the bioavailability of 2 amino acids that are required for rapidly growing tumors.

Pauling reported in 1976 and 1978 that a high-dose of 10 grams of intravenous vitamin C per day for 10 days, and orally afterwards, “increased the average survival of advanced cancer patients” (Ohno et al, 2009). The doses of IV vitamin C given to cancer patients range from study to study: 15 grams to 19,075 grams (Jackson, Riordan, Bramhall & Neathery, 2002), 15

grams to 65 grams (Padayatty et al, 2006), 70 grams to 110 grams (Stephenson, Levin, Spector & Lis, 2013), and fixed doses of 0.4, 0.6, 0.9 and 1.5g/kg based on weight (Hoffer et al., 2008).

However, in all these studies, the participants showed no objective anticancer response.

Although some trials have shown positive outcomes for individuals accessing high doses of intravenous vitamin C for cancer and fatigue, in combination with other conventional therapies, no trials have produced results that provides sufficient evidence that intravenous vitamin C alone is capable of producing a therapeutic effect (Suh et al., 2012).

It has been argued that many of the clinical trials completed with the use of high-dose vitamin C for cancer, failed to randomize or blind the participants, therefore the participants may have felt better subjectively, knowing that they are receiving a treatment (the Hawthorne effect) (Gauvura, 2013). Padayatty et al., (2006), reviewed three cases of advanced carcinoma patients using high-dose IV vitamin C therapy and found that it effectively reduced the progression of a malignant tumor. However, information on the serum concentrations is not available to “establish a causal relationship between the route of administration, the effective concentration, and the observed effect” (Ohno et al., 2009). The clinical trials that are currently available and those that suggest a therapeutic benefit of IV vitamin C in patients with cancer are equally inconsistently reproducible (Heaney et al., 2008, p. 8031). Suh et al., (2012) studied the effect of intravenous vitamin C on fatigue and concluded that although fatigue was reduced after two hours, the effect only persisted for a day, and there were no significant differences noted between the treatment and placebo groups. They concluded that the benefit of IV vitamin C was only noticeable in those participants who had relatively low baseline levels, concluding that they were essentially just replacing what was already depleted (Suh et al., 2012).

Efficacy of the Myers' Cocktail

Published studies on the efficacy of IVMM therapy to treat fibromyalgia symptoms have claimed that there were decreased pain levels, decreased fatigue, and increased ability to perform activities of daily living, however, no participants were able to report complete or lasting results (Massey, 2007; Ali et al., 2009). Both authors stated that further research is required because the efficacy of IVMM therapy relative to a placebo remains uncertain. Studies published for the use of IVMM therapy to treat asthma also conclude that improvement was only noted in short term pulmonary function (Ciarallo, Sauer & Shannon, 1996). Ciarallo et al (1996) and Shrader (2004) also noted that IVMM therapy should be an adjunct therapy and not the main asthma treatment because some study participants appeared to worsen immediately after an infusion, and required emergency treatment. The authors were unable to determine which nutrients caused the adverse events.

Intravenous Administration and Risks and Benefits of IV Therapy

The Myers' Cocktail and high doses of vitamin C are administered via a small catheter that is inserted into a peripheral vein, and the infusion is given over 5-60 minutes, depending on the provider and the volume being infused.

The side effects reported vary from as simple as phlebitis, to complications such as diarrhea, flatulence, generalized urticaria, angioedema, asthma, rapid administration causing hypotension, light-headedness, syncope, glucose 6 phosphate dehydrogenase deficiency, kidney stones and others (Ohno et al., 2009; Gaby, 2002; Gavura, 2013). High doses of IVVC have serious side effects for those who have certain risk factors such as a history of kidney disorders, kidney failure, hemolysis and hemochromatosis (National Cancer Institute, 2017). Overall, benefit of the Myers' Cocktail, IVMg and high doses of IVVC have been shown in only a small

number of published studies. Despite over 60 years of research on the use of intravenous nutrients, the evidence in support of its efficacy is still limited. Mainly seen in the studies is a temporary relief of symptoms of fatigue, asthma, pain and others, however, no long-term benefit unless there is regular maintenance therapy, and the cost of maintenance can be expensive.

Community Use

In searching for literature to analyze this topic, several local naturopathic clinics were contacted via email, phone and in person to gather supporting clinical evidence of IV vitamin therapy in the community. I contacted clinics within the lower mainland and the response was surprising - no clinic was willing to share any clinical information on the therapy (other than their public marketing materials).

No evidence was found available to describe details of the dosage, and frequency of use of the Myers' cocktail, IVVC and IVMg among the many CAM providers in the community. However, in the literature search, there were many clinics and mobile units noted that advertised IV vitamin therapy for a number of conditions. These included: The Polo Health and Longevity Centre (New Westminster, BC), Vitalia Healthcare Naturopath (Vancouver, BC), IV Wellness Boutique (Vancouver, BC), IV Drip (Vancouver, BC), The Electra Health Floor (Vancouver, BC) and other naturopathic clinics around the lower mainland. These clinics claimed that IV therapy benefits individuals experiencing fatigue, depression, muscle spasms, weak immune system, chronic infections, migraines, headaches, seasonal allergies, respiratory conditions, high blood pressure, athletic recovery, diabetes, detoxification, hepatitis, heart disease, stress and anxiety, hangovers, sleep, hydration, immunity, energy, jetlag, hormone imbalances, weight loss, headaches and others. Yet, when approached to share evidence in favour of IV therapy, no clinic

was able to share any information. Therefore, regardless of the lack of evidence available to justify the use of IV vitamin therapy, it continues to be on the rise among CAM providers.

Chapter 3: Methodology

In this chapter, I describe the overall approach and methods used to conduct this research. I utilized a rapid evidence assessment (REA) process and explore the following research questions:

1. What is the scientific evidence that intravenous mega dose multivitamin therapy is an effective treatment for fibromyalgia, chronic fatigue, cancer and asthma?
2. What is the quality of the published research in the last 30 years on the value of intravenous mega dose multivitamin therapy as an effective therapy for individuals with fibromyalgia, cancer, asthma and chronic fatigue?

Rapid Evidence Assessment

An REA allows researchers to obtain a quick overview of existing literature on a constrained topic (Government Social Research Service (GSRS), 2009). The process of an REA involves formulating a research question, defining a theoretical framework, conducting an evidence assessment, and assessing the quality and relevance of the studies using inclusion and exclusion criteria (GSRS, 2009). This process enables researchers to carry out a systematic review to search for and critically analyze existing literature to produce information in a short period of time (GSRS, 2009; Tricco et al., 2015). Furthermore, an REA is rigorous and explicit in methodology, however, the comprehensiveness of the search and review stages may be limited (GSRS, 2009; Hemmingway & Brereton, 2009).

An REA falls just below a traditional systematic review in terms of confidence in review studies, but above a quick scoping review. It is also a useful systematic literature review methodology when there is uncertainty around the effectiveness of a service or policy, and to support further research by identifying evidence gaps (GSRS, 2009). However, an REA does

have limitations. As a rapid and constrained review there is a risk of providing a an incomplete analysis or bias, due to the limited timeframe, limited reviewers engaging in the analysis, and by limiting research to only published literature, within a specific frame (GSRS, 2009).

An REA is an appropriate strategy for this research paper over a literature review, scoping review and a full systematic review as there is a need to evaluate the evidence base for the use of IVMM therapy and high dose intravenous vitamin C as an adjunct therapy in the treatment of multiple conditions. Although there are numerous studies available, they are not scientifically rigorous in design or methodology (GSRS, 2009). An REA is also valuable for this paper due to the limited published material available in this area. Among the published literature for IVMM therapy and the use of high dose vitamin C, there have been a variety of conditions explored, therefore limiting the amount of literature available for a given condition. Due to the limited published literature for a variety of conditions, a full systematic review is not practical (GSRS, 2009).

