CJNM
Canadian Journal
of Naturopathic Medicine

Issue 2 September 2021

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Publisher's Letter

Adapting

The pandemic has caused the majority of Canadians to make many changes in day-to-day life. Such changes aren't always easy, yet they are certainly a requirement. Essentially our resiliency is being tested, and I am impressed every day at the ability of people to adapt.

Some of the challenges? Who ever heard of Zoom? I'm really missing travel across Canada and the USA. Visiting a doctor has changed immensely, and major challenges in keeping business going and growing. Some of the pro's? Spending a lot more time with family, which has been a true blessing. We are learning to cook things we never imagined trying before, and our home has been turned into a cottage in the city.

Adapting requires resiliency, and tools. As our readership adapts to changes in the way their lives and practices operate, we hope CJNM can serve as one such tool. We hope each issue provides you with something (or several things) that you are able to bring into your daily lives and improve patient outcomes.

Thank you to all the Authors who contributed to this issue, as well as to the individuals who participated as Referees. Your efforts make this important project possible.

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Editor's Letter

Sauce Season!

September has always held a special place in the Rouchotas household, as we scramble to preserve our hard work over the summer for the winter. Kids have made the process so much more enjoyable, and interesting. A delivery arrived at the house in the middle of a batch, the driver saw myself and two young children covered in red and likely thought something far more nefarious was going on! Seems popularity of canning has exploded, which I suppose is one very positive thing to emerge from current happenings.

The issue begins with an Invited Commentary from Bob Bernhardt, the current President of the Canadian College of Naturopathic Medicine (CCNM). Bob showcases some very interesting changes to the training of ND's and practice itself over his 17 years in the profession.

Rebecca Word delivers a wonderful summary of human evidence in relation to the herb *Melissa officinalis*. I was unaware of how far human evidence has progressed regarding this herb, and was grateful for being brought up-to-speed.

Akbar Khan provides a compelling critique of the use of chemotherapy for advanced colon cancer. This is an area of controversy my wife and I have witnessed play out in our private practice. The article will prove indispensable to anyone working in this area of patient care.

Aoife Earls introduces naturopathic doctors (ND's) to an area that we all likely require an update. The article eloquently defines various types of grief, provides amazing insight into quantifiable physiological consequences of grief, and educates the reader in identifying grief and settings where an ND should consider referral to individuals with a specialty in grief counselling.

Polina Mak showcases evidence linking hypothyroidism with small intestinal bacterial overgrowth (SIBO). The evidence is compelling, and the argument is made for fairly aggressive screening of SIBO among patients with hypothyroidism. Evidence of SIBO treatment is also highlighted.

I had the privilege of partnering with several colleagues from BC to deliver an article on injectable hyaluronic acid (HA) for knee osteoarthritis. The team from BC does an excellent job of showcasing appropriate techniques for administration of the medicine. The article also summarizes available human evidence of safety and efficacy. One goal of the article is to try to create a tool to be used by ND's and associations in jurisdictions that allow injections yet do not include HA on their approved list to pursue addition of new, safe and effective treatments.

Rochelle Fernandes delivers an update of evidence in relation to omega-3 supplementation for attention deficit disorder (ADD). It is remarkable to see how rapidly this important area of research evolves.

The CJNM team wishes everyone a happy autumn and we look forward to delivering our next issue at the end of 2021!

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Canadian Journal of Naturopathic Medicine

Invited Commentary: A Changing Profession with Changing Challenges

Bob Bernhardt, PhD

Bob Bernhardt, PhD
President and CEO, The Canadian College of Naturopathic Medicine

Invited Commentary: A Changing Profession with Changing Challenges

I have been invited by the Canadian Journal of Naturopathic Medicine to provide a retrospective view of how the naturopathic profession has changed since 2004 when I became president of The Canadian College of Naturopathic Medicine (CCNM), as well as my thoughts as to what the future might hold. I am very pleased to have the opportunity to do so. I will do this through an examination of the changes I am observing with respect to each of the CCNM ends, as defined by the CCNM Board of Governors.