Search Strategy

I initially consulted with a University of British Columbian subject specialist librarian to establish the most appropriate databases to access for this research topic. The following databases were then utilized: The Cumulative Index to Nursing and Allied Health (CINAHL), PubMed Central, Medical Literature Analysis and Retrieval System Online (Medline), and Google Scholar. I also accessed ClinicalTrials.gov, the North American clinical trials registry and results database where clinical studies involving human participants around the world, to find published clinical studies involving the use of IVMM therapy and high dose intravenous vitamin C.

Sources Described

CINAHL is a database of English language and selected other language journal articles about nursing, allied health, biomedicine, and healthcare (Wikipedia, 2017). CINAHL was launched in the 1940s, however, it incorporated allied health in 1977 (Wikipedia, 2017). PubMed Central, is a freely accessible database that archives publicly accessible full-text scholarly articles that are published within the biomedical and life sciences literature (Wikipedia, 2017). Medline, is a bibliographic database of life sciences and biomedical information (Wikipedia, 2017). It includes bibliographic information for articles from academic journals covering medicine, nursing, pharmacy, dentistry, veterinary medicine, and health care (Wikipedia, 2017). Google Scholar is a freely accessible web search engine that allows for a broad search of scholarly literature. Google Scholar launched 12 years ago in 2004, and includes most peer reviewed online academic journals, books, papers, theses and dissertations, abstracts, reports and much more (Wikipedia, 2017).

Inclusion and exclusion criteria

The 11 articles selected for this paper, identified the use of the Myers' Cocktail or a high intravenous dose of ascorbic acid, Vitamin C as an adjunct therapy for fibromyalgia, cancer, asthma and fatigue. The inclusion criteria included: studies written in the English language, because I am unable to interpret any other language; restricted search from 1987 to 2017 because there is very limited research available to analyze regarding IVMM therapy. Also, studies published prior to 1987 were considered to be unrepresentative of the current development of the use of IVMM therapy. The search was also filtered to only include the conditions fibromyalgia, chronic fatigue, cancer and asthma, because studies have been done with a variety of medical conditions, however very minimal quantity per condition is available. Also, many studies found

were conducted on animals rather than humans. Including multiple conditions allowed me to gather enough information to evaluate the effect of Myers' Cocktail or high doses of intravenous vitamin C. Exclusion criteria consisted of grey literature, personal reports, duplicate reports of studies, animal studies, and studies evaluating the effect of multiple interventions.

Search terminology

The search terms used for all the databases, in order to avoid repetition were: Intravenous vitamin therapy, intravenous nutrient therapy, nutrient therapy, intravenous micronutrient therapy, Myers' Cocktail, Myers' Cocktail and cancer, Myers' Cocktail and fatigue, Myers' Cocktail and asthma, Myers' Cocktail and fibromyalgia, intravenous ascorbic acid and fatigue, intravenous vitamin c and fatigue, high dose vitamin c and cancer, intravenous vitamin c administration, Myers' Cocktail and human trials, high dose vitamin C therapy, nutrition therapy, ascorbic acid, intravenous infusions, intravenous vitamin C and fibromyalgia, fibromyalgia or vitamins or minerals or infusions/intravenous, intravenous vitamins and asthma, intravenous/administered vitamin C or ascorbic acid for cancer therapy/treatment, intravenous vitamin C or ascorbic acid for chronic fatigue/fatigue, intravenous nutrients or Myers' cocktail for chronic fatigue or fatigue, intravenous micronutrient therapy/treatment for fatigue, antineoplastic agents/therapeutic use, vitamins/adverse effects, placebos, fatigue/drug therapy, intravenous mega dose multivitamins, intravenous Myers' Cocktail, intravenous micronutrient therapy, intravenous vitamin C and cancer, intravenous Myers' Cocktail and fibromyalgia, intravenous Myers' Cocktail and cancer, intravenous Myers' Cocktail and asthma, intravenous Myers' Cocktail and chronic fatigue, and intravenous Myers' Cocktail and fatigue, Mega dose intravenous vitamins, and mega dose intravenous vitamin C.

Search Process

Databases listed above were searched with a variety of keywords and the inclusion and exclusion criteria was also applied when selecting articles. The articles were then further refined after analyzing the articles titles and abstracts and exploring their relevance to the REA questions.

Data Extraction and Assessment

Summary data from all of the selected eleven studies were added to a spreadsheet using a data extraction matrix created from the original research questions, and review tools were based on the evidence for policy and practice information centre (EPPI) review guidelines for extracting data (GSRS, 2009).

REA Tools for Quality of Evidence

The gathered data was then analyzed through several tools recommended by the REA toolkit, including the GRSS Weight of Evidence criteria (GRSS WoE), the Maryland Scale of Scientific Methods for impact studies (MSSM) and the Critical Appraisal Skills Program (CASP) for qualitative studies (GSRS, 2009). Finally, the risk of bias was assessed for all included studies using the Cochrane Collaboration's tool for assessing risk of bias, which looks at selection bias, performance bias, detection bias, attrition bias, reporting bias, and any other bias (GSRS, 2009).

The GRSS Weight of Evidence Tool

The GRSS WoE tool (Appendix A) was developed by the Evidence for Policy and Practice Information and Co-ordinating Centre (EPPI-Centre). This tool is comprised of “question-specific quality and relevance criteria to determine how much ‘Weight of Evidence’

should be given to the findings of a research study in answering a particular research question” (Gough, 2007, p. 214). This framework is organized into three dimensions:

- A. “Non review-specific judgment about the coherence and integrity of the evidence”
- B. “Review-specific judgement about the appropriateness of that form of evidence for answering the review question”
- C. “Review-specific judgement about the relevance of the focus of the evidence for the review question”) (Gough, 2007, p. 223).

These three dimensions are then combined to form dimension D, which is the overall Weight of Evidence assessment (Gough, 2007; GSRs, 2009).

The Maryland Scale of Scientific Methods Tool

The MSSM tool (Appendix B) was developed by Sherman, Gottfredson, MacKenzie, Eck, Reuter and Bushway (1998). This tool is comprised of a five-point scale to classify the strength of methodologies used (GSRs, 2009). Sherman et al., (1998) originally developed this scale for the social sciences and specifically for application in the criminology field. However, due to the generic qualities of the five levels in this tool, it is well suited for application to other areas of social science (GSRs, 2009; Sherman et al., 1998).

The Cochrane Risk of Bias Assessment Tool

Finally, the Cochrane risk of bias (RoB) assessment tool was applied (Appendix D). This tool, introduced in 2008, is specifically designed to help examine specific bias attributes (such as selection bias, performance bias, detection bias, attrition bias, reporting bias) or other forms of bias that may be present in the research articles (Higgins et al., 2011). Analyzing research and providing reviews presents health care providers, patients and policy makers with information that enables them to make informed decisions (Turner, Boutron, Hróbjartsson, Altman and

Moher, 2013). The RoB, therefore, allows those who are conducting reviews to be cognizant of the potential biases found within published literature, such as flaws in design, conduct, analysis, and over or under reporting results (Higgins et al., 2011; Turner et al., 2013). The aim for developing this tool was to facilitate an improved appraisal of evidence by policy makers and patients to overall lead to better health care (Higgins et al., 2011). For researchers to better understand the ways in which flaws can occur in research designs and cause bias, future trials may provide more reliable evidence (Higgins et al., 2011).

Therefore, the methods selected supported a systematic analysis of the evidence with limited resources available.