The Board has defined five ends, directing the College with respect to what the Board expects it to achieve:

1. Excellence in Education: Educate NDs on the basis of clear and focused curriculum, delivered by the most competent faculty and graduate high quality NDs.
2. High Quality Clinical Services: Provide high quality naturopathic care in a clinical setting, resulting in positive educational experiences for students and positive outcomes for patients.
3. Excellence in Research: Conduct and disseminate research relevant to naturopathic medicine and help develop skills among faculty, students, and graduates that foster research activity and a culture of evidence-informed clinical practice.
4. Leading Voice: Increase awareness and trust of CCNM as a leading voice for naturopathic medicine.
5. Change Agent: Be a leader and advocate of naturopathic medicine as positive change to our health, our environment and our healthcare system.

Excellence in Education

I have been impressed with the quality of the education at CCNM (both Toronto and Boucher campuses) ever since I joined the College. It is a challenging medical program that draws some of the very best students I have encountered in my over forty years of experience in postsecondary education. I visited CCNM once before joining the College and in that visit I was immediately struck with the positive energy in the building – I knew at once that it was a very special community. As many of you have heard me say, our students are some of the brightest, most socially concerned, environmentally conscious, and *nice* that I have ever dealt with.

However, that is not to suggest the nature of students has not changed over the last 17 years. In 2004, most of the new students entering the program were highly committed to naturopathic medicine as the only choice they wanted to have for their future. Today, students are still committed to naturopathic medicine, but many more have considered it as one of a number of

appealing career choices. In many ways, we have become more mainstream. When we ask our new students to state in one word why they chose CCNM the most frequent word is “help”, followed by “health” and “people”. These are individuals seeking to help keep others healthy, they are seeking the best path to do so.

In the early days, I was frequently impressed by the extreme passion students had for the program. Sometimes this passion may have gotten in the way of graduate success, as we had to convince new graduates that charging patients, and making money, were good things. Today, I think many of our students are better prepared for success upon graduation. This is a result of the practice management training we provide, as well as the more career focused orientation of the students.

One change that has been worrisome is the drop in applications to a number of programs, particularly in the United States. The University of Bridgeport program has been discontinued, and other programs have seen their starting student numbers drop significantly. Although I think there are a variety of factors contributing to this, I am worried that the US programs have become too expensive for many potential applicants, with typical US programs exceeding $35K USD in annual tuition.

The pandemic has had a significant impact on the nature of instruction. CCNM, along with most other postsecondary institutions has moved most didactic instruction to virtual delivery. Although this has not pleased all students, the vast majority want some level of virtual delivery in the future. They appreciate the opportunity to schedule their learning to meet their life needs and appreciate the opportunity to speed-up, slow-down, or repeat portions of the instruction.

What do I predict for the future? The doctor of naturopathic program will become more case-based and clinically-focused. Approximately 40% of the program will be delivered virtually. There will be opportunities for some to schedule their learning such that they can spend greater time in remote locations with somewhat less time in Toronto or Vancouver.

High Quality Clinical Services

Over the years, CCNM has offered an increasing number of focused shifts in its clinics. These shifts cover both population demographics (e.g. pediatrics) and conditions (e.g. cancer, fibromyalgia, mental health). In addition, we offer third year electives in many of these areas. This is important, because similar to master and PhD programs in universities, the expertise that is developed and fostered as a result of focused shifts and electives, informs the overall curriculum in these areas.

CCNM implemented a teaching clinic within a hospital at Brampton Civic Hospital. This served to foster a greater understanding among hospital staff with respect to the opportunities and benefits associated with naturopathic care. Due to the pandemic, this has been moved to an urgent care facility associated with the hospital.

During the early stages of the pandemic, CCNM, similar to many health-care providers, offered clinical services either primarily, or fully, virtually. Today, approximately a third of our visits are delivered virtually. Patients appreciate the convenience of not having to travel to the clinics, if their care needs are such that this can be appropriately accommodated.

My projection for the future is that we will see continued use of virtual care (25-30% of visits), closer integration with other medical providers, and an increased use of focused shifts allowing students to develop higher levels of competence in targeted areas.