Chapter 4: Results

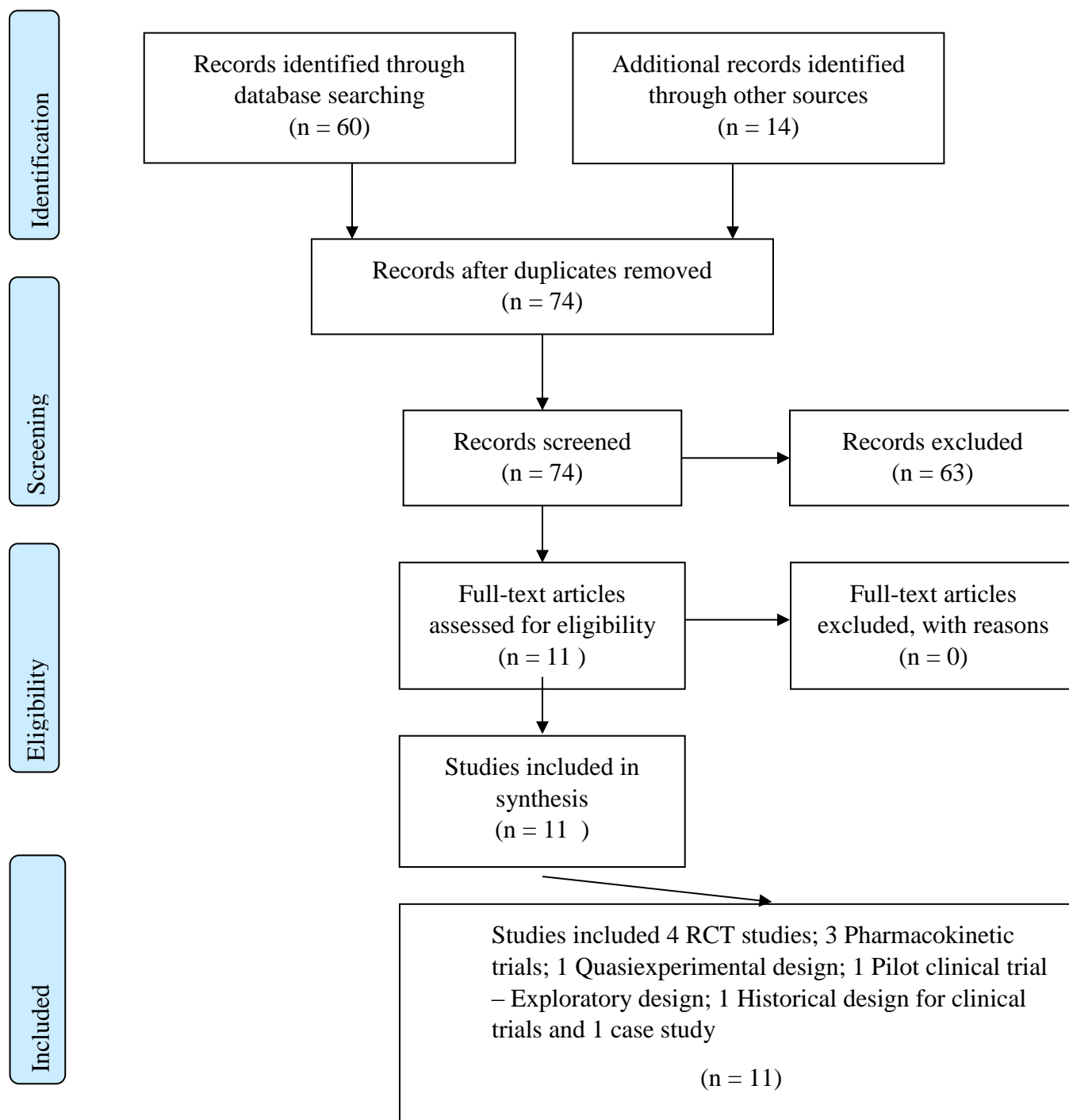
In this chapter, I provide an overview of each study and discuss the quality appraisals of each study.

Search Results

Within the literature, I reviewed a total of 74 abstracts and/or titles: 21 from CINAHL, 16 from PubMed, 8 from Medline, 15 from Google Scholar and 14 from the U.S. National Library of Medicine Clinical Trials website. After scanning the reviewed abstracts and titles, I excluded 63 articles as they did not include the therapies of interest, the route of administration was not included, other vitamins and complementary therapies were included in addition to intravenous therapy or the studies did not address the conditions that I was interested in. Some papers were also reviews of previous work and no new information was presented, therefore the primary source was used. I also searched for articles in other health databases such as the Cochrane database, but was unable to find articles that fit my research aims.

The initial literature review revealed a sparse amount of published works regarding the use of the Myers' Cocktail or high doses of Intravenous Vitamin C (IVVC). Therefore, the research was expanded to cover other conditions where mega-dose IV vitamin therapy had been reported, to obtain a sufficient evidence to analyze.

The 11 resulting studies that I included in the REA paper are listed in Table 1. These were appraised using the REA toolkit.

Figure 1. Study flow diagram

Findings

A total of 11 papers met the expanded inclusion criteria, for human studies examining the safety and effectiveness of Myers' Cocktail or therapies involving mega-doses of intravenous vitamins for patients with asthma, fibromyalgia, fatigue and cancer. These papers are listed below, in Table 2. The studies are listed in the order of medical conditions being examined.

Types of Studies

There were a variety of studies identified within the search, comprising of four randomized control trials (RCTs), one case study design, one historical design, one exploratory (pilot) design, one quasi experimental design and lastly three pharmacokinetic trials included in this REA. The quality appraisal and analysis for each included study is summarized in Table 2.

Table 2: Quality Appraisal and Analysis for each article included within the REA

#	Author	Type	Condition	Treatment	Age Range	Sample Size	Findings	GSRS (3-9)	Maryland (1-5)	Bias Risk (0-7)
1	Suh et al., 2012	RCT	Chronic Fatigue	IV Vitamin C	20-49	141	No significant difference	Low	3	Medium
2	Ciarallo et al., 1996	RCT	Asthma	IV Mg	6-18	31	No significant difference	Low	4	High
3	Shrader., 2004	Quasi-experiment	Asthma	IVMg/modified Myers' Cocktail	Average 52	43	Might have benefit	Low	2	High
4	Massey., 2007	Pilot clinical trial	Fibromyalgia	Myers' Cocktail	38-65	7	No complete or lasting effect	Low	2	High
5	Ali et al., 2009	RCT	Fibromyalgia	Myers' Cocktail	18-75	31	No statistically significant difference	Medium	4	High
6	Jackson et al., 2002	Historical design for clinical trials	Cancer	IV Vitamin C	Not stated	273	Reported safe and effective – no real clinical data	Low	1	High
7	Padayatty et al., 2006	Case Study	Cancer	IV Vitamin C	49-66	3	Might have an effect under certain circumstances	Low	2	High
8	Stephenson et al., 2013	Pharmacokinetic trial	Cancer	IV Vitamin C	40-72	17	No anti-Cancer effect	Medium	2	Medium
9	Hoffner et al., 2008	Pharmacokinetic trial	Cancer	IV Vitamin C	21-88	24	No Anti-Cancer effect	Medium	2	High
10	Hoffner et al., 2015	Pharmacokinetic trial	Cancer	IV Vitamin C	47-76	14	Neither proves or disproves	Medium	2	Medium
11	Ou et al., 2017	RCT	Cancer	IV Vitamin C	46-72	15	QOL improved when patients receive IVVC and mEHT*	Low	2	High

* mEHT – modulated electro-hyperthermia treatment

Description of the Studies

Participants

Among the eleven studies, there were a total of 599 participants. Of those participants, 225 were men, and 374 were women. All studies were human trials with participant's ages ranging between 6 years old (asthma study) to 88 years old (cancer study). Of the articles found for this REA, one included chronic fatigue patients, two for included asthma patients, two included fibromyalgia patients and six cancer patients.

Types of Intervention

The interventions consisted of receiving an IV Myers' Cocktail, high dose of IVVC, or intravenous magnesium. The majority of the research available on this topic was based upon the use of Linus Pauling's high dose vitamin C therapy. The concentrations, doses and frequency of interventions varied study to study. Doses varied from 0.4g/kg to 19,075g per individual, per administration. Frequency of treatments varied from once a week, to twice a week and from a single dose to long term for three or more months.

Overview of Studies

Suh et al., (2012) evaluated the effect of mega-dose IVVC on fatigue in office workers. This was a randomized, double-blind, controlled clinical trial with the intervention group receiving a single intravenous treatment of 10 grams of IVVC with normal saline. The placebo group received the equivalent volume of normal saline (with no vitamins) intravenously. There were a total of 141 adult volunteers sample within two Korean companies of salespeople. There were 150 individuals assessed for eligibility, and 3 were excluded for not meeting the study inclusion criteria, and two participants were lost from each group, leaving an actual sample of 72 participants for intervention group (31 men and 39 women), and 73 for the placebo group (28 men and 43 women). The participants ranged from 20 to 49 years of age. The study included

both men and women for both the intervention and placebo group. The intervention was given as a single dose one day and measured two hours post intervention and one day after the intervention. Although the fatigue scores at 2 hours post infusion and the next day were significantly different between the two groups, when dividing the participants into subgroups based on pre-intervention plasma vitamin C levels, fatigue was only reduced in the group with the lower baseline vitamin C level group. Measures for this study included a fatigue score using numeric rating scale (0-10), and oxidative stress levels were measured by Free Oxygen Radicals Monitor Plus, which measures plasma vitamin C concentration (Suh et al., 2012). These tools appear to be valid forms of measuring fatigue scores for this study. Authors reported that there were no significant differences among the outcomes assessed at two hours after intervention and one day after the intervention, as there was no difference between the two groups in “usual fatigue” and “worst fatigue” during the 24 hours, however statistical analysis data was not presented (Suh et al., 2012). The researchers concluded that the effect of the intervention was strongest in subjects with lower baseline levels of vitamin C (Suh et al., 2012).

Ciarallo et al., (1996) evaluated the effect of IVMg therapy for moderate to severe asthma exacerbations in pediatric patients. This was a randomized, double-blind, placebo-controlled, clinical trial where the trial group received a magnesium sulfate infusion of 25mg/kg and the placebo group received an equivalent saline solution for 20 minutes. The intervention was performed a single time on one day and measured forced expiratory volume at 1 second, and physical examination for 110 minutes and the serum magnesium concentrations measured before and after the 20-minute infusion (Ciarallo et al., 1996). The study consisted of 31 participants aged 6-18 years old. The placebo group consisted of seven males and nine females; the intervention group consisted of seven males and eight females. Selection method for participants

was not disclosed explicitly or the number of participants that may have withdrawn. The participant's vital signs, blood oxygen saturation by pulse oximetry, peak expiratory flow rate, forced vital capacity, forced expiratory volume, and physical examination was measured before and after the 20 minute infusion. These tools appear to be valid forms of measurement for this study. The researchers reported that there was greater improvement in short term pulmonary function without any significant alterations in vital signs; however, no significant differences occurred between the groups with respect to respiratory rates of oxygen saturation levels at any point in the study (Ciarallo et al., 1996). The therapy group had significant improvement at 50 minutes and even greater at 110 minutes (Ciarallo et al., 1996). Overall, IVMg was reported to be safe and effective, however, outcomes were better when used in conjunction with b2-agonist and corticosteroid therapy (Ciarallo et al., 1996).

Shrader (2004) investigated the use of a modified Myers' Cocktail, with magnesium, vitamin C, trace minerals, manganese and zinc in the treatment of both acute and chronic asthma. This was a pre-test/post-test, non-blinding, outcome study. A convenience sample was used for this study as participants were recruited from the researcher's private clinic. The researchers did not disclose how many participants withdrew from the study, however, researchers excluded six participants who did not show any sign of results in the trial infusion, creating a selection bias and reporting results in their favor (Shrader, 2004). The actual sample for this study consisted of 43 adults (16 males and 27 females). Average age for participants was 52 years old. All patients were evaluated pre and post IV treatment with spirometry. Other measures used for this study were Total forced vital capacity, forced expiratory flow in 1 second, peak expiratory flow, forced expiratory flow through 25-75% of exhalation, and forced expiratory flow through 75-85% of exhalation (Shrader, 2004). These tools appear to be valid forms of measurement for this study.

The longer term “trend” group was broken into subgroups of short duration of therapy (1 month or less), which had four participants, three females and one male with an average age of 62 and an average of 3.25 infusions (Shrader, 2004). The other subgroup, long duration of therapy (treatment for up to 19 months) had nine participants, six females and three males, with an average age of 53 years old and therapy for 12.58 months and 9.8 infusions (Shrader, 2004).

Shrader (2004) reported that although there may be a ‘loading’ period, or dose accumulation of the nutrients investigated, the participants did not improve immediately and some even appeared worse immediately after infusion initiation. Researchers stated that over time, the IV vitamin therapy might have considerable benefit (Shrader, 2004). Massey (2007) aimed to evaluate the effectiveness of a modified Myers’ formula of intravenous nutrient therapy on the symptoms of fibromyalgia in therapy resistant patients. This was a pilot trial with only a small cohort of 7 participants wherein the modified Myers’ formula was only given once a week for 8 weeks over 20-30 minutes (Massey, 2007). The seven participants were all females, aged 38 to 65. Outcome measures included baseline and weekly evaluations of pain using a human analog pain scale (0=no pain, 10=severe pain); fatigue using a simple numeric scale (5=high energy/ability to complete all ADLs; 0=low energy/inability to complete ADLs); activities of daily living. The tools used to measure participant responses seem to be appropriate and valid. Although they found positive results for short term improvements in pain, fatigue and activities of daily living (ADL), all participants reported that there was no complete or lasting effect on pain or fatigue (Massey, 2007). The researcher reports that a larger RCT is required to answer further questions in regards to its efficacy.

Ali et al., (2009), also studying the effect of Myers’ Cocktail on fibromyalgia, reported that there was no statistically significant difference between the treatment and placebo groups in

any of the outcome measures for this study. This was a randomized, double-blinded, placebo controlled clinical trial where they assessed the feasibility and safety of the Myers' Cocktail therapy and provide insights about efficacy (Ali et al., 2009). The researchers screened 263 potential participants and only 55 were eligible. In the end, only 31 subjects remained in the study until study completion (30 females and 1 male). Their ages varied from 18-75 years old. The treatment group consisted of 16 participants and the placebo group 18 participants. Treatment group received weekly infusions of the Myers' Cocktail and the placebo group received weekly infusions of Lactated Ringer's solution for 8 weeks). The outcome measures included change in tender point index, Visual Analog Scale to assess global pain, validated measure of physical function (Fibromyalgia Impact Questionnaire), mood (Beck depression Index), QOL (Health status Questionnaire 2.0) at baseline, in the end at 8 weeks, and again 4 weeks later (12 weeks). Overall, the researchers report that since both the treatment and placebo group showed strong symptomatic relief after eight weeks of treatment, the efficacy of IV nutrient therapy relative to Ringer's lactate remains uncertain (Ali et al., 2009).

Jackson et al., (2002) reported a 16 year history with the use of high dose IVVC treatment for various types of cancer. They collected data from 153 patients with a cancer diagnosis, which consisted of 66 males and 87 females. Cancer types included breast, prostate, lung, pancreas, colon myeloma, liver, bone, brain and others. Among the 153 patients, they received 3,239 IVVC injections. The lowest dose was 15 grams compared to 19, 075 grams for the highest total dose given to one patient. The authors also looked at other diseases such as fatigue, upper respiratory infection/influenza, arthritis, virus infection and more (Jackson et al., 2002). This data was collected from 120 patients, consisting of 32 males and 88 females. The lowest dose for these diseases was 15 grams and highest dose given was 11,947 grams. Their

data then consisted of 275 patients with no serious side effect noted over a 16-year period. There are a number of limitations for this study as there is no mention of patient recruitment, age, severity of illness, frequency and length of treatment, the tools used to measure outcomes and whether the study was an RCT or not, blinding or not. Overall, over their 16 year history, IVVC is 'safe and effective' for many diseases as there were no signs of serious side effects (Jackson et al., 2002).