Excellence in Research

One of the areas of change in the College in which I am the proudest is the expansion of our research program. Through research leaders such as Dr Edward Mills PhD, Dr Dugald Seely ND and Dr Kieran Cooley ND our research has expanded in both breadth and scope. We now typically have over $10 million in research studies underway. The Canada Post studies have helped drive increased regulation and scope for naturopathic doctors across North America. The leading example of this is the study on reducing the risk of a cardiovascular event through the adjunctive use of naturopathic medicine, published in the Canadian Medical Association Journal (Seely et al 2013). This study, along with the study on chronic back pain, underpinned associated economic studies (Herman et al 2008, Herman et al 2014).

The four Canada Post studies, along with these two economic studies were referenced in an article I wrote for the Benefit and Pensions Monitor on the potential saving for employers if they facilitated greater access to naturopathic medicine for their employees (Bernhardt 2016). I mention this because I believe we will see greater use of CCNM research to drive changes in the acceptance of naturopathic medicine. Many of our graduates are expressing an interest in public health as they look to advance population health. A research paper on vaccine hesitancy was used by CCNM to promote the use of NDs in providing vaccinations in Ontario, as is done in British Columbia.

CCNM is starting to examine ways in which it can use research to assist in the goal of advancing equity, diversity and inclusion, both in the College and for the profession more broadly. Many individuals do not appreciate the challenges faced by BIPOC individuals in our environment, and we believe research can help us establish evidence of the current situation, as well as a base against which improvement can be measured.

As for the future, I see greater acceptance from the profession for the application of research in determining what lacks efficacy as well as what works well. This is an important part of medical research and it must drive the profession’s practices. CCNM will continue its strong leadership in oncology research, within the Patterson Institute for Integrative Oncology Research. And, as identified above, I see greater use of research from naturopathic institutions in driving changes in health care. CCNM is one of ten institutions in a consortium organized by the RAND

Corporation in the US, which has driving changes in public policy as one of its primary objectives.

Leading Voice

CCNM, along with the other leading professional players in naturopathic medicine across North America, has learned when to speak up, and when we should not. Our goal for over a decade has been to serve as the respected voice of expertise in naturopathic medicine. In doing so, it is not helpful to enter into the social media maelstroms that dominate many of today's social debates. CCNM uses its research, and the expertise of its faculty and researchers, to provide respected media outlets with verified information on the issues they are exploring.

As identified above, we are mobilizing our research in support of changes in public policy, government regulations, and employer acceptance of naturopathic care. I suspect this to become more significant in the future.

Change Agent

A primary goal of CCNM has been to drive greater acceptance of naturopathic medicine. The College plans to do that through the application of its research in the manner provided above. Naturopathic medicine has been largely absent in the discussion of public health issues, even though its tenants align so closely with those of public health.

Through the use of virtual delivery, the College will endeavor to make the program more accessible to students across Canada. Strong integration of virtual learning and on-site practicums appears to be effective both from a learning standpoint and from the view of the learner.

CCNM hopes to use its research to forward the goals of equity, diversity, and inclusion within the profession. This will involve an examination of the barriers to entry that Black, Indigenous, and People of Color (BIPOC) experience, as well as the exploration of the range of challenges they encounter upon entering the profession.

The World Ahead

As I write this, in the throes of a pandemic that has lasted far longer than most initially anticipated, the future is signaling that it will be different from the past. With the increased focus on health, and the heightened concern for planetary health, the world has never been more primed for the benefits that naturopathic medicine provides. However, to get there will require the use of research evidence in far more profound ways than in the past – research that drives changes in broader health care at the same time that it causes the profession to question its own assumptions and values. The future is ripe for a dramatic increase in the use of naturopathic approaches, will the profession be positioned to ensure that it is the provider of these services?

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Canadian Journal of Naturopathic Medicine

Melissa officinalis: Review of Published Evidence in Humans

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Acknowledgements
None

Conflicts of Interest
The Author declares no conflicts of interest

Melissa officinalis: Review of Published Evidence in Humans

Abstract

Melissa officinalis (MO) is broadly distributed across the globe, and as a member of the mint family can grow in seemingly inhospitable conditions. In addition to a rich history as a revered medicinal plant, a large and growing body of human level evidence has emerged evaluating MO for a very broad range of applications. Human evidence has emerged for a role of MO in neurodegeneration, mental health, and cardiovascular health. There is also evidence supporting a role of MO for use in children, dysmenorrhea, and a selection of other indications with limited yet existing human level evidence. The herb is administered in a variety of forms (crude herb, tea, aqueous or ethanolic extracts) as well as in a variety of methods (topical, aromatherapy, oral ingestion). This review will assimilate existing human level evidence of MO in hopes of reacquainting healthcare providers with this important medicine.

Introduction

Melissa officinalis (MO), also known as lemon balm, bee balm, garden balm, Melissa, melissengeist (Rasmussen 2011), has been used for ages across many cultures and with a wide variety of applications. This plant was first seen in print in the famous first century work "De Materia Medica" by the Greek physician Dioscorides. MO is a pleasant, aromatic member of the mint family (*Lamiaceae*) that will literally take over anywhere it finds itself with soil and a bit of sun. Melissa reveals a wide variety of constituents: volatile aromatic compounds, triterpenoids, phenolic acids and flavonoids to name just a few considered to have therapeutic benefit. It is used as infusion, tincture, essential oil, freeze-dried, and as a cooking herb that enhances digestion (Valussi 2012). More recently isolated constituent compounds have received attention for a wide variety of clinical applications. Regarding the literature in humans, crude preparations and specific extractions from MO exhibit numerous pharmacological effects. Anxiolytic, antiviral, antispasmodic, and anti-arrhythmic activities as well as benefit on mood, cognition, and memory have been shown in clinical trials (Shakeri et al 2016). There is a plethora of studies on MO evaluating in vitro and animal models, yet the focus of this review will be to examine what the literature has to offer for us humans in detail.

Neurological/Cognitive/Mood

Monoterpenes and sesquiterpenes are proposed to provide the main neurological enhancement on memory and mood. Relevant effects including antioxidant activity, activation of the cholinergic system (including cholinesterase inhibition) leading to increased acetylcholine, up regulation of GABA, as well as inhibition of matrix metalloproteinase-2 are the main mechanisms proposed for the widely discussed neurological effects of this incredibly useful and accessible plant (Shakeri et al 2016, Wightman 2017). This is very promising, especially given the startling rise in degenerative neurological diagnoses in recent years and the lack of well-tolerated and effective pharmaceutical intervention. MO and other non-toxic botanicals have long historical use for cognitive longevity. MO extracts have most notably been shown to bind directly to both nicotinic and muscarinic receptors in human brain tissue and exhibit acetylcholinesterase inhibition supporting memory functions. "Given the side effect profile of prescribed cholinesterase inhibitors, and a current lack of a well-tolerated nicotinic receptor agonist, these herbal treatments may well provide effective and well-tolerated treatments for dementia, either alone, in combination, or as an adjunct to conventional treatments" (Kennedy and Scholey 2006). What do the studies reveal?

Twenty healthy, young participants received single doses of 300, 600 and 900mg of MO or a matching placebo at seven-day intervals with assessment at one, 2.5, four and six-hour intervals. Benefits were seen in memory and calmness scores at 600mg. "Alertness" was shown to be reduced at highest dosing (Kennedy et al 2002). Another trial led by the same author again tested 20 healthy, young participants with single doses of 600, 1000, and 1600mg of encapsulated dried leaf, or a matching placebo, at seven-day intervals. Cognitive performance and mood were

assessed pre-dose and at one, three, and six-hours post-administration. Again, calmness and improved memory performance were observed, especially at the highest dose. Results “suggest that doses of MO at or above the maximum employed can improve cognitive performance and mood and may therefore be a valuable adjunct in the treatment of Alzheimer's disease” (Kennedy et al 2003).

A small 2018 two-week pilot study (44 subjects) found that an oral ethanol extraction of *Salvia officinalis*, *Salvia rosmarinus* (formerly *Rosmarinus officinalis*) and MO is more effective than a placebo in supporting verbal episodic memory in healthy subjects under 63 years of age (Perry et al 2018). Another study in healthy young adults confirmed absorption of rosmarinic acid as a marker for acute lemon balm administration and found self-reported enhancement of mood and cognitive performance (Scholey et al 2014).