Padayatty et al., (2006) examined 3 well-documented cases of advanced cancers, where patients had unexpectedly long survival times after receiving high dose IVVC therapy. Clinical details of each case were examined based on the National Cancer Institute Best Case Series Guidelines. The 3 patients consisted of a 51-year-old female, a 49-year-old male and a 66-year-old-female. These 3 patients only received IVVC therapy as their only significant cancer therapy. The 51-year-old female had a tumor involving her left kidney and received 65g of high-dose IVVC twice per week for 10 months, however she used other alternative therapies as well such as thymus protein extract, niacinamide and more (Padayatty et al., 2006). The 49-year-old male had a bladder tumor and received 30g of IVVC twice per week for 3 months, followed by 30g once every 1-2 months for 4 years, however he also received frequent infusions randomly throughout (Padayatty et al., 2006). The last case was that of a 66-year-old female with a large left paraspinal mass medial to the iliopsoas muscle (Padayatty et al., 2006). She received a 5-week course of local radiation therapy and 15g of IVVC twice per week for about 2 months, and then 15g once or twice per week for about 7 months followed by 15g once every 2-3 months for about a year. Outcome measures included chest radiography, transthoracic biopsy, barium studies and a computerized axial tomography scan. The 3 cases were selected by the researchers, however no information on the type of original study was stated. Padayatty et al., (2006) reported

that none of the 3 cases provided definitive information to confirm that it was IVVC therapy that was responsible for the patients' favorable clinical course, therefore suggesting that further clinical studies are warranted.

Stephenson et al., (2013) carried out a non-comparative, single-center, phase I clinical trial to evaluate the safety, tolerability, and pharmacokinetics of high-dose intravenous ascorbic acid in patients with advanced solid tumors. Five cohorts of 3 patients received IVVC therapy administered at 1g/min for 4 consecutive days a week for 4 weeks. The first cohort received 30g/m², subsequent cohorts was increased by 20g/m² until maximum tolerated dose was noted. The five cohorts' received either 30, 50, 70, 90 or 110g/m². Participant selection and recruitment methods were not stated in the study, however there were initially 17 participants, and one dropped out for unknown reasons leaving a total of 16 participants, ranging between 40-72 years old (6 males, 11 females). The outcome measures included physical exam, height, weight, vital signs, urine and blood analysis, baseline EKG and the European Organization for the Research and Treatment of Cancer Quality of Life questionnaire, which were completed at baseline prior to treatment and then weekly. Blood tests were taken before, mid and at the end of the infusion. Overall, they reported that IVVC was generally well tolerated by the 16 participants, but no patient experienced an objective tumor response. An objective tumor response would be evident when a decrease in tumor size is used to evaluate the effect of a therapy (Rimm, Ahlstrom & Bross, 1967). However, three patients had stable disease and 13 had their condition progress (Stephenson et al., 2013). Hoffner et al., (2008) carried out a dose finding and pharmacokinetic study of IVVC in patients with advanced malignancies. This was a "single-center, phase I dose escalating trial of IVVC with primary objective to determine phase II dose" (p. 1970). Patients were assigned to sequential cohorts and infused with 0.4, 0.6, 0.9 and 1.5grams of ascorbic

acid/kg body weight for 3 times a week for 10-30 weeks total. Researchers did not state how participants were recruited nor if any withdrew. There was a total of 24 participants, aged between 21-88 years old. There were 16 males and 8 females. Their aim was to document the “safety and clinical consequences of IVVC in a dose sufficient to sustain plasma ascorbic acid concentrations $> 10\text{mmol/l}$ for several hours in line with the emerging concepts regarding its potential in vivo anticancer activity” (p. 1969). Outcome measures consisted of a physical exam, blood test, CT for staging cancer, toxic effects, detect any preliminary antitumor effects, monitor for preservation of or improvement in quality of life using Functional Assessment of Cancer Therapy (FACT-G) and determine the effects of different IV doses on plasma ascorbic acid. Overall, although IVVC was tolerated well, no patient had an objective tumor response, and all of the patients eventually experienced progression of their disease. There was also no change in social, emotional or functional aspect of QOL in any cohort.

Hoffner et al., (2015) carried out a “phase I-II safety, tolerability, pharmacokinetic and efficacy trial of IVVC combined with chemotherapy in patients whose treating oncologist judged that standard-of-care or off-label chemotherapy offered less than a 33% likelihood of a meaningful response” (p.13). Researchers used a convenience sample as the study was carried out among patients attending a large medical school, which was affiliated with a cancer center attached to a clinic research unit specialized in early-phase clinical trials of novel cancer therapies (Hoffner et al., 2015). Researchers had a target enrolment of 24 patients due to limitations of time and funding, however only 14 patients between the ages of 47-73 were recruited. There were 7 males, and 7 females. The duration of the intervention varied patient to patient between 11 and 580 days, from 6 infusions to 173 infusions. The outcome measures included pre/post chemotherapy vitamin C and oxalic acid pharmacokinetic profiles, physical

exam, blood work, CT scan, FACT-G QOL questionnaire, Total mood disturbance Score of the profile of Mood states-B Questionnaire at baseline, 2 weeks and 1 month after. Hoffner et al., (2015) reported that their study neither proves nor disproves the value of IVVC in cancer therapy. They stated IVVC is generally well tolerated and safe, however there was no anticancer effects when IVVC therapy was used as the sole treatment.

Ou et al., (2017) carried out a pharmacokinetic clinical trial to evaluate the safety, pharmacokinetics and efficacy of ascorbic acid infusion and modulated electro-hyperthermia (mEHT) in patients with stage III-IV non-small cell lung cancer (NSCLC). The treatment regime of mEHT was 60 minutes per session, and all dosages of IVVC were infused in 120 minutes. The 15 participants were randomized allocated into 3 groups, consisting of seven males, and eight females between the ages of 46-72. The researchers had initially recruited 35 patients, however only 15 patients with stage III-IV satisfied the inclusion and exclusion criteria. First group received IVVC when mEHT was finished; the second group received IVCC simultaneously with mEHT; and the third group received IVVC first, followed with the mEHT 3 times a week (Monday, Wednesday and Friday) for 4 weeks. The groups received doses 1.0, 1.2, 1.5g/kg vitamin C infusions. The outcome measures used for this study was blood work and the European Organization for the Research and Treatments of Cancer Quality of Life questionnaire. Overall, the average scores for the functioning scaled continuously increased, and the average values for the symptoms gradually decreased, therefore the QOL was improved when patients received IVVC and mEHT, however, there was no mention of the effect this therapy had on the lung tumours of participants.

Study Quality of Evidence

The eleven papers included in this REA were appraised for quality by using the REA toolkit (GSRS, 2009). The quality appraisal tools included the GSRS Weight of Evidence Scoring, Maryland Level of Quality Assessment Criteria and the Cochrane Collaboration Risk of Bias Assessment.

The highest quality of evidence was reflected in the study by Ali et al., (2009), regarding fibromyalgia and the Myers' Cocktail scoring medium for GSRS Weight of Evidence, however, high in RoB (Refer to Table 1 and 2 for a summary). The three cancer studies of higher quality were by Stephenson et al., (2013); Hoffner et al., (2008) and Hoffner et al., (2015). However, many of the RCTs were poorly designed and reported, noting the small sample sizes, lack of blinding, convenience sampling, and minimal exclusion criteria. The majority of the RCT's only had between 14-31 participants, with the exception of the fatigue study, where there were 141 participants. Of the 11 studies, 7 scored low for GSRS Weight of Evidence, and 4 scored medium. Low GSRS scored studies included RCT studies, a case study, a historical design and a quasi-experimental design. The medium scored studies were all RCT studies.

Risk of Bias

Of the 11 studies that were assessed, none demonstrated a low risk of bias (see Table 3 for summary and Appendix D for RoB assessment criteria). There were three studies assessed as having a medium level risk of bias, which were RCT's and the better reported studies (see Table 1 for a summary). Overall, the risk of bias was generally high for the studies analyzed. Some of the factors contributing to a medium to high risk of bias assessment included, small sample sizes and limited mixed-gender studies. Participant selection was mainly convenience sampling, recruitment methods not being provided and self-reported fatigue, skewing findings in favors of

positive results, poorly controlled confounding factors (e.g. participants taking other supplements or medications) and inadequate blinding.

Table 3: Quality Appraisal details

#	Author	Condition	GSRS (3-9)	Maryland (1-5)	Risk of Bias (0-7)
1	Suh et al., 2012	Chronic Fatigue	Low – self-reported fatigue with questionable tool; poor research design	3	Medium – only office workers; not generalizable; no recruitment methods stated
2	Ciarallo et al., 1996	Asthma	Low – small sample size	4	High – in favor of patients already admitted in emergency; conclusion overstated
3	Shrader., 2004	Asthma	Low – small sample size; no blinding; no control; self-selected patients; minimal exclusion of confounding factors	2	High – skewed in favor of positive outcome as 6 patients showed no initial response to the first treatment and were excluded from the study ; no age matched control patients
4	Massey., 2007	Fibromyalgia	Low – small sample; poor methods; not blinded or controlled; diagnostic validity for inclusion vague; minimal exclusion/control confounding factors	2	High – small sample size; self-selected participants from researchers private clinic; participants taking additional supplements
5	Ali et al., 2009	Fibromyalgia	Medium – small sample size; single blinding	4	High – mainly middle aged Caucasian women
6	Jackson et al., 2002	Cancer	Low – no real clinical details provided	1	High – no clinical details provided
7	Padayatty et al., 2006	Cancer	Low – small sample; missing information	2	High- results not generalizable
8	Stephenson et al., 2013	Cancer	Medium – small sample	2	Medium – additional therapies included; patient withdrawal therefore fewer data from patients in one of the groups
9	Hoffner et al., 2008	Cancer	Medium – small sample; no blinding	2	High – discontinued IVVC is the disease progressed – favorable results; participant selection unclear
10	Hoffner et al., 2015	Cancer	Medium – small sample; inability to exclude confounding effects of chemo and different types of cancer	2	Medium – small sample; convenient sample; performance bias
11	Ou et al., 2017	Cancer	Low- Small sample, single blinding	2	High – selection bias; sample is not representative of all late stage NSCLC

Summary

To summarize, there were very few research studies that were identified exploring the use of mega-dose IV nutrient therapies. Combining the 11 studies, there were less than 600 participants, and most studies were not of high quality, with significant risk of bias.

Chapter 5: Discussion

In this REA, the selected studies, which consisted of RCT's, pharmacokinetic trials, case study's and historical designs, demonstrated that the clinical benefit of IVMM therapy for fatigue, asthma, fibromyalgia and cancer was very minimal. The studies do not provide concrete evidence to support the use of IV vitamin therapy in mainstream health care settings such as hospitals or medical clinics. IV vitamin therapy continues to be advertised by CAM providers for many conditions, beyond what was explored for the purpose of this review.

Effects of IV Vitamin Therapy

Fatigue

There was insufficient published literature available to compare and contrast the effects of IV vitamin therapy on patients experiencing just fatigue and not secondary to cancer or other diseases. Suh et al., (2012) reported that IVVC administration reduced fatigue in office workers in a RCT study. They studied the efficacy of IVVC on fatigue in office workers whom were otherwise healthy individuals. This study was completed on adults from a Korean office, therefore limiting generalizability to other settings. Although they had a relatively large sample size of 72 participants for the intervention group and 73 in the placebo group, it is difficult to make assumptions that this therapy could improve fatigue since the study results were based on a single IVVC treatment or a single treatment of saline solution. Suh et al., (2012) also stated that there were significant differences noted among the two groups at the two hour mark and one day after, however the results of the statistical analysis were not provided and there was also no difference noted between the two groups in "usual fatigue" and "worst fatigue." Suh et al., (2012) also used a numeric rating scale for evaluating fatigue, and asked open-ended questions that were subjective to each individual's understanding of fatigue, as everyone can interpret levels of fatigue differently. They failed to include a list of adverse events experienced by the

participants. Overall, this study reiterated that IV Vitamin C was strongest in participants with pre-existing low levels of Vitamin C, but did not benefit participants who had normal vitamin C levels, therefore, only replacing depleted vitamins and excreting excess. Suh et al., (2012) also recommend this therapy to individuals with severe fatigue, such as “cancer patients and patients at risk for vitamin C deficiency” (p. 7).

Asthma

The two studies analyzed for the use of IV therapy and asthma were by Ciarallo, Sauer and Shannon (1996) and Shrader (2004). Ciarallo et al., (1996) carried out a double blind, randomized placebo-controlled trial, whereas Shrader (2004) conducted a quasi-experimental non-blinded outcome study of one group pre-posttest design, with no blinding, no control, and self-selected patients.

Ciarallo et al., (1996) analyzed the use of IVMg therapy for moderate to severe pediatric asthma, while Shrader (2004) reported on the use of IVMg and other IV nutrients for short- and long-term treatment of asthma exacerbations. The purpose for both studies was to determine the efficacy of high dose IVMg and the effect of nutrients on asthma treatment. Both studies measured forced vital capacity, peak expiratory flow rate and forced expiratory volume. Shrader (2004) also measured forced expiratory flow and Ciarallo et al., (1996) also measured Wright Peak Flow, vital signs, a physical examination, and pulse oximetry.

Ciarallo et al., (1996) reported that there was greater improvement in short term pulmonary function without any significant alteration in vital signs. However, there were no significant differences between the groups' respiratory rates or oxygen saturation levels at any point in the study. Overall, both studies concluded that IV therapy may have considerable benefit, however, Ciarallo et al., (1996) stated IV therapy's benefit is greater when used in

conjunction with b2-agonist and corticosteroid therapy. Of note, there was selection bias in the Shrader (2004) study because the participants were recruited from the researcher's clinic, and no volunteer was excluded unless the therapy appeared to fail, skewing the results in favor of a positive outcome.

The differences in these findings could be attributed to different study populations because Ciarallo et al., (1996) studied the effects of IV Mg on pediatric patients, whereas Shrader (2004) studied the effects of IV nutrients on adults. Pediatric patients consisted of 31 patients between the ages of 6 and 18, whereas Shrader (2004) had a sample of 43 patients between the ages of 62 years old in the short term treatment group and 53 years old in the long term treatment group. There were also many limitations noted in the study by Ciarallo et al., (1996) because the reliability of the peak expiratory flow rate measurements can be questionable in children due to the effort dependent nature of the test. Also, the decision to hospitalize was made before entry into the study and although patients were randomly assigned, and treatment was administered in a double blind fashion, the finding that the magnesium group started with a lower forced expiratory volume gave this group room for improvement, potentially magnifying the differences in the rates of improvement. Ciarallo et al., (1996) stated that IV Mg is effective, however, 11/15 participants in the intervention group and 12/16 from the placebo group received methylprednisolone immediately before receiving the vitamin therapy, which is used to treat lung conditions. Therefore, the true efficacy of IV Mg cannot be trusted in this study.

Fibromyalgia

Massey (2007) and Ali et al., (2009), both reported on the use of a modified Myers' Cocktail and its effects on fatigue, pain and ability to complete daily activities of life. Both

studies had varying vitamins and concentrations in their modified cocktails, therefore straight comparison between the studies is difficult.

Risk of bias was high for both studies because there was a small self-selected sample size of 31 participants from the researcher's clinic, single blinding, and mainly middle aged Caucasian women (Ali et al., 2009). Massey (2007) also had a low sample of only 7 participants which were selected from the author's private clinic. In addition, Massey (2007) had poor methods for carrying out this study, lacking blinding and having a control, and the diagnostic validity is vague for inclusion criteria. There was also minimal exclusion and control of confounding factors, and participants were taking additional supplements. Therefore the findings cannot be attributed to just the effects of the Myers' Cocktail.

Massey (2007) analyzed initial and weekly pain and fatigue levels and by the second administration of IVNT, all participants reported a decrease in both pain and fatigue; however, none of the participants achieved a pain free or fatigue-free state. The participants reported an increased energy level 24-48 hours post treatment. In contrast, Ali et al., (2009) noted that the variables in their study did not reach statistical significance because no significant differences were seen in participants assigned to IVMT or Lactated Ringer's solution after 8 weeks of treatment. Therefore, the efficacy of IV therapy for fibromyalgia, relative to placebo is still quite uncertain.

Cancer

Research on the effectiveness of IV vitamin C as an adjunct therapy for cancer has increased in recent years. For this REA, six articles were analyzed that focused on the use of high dose IVVC to treat various types of cancer.

Jackson et al., (2002) undertook a historical design reporting on 16 years of published work, Padayatty et al., (2006) examined 3 well reported case studies, Stephenson et al., (2013), Hoffner et al., (2008) and Hoffner et al., (2015) all undertook pharmacokinetic trials, and Ou et al., (2017) conducted a randomized control trial. The demographics of participants in these studies is comparable among Padayatty et al., (2006), Stephenson et al., (2013), Hoffner et al., (2015) and Ou et al., (2017) as the participants range from 40-72 year old adults. However, Hoffner et al., (2008) study had a wide range in participants from 21 years old to 88 year old. All studies included men and women with similar numbers in the treatment and placebo groups. Treatments ranged from 15g-65g of IVVC and the duration of the studies varied from a single dose, to two-three doses a week for up to four years.

The risk of bias within all six studies ranged from medium to high. Although each study reported that IVVC as an adjunct therapy for cancer is safe, and generally well tolerated, there were no objective anticancer responses noted. All studies except for Jackson et al., (2002) had a small sample size ranging from 3-24 participants, whereas Jackson et al., (2002) had 153 participants for cancer, and 120 participants for other diseases. Although Jackson et al., (2002) had a larger sample size due to its historical design on reporting on 16 years of IVVC use, they failed to report any adverse events, and no real data was presented either, such as demographics, health of individuals, settings etc., having a high risk of bias. Padayatty et al., (2006) and Ou et al., (2017) had high RoB due to low sample sizes and selection bias, while Hoffner et al., (2008) had a high RoB because they discontinued the IVVC therapy for individuals whose cancer was progressing, therefore reporting favorable results only. Stephenson et al., (2013) and Hoffner et al., (2015) had medium risk of bias due to having a small sample, using additional therapies

along with IVVC and the inability to exclude confounding effects of chemo and different types of cancer.

Padayatty et al., (2006) reported that all 3 of the cases they analyzed effectively reduced the progression of malignant tumors and improved the health status of these patients, however the plasma vitamin C concentrations were not provided, and thus, the relationship between the route of administration, the concentration of IVVC and the effect cannot be grounds for advocating IVVC for cancer treatment (Ohno et al., 2009). All 3 patients were also taking other medications and receiving radiation, therefore the effect of IVVC cannot be proven. Stephenson et al., (2013), Hoffner et al., (2008) and Hoffner et al., (2015) all reported that although IVVC was safe and generally well tolerated, the studies neither prove nor disproves IVVCs value in cancer treatment, as no patients exhibited an objective tumor response. Ou et al., (2017) reported that QOL was improved when IVVC and modulated electro-hyperthermia treatment was given simultaneously, however, no significant differences between the groups was observed for QOL changes. Therefore, the benefit of IVVC remains uncertain.

Overall, among the six studies that analyzed the effect of high dose IVVC on cancer, IVVC was found to be safe and generally well tolerated. Yet, no anti-cancer effect was noted, and the risk of bias for each study is too high to render the results acceptable to proceed with recommending IVVC as a conventional therapy for cancer.

Adverse Events and Outcomes

The side effects varied among the different studies analyzed, with some overlap noted. Suh et al., (2012) reported itching and pain at the IV sit, dry mouth and diarrhea. Ciarallo et al., (1996) reported a relaxed sensation and Shrader (2004) reported side effects of increased respiratory distress, admission to hospital required, exacerbated asthma symptoms after infusion,

feeling light headed, nausea and fainting. Ali et al., (2009) reported dyspepsia, insomnia, depression and a rise in blood pressure. Massey (2007) reported no side effects.

The side effects reported within the cancer studies consisted of: hyponatremia, abdominal distention, constipation (Padayatty et al., 2006); hypercalcemia, transient hypertension (Stephenson et al., 2013); nausea and headache (Stephenson et al., 2013; Hoffner et al., 2008; Ou et al., 2017; Hoffner et al., 2015); moderate to severe hypernatremia and hypokalemia, insomnia, abnormal urine color, loss of appetite (Stephenson et al., 2013); fatigue (Stephenson et al., 2013; Hoffner et al., 2008; Ou et al., 2017), chills (Stephenson et al., 2013; Hoffner et al., 2015), hyperglycemia (Stephenson et al., 2013), abdominal cramps (Hoffner et al., 2008), diarrhea (Hoffner et al., 2008; Ou et al., 2017)), vomiting (Hoffner et al., 2008; Ou et al., 2017; Hoffner et al., 2015), dizziness (Hoffner et al., 2008; Hoffner et al., 2015), facial flushing (Hoffner et al., 2008; Ou et al., 2017), perspiration and general weakness (Hoffner et al., 2008); thirsty (Hoffner et al., 2015; Ou et al., 2017); increased urine, fluttering sensation in upper abdomen, and increased leg edema (Hoffner et al., 2015).

Although these risks may not seem severe to some, they most definitely outweigh the potential benefit of a few hours or a day of a minimally diminished pain, fatigue or difficulty breathing. One must also consider the fact that IV vitamin therapy is not administered in hospital settings, so should there be a severe reaction, these clinics may not be properly equipped to respond to an emergency situation.

Studies also reported that they excluded patients with renal failure, kidney stones presently or a history of, and those with a deficiency of G6PD, an enzyme that could cause cell destruction. Upon analyzing published studies, there is also no mention of the effect IV vitamin

therapy could have on pregnant women and children. Only the asthma studies explored the effects of IVVC on children, which was minimal.

Professional Implications for administering IV Vitamins

Professionals who administer IV vitamin therapy must be aware of all the potential side effects that could occur to their clients. They must be knowledgeable about possible drug interactions if the client is taking medications, and if so, what effect IV vitamins would have on their condition. They must also be cognizant of signs and symptoms of a potential overdose as this therapy uses higher concentrations of vitamins than the daily recommended amounts. One of the main precautions these clinics must practice, is being prepared for a severe reaction and having available the necessary medications and equipment required to take action immediately.

The influence of Media on the Use of IV Vitamin Therapy

The rise in IV therapy in recent years is likely the result of businesses and celebrities promoting and endorsing the use of this adjunct therapy for daily recreational use. Celebrities such as Madonna, Rihanna, Gweneth Paltrow, Simon Cowell and others, promote the use of IV vitamin therapy as a weekend boost, for jet lag, hangovers, flu, exercise fatigue, general exhaustion and much more by sharing on their media outlets such as Instagram, Snapchat and Facebook (Saner, 2012). As the rise in popularity continues for the use of IV vitamin therapy for multiple purposes, the number of clinics offering this therapy is on the rise, with even mobile and home-visit options wherein medical personnel administer the ‘boost’ therapy to the patient in their home. In the Vancouver lower mainland alone, there are more than a dozen clinics that offer this adjunct therapy for a variety of reasons, however when contacted, no naturopath was willing to share any information on its use and why they think it is effective.

Applicability of Evidence

At present, the majority of the studies use small sample sizes, and few published studies carried out RCTs with a treatment and placebo group to effectively evaluate the effect that was seen in some of the studies. Although the results may have been positive, the sample sizes were far too small to make generalizations and overall the results unimpressive. The asthma studies looked at IVMg and asthma exacerbations but there were no control groups with which to compare results. Participants in both of the fibromyalgia studies did not experience any significant improvement and these studies was missing a control group with which to compare effects as well. The cancer studies analyzed also came short in proving its efficacy in treating or prolonging cancer progression and focused on the low risk side effects. Therefore, there is insufficient evidence to conclude that IV Vitamin therapy is beneficial for all individuals and to support the continued use in clinics.

Summary of Main Findings

Overall, the results from this REA suggests that IVVC, IVMg and the Myers's Cocktail may have some benefit for a short period of time, however the effects of IV therapy are not long term and require maintenance. If an individual cannot keep fluids down and has a severe case of vomiting and diarrhea that depletes their vitamins and minerals, only then would IV Vitamin therapy be beneficial in restoring the body's' reserve. However, even replacement therapy should be done correctly with eating proper, nutritious meals and keeping hydrated. The studies indicated that further research in this area is required, and furthermore, more RCT's are required in order for this therapy to be considered by mainstream physicians. In addition, the studies also indicate that no firm conclusion can be drawn due to the bias within the articles, and the very small sample sizes noted within each study.

IV vitamin therapy is effective at replenishing depleted vitamins and minerals quickly because it bypasses the digestive system, however, our bodies are designed to get our vitamins and minerals through our gastro-intestinal tract, through nutritious meals. Given the evidence to date, it would seem only those with digestive problems should be considered for this therapy. However, the use of this therapy is on the rise, there is more interest noted in the media for advertising not only to adults, but also to children as well.

Limitations

A REA in itself has many limitations and an increased risk for bias as described by the REA Toolkit (GSRS, 2006). This REA was completed by me, from searching for studies, the screening process, selection, appraisal and reporting. There was no peer review conducted allowing for personal bias (Gough, 2007; GSRS, 2006). The literature search was limited to four databases, limited to studies only published in English and human subjects, and only available online. Although attempts were made to find more current literature, this topic does not have much published material and local naturopathic clinics were unwilling to provide any information for their basis of advocating for this therapy.

Due to the variations of the I.V. vitamins therapy, and the multiple conditions used to explore this topic, there is limited information available to evaluate. The effects of the Myers' Cocktail, IV Mg, IVVC and other variations of the Myers cocktail are questionable. Not only is there a lack of reporting from the physicians that promote this therapy, but also a flaw in study designs to come to a conclusion whether IV vitamin therapy is in fact beneficial for cancer patients, asthmatic patients, patients struggling with fatigue and fibromyalgia. Majority of the studies also had small sample sizes and convenience sampling.

Chapter 6: Conclusion

The intended purpose for this paper was to evaluate the literature available in analyzing the rise of IV vitamin therapy and its effects. This paper met the purpose of examining the effects of efficacy of the Myers' Cocktail, IV Mg, and IVVC therapy for multiple conditions and answered the following research questions:

1. What is the scientific evidence that intravenous mega dose multivitamin therapy is an effective treatment for fibromyalgia, chronic fatigue, cancer and asthma?
2. What is the quality of the published research in the last 30 years on the value of intravenous mega dose multivitamin therapy as an effective therapy for individuals with fibromyalgia, cancer, asthma and chronic fatigue?

As noted within the paper, the scientific evidence that IVMM therapy is an effective treatment for fibromyalgia, chronic fatigue, cancer and asthma is limited due to the lack of RCT studies and not enough data being published by complementary therapy advocates. All studies emphasized the minimal adverse events that are noted during treatment, which may be underreported or unreported. There is also little to no concrete evidence that high doses of intravenous vitamins can alleviate fibromyalgia symptoms for long term, or cure asthma, cancer or fatigue. In the studies analyzed, it is evident that intravenous vitamins do minimize fatigue, asthma symptoms, and pain associated with fibromyalgia and cancer, however the effects are not long term and it appears that whatever positive effect IV vitamins have on patients, is due to their low plasma levels of that certain vitamin. Any excess vitamins are excreted and within 24-48 hours, and the patient is back to square one.

The quality of the published research available on this topic is quite low, as demonstrated within this paper. The weight of evidence scores for majority of the studies is low, as only four

studies scored a medium (three cancer studies, and one fibromyalgia study), and none scored high. The risk of bias is high for all but three studies (chronic fatigue and two cancer studies).

In conclusion, although there may not be any clinical downside to receiving IVMM therapy (apart from the risks associated with intravenous access), there is also no real good evidence supporting the use of IVMM therapy for medical conditions. This REA shows that the Myers' Cocktail, IVMg, and IVVC appear essentially free of any major risk and side effects when simple precautions are taken (Hoffner et al., 2008). The evidence of therapeutic benefits for those who receive IVMM therapy is only reported in a few studies and also longer term health benefit, other than a few hours of rehydration have been questioned (Gavura, 2013). IVMM therapy may be useful to replace dietary sources, but there is some question as to its value, as only those who have gastrointestinal illnesses appear to truly benefit due to malabsorption issues (Gavura, 2013).

Implications of findings for Practice and Research

The use of IV vitamins is on the rise and seemingly becoming readily available to the public. However, there remains a lack of information available to justify its use, especially when it comes to using IV vitamin therapy as a sole treatment for life threatening diseases. Overall, as the use of this adjunct therapy rises, substantial research will be required for it to be accepted by mainstream health care professionals, included nurses and physicians. Currently, there is no good evidence for patients to delay traditional treatment methods for IV vitamin therapy. It is evident from the literature reviewed in this paper that further research is required to understand this adjunct therapy with an evidence-based approach. This complementary therapy continues to be ignored by conventional cancer investigators, yet is widely prescribed by complementary cancer therapists with no real clinical data being shared with the general public of its benefits and side-

effects aside from statements that there are no real risks of IVVC, IVMg and the Myers's Cocktail (Hoffner et al., 2015). In order for it to be considered by mainstream health care professionals, studies with greater rigor, including randomization, blinding, larger sample sizes, lower risk of bias, repeat studies and increased generalizability must be reported. By performing more extensive studies including RCTs researchers would be able to more effectively demonstrate whether IVMM therapy is in fact, beneficial for the conditions it is currently being prescribed for.

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Appendix A: United Kingdom Civil Service Weight of Evidence Scale

Weight of Evidence A	Generic on quality of execution of study	High = 3 Medium = 2 Low = 1
Weight of Evidence B	Review specific on appropriateness of method	High = 3 Medium = 2 Low = 1
Weight of Evidence C	Review specific on focus/approach of study to review question	High = 3 Medium = 2 Low = 1
Weight of Evidence D	Extent that study contributes evidence to answering a review question	High = 7-9 Medium = 4-6 Low = 3

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Appendix B: Maryland Scale of Scientific Methods

Level 1	Observed correlation between an intervention and outcomes at a single point in time. A study that only measured the impact of the service using a questionnaire at the end of the intervention would fall into this level.
Level 2	Temporal sequence between the intervention and the outcome clearly observed; or the presence of a comparison group that cannot be demonstrated to be comparable. A study that measured the outcomes of people who used a service before it was set up and after it finished would fit into this level.
Level 3	A comparison between two or more comparable units of analysis, one with and one without the intervention. A matched-area design using two locations in the UK would fit into this category if the individuals in the research and the areas themselves were comparable.
Level 4	Comparison between multiple units with and without the intervention, controlling for other factors or using comparison units that evidence only minor differences. A method such as propensity score matching, that used statistical techniques to ensure that the programme and comparison groups were similar would fall into this category.
Level 5	Random assignment and analysis of comparable units to intervention and control groups. A well conducted Randomised Controlled Trial fits into this category.

High: 4-5

Medium: 2-3

Low: 1

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Appendix C: Cochrane Risk of Bias Assessment Tool

Domain	Support for judgement	Review authors' judgement
Selection Bias		
Random sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.
Performance Bias		
Blinding of participants and personnel. Assessments should be made for each main outcome (or class of outcomes).	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.
Detection Bias		
Blinding of outcome assessment. Assessments should be made for each main outcome (or class of outcomes).	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Detection bias due to knowledge of the allocated interventions by outcome assessors.
Attrition Bias		
Incomplete outcome data. Assessments should be made for each main outcome (or class of outcomes).	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Attrition bias due to amount, nature or handling of incomplete outcome data
Reporting Bias		
Selective reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Reporting bias due to selective outcome reporting.
Other Bias		
Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	Bias due to problems not covered elsewhere in the table.

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