Another study showed that once daily usage for two weeks of MO essential oil as aromatherapy significantly reduced agitation in elders living in residential care who had not been diagnosed with dementia. Interestingly, *Lavandula* essential oil once daily for two weeks was more effective for those with agitation plus diagnosis of dementia. Placebo treatment of sunflower seed oil yielded no discernible benefit for agitation. Results were quantified using Neuropsychiatric Inventory (NPI) and Cohen-Mansfield Agitation Inventory (CMAI) (Watson et al 2019).

Disappointingly, the detailed methodology of this small trial (49 elders) was not well explained. Were the oils applied topically or inhaled? This is a harmless (and pleasant) intervention that could easily be applied widely in eldercare settings, however, it is worth noting that the price difference between *Melissa* and *Lavandula* essential oils is significant (*Melissa* is expensive when pure and appropriately extracted) (Watson et al 2019).

A 2018 RCT from Iran looked at a combination of *Melissa* and *Boswellia serrata* (BS) for memory support in 70 elder participants. Thirty-five subjects received tablets and 35 received placebo for one month. Using a demographic questionnaire and the Wechsler Memory Scale-Revised (WMS-R), the results showed auditory immediate, immediate memory, visual immediate and working memory were increased after consumption of the BS and MO tablets (Taghizadeh et al 2018).

The following 24-week double blind RCT of 23 participants diagnosed with mild dementia examined safety and tolerability of MO extract containing rosmarinic acid (500mg/d). The intervention was well tolerated. Cognitive effects were assessed via NPI-Q and improved 0.5 in the treatment group, while decreasing 0.7 in the placebo group, showing a small but significant result (Noguchi-Shinohara et al 2020). Another small study (n=11) also investigated safety of the same dosage of MO with rosmarinic acid and found that it did not affect liver, kidney, or blood cell function parameters. No adverse effects were reported (Noguchi-Shinohara 2015).

A separate four-month study of 42 Alzheimer's patients found that MO extract was beneficial for management of mild to moderate Alzheimer’s disease and had a positive effect on agitation (Akhondzadeh et al 2003).

Another aromatherapy RCT looked at MO essential oil for 72 patients in the UK with clinically significant agitation in the context of severe dementia. In this study either the MO oil or sunflower oil was put into a base cream and massaged into the face and arms of participants twice daily. Both groups showed benefit via Cohen-Mansfield Agitation Inventory, 35% in the MO group vs 11% in the placebo group. Quality of life scores also improved in the treatment group (Ballard et al 2002). This study suggests two important areas for further investigation: First the clinical application of MO aromatherapy, and second, the benefit of physical touch in dementia patients.

As a follow up to that thought, another trial utilizing applied MO aromatherapy, placebo or donepezil in elders with diagnosed or probable Alzheimer’s disease found no evidence that MO aromatherapy is superior to placebo or donepezil for agitation. However, there was a large, positive placebo effect, suggesting that non-specific benefits of touch and interaction in the treatment of agitation may be occurring (Burns et al 2011).

Mood

A 2020 RCT compared the use of three agents in subjects meeting DSM-5 criteria for Major Depressive Disorder. Forty-five participants were divided into three groups receiving either: 2g/day of *Lavandula angustifolia*, 2g/day of MO, or 20mg/d fluoxetine for eight weeks. Hamilton Rating Scale for Depression was used as the main endpoint measure. The outcome showed that both *Lavandula* and *Melissa* were comparable to fluoxetine for mild to moderate depression (Araj-Khodaei et al 2020).

Eighty individuals diagnosed with stable angina were randomized to receive 3g/day of MO versus placebo for eight weeks. The MO group was judged to have improvements in anxiety, depression and insomnia associated with their diagnosis. Measurements were taken before and after the eight-week study using the shortened 21-item version of the depression, anxiety, and stress scale (DASS-21) and Pittsburgh Sleep Quality Index (PSQI) (Haybar et al 2018).

Twenty volunteers participated in a 15-day study using a patented MO extract called Cyracos, standardized to consist of more than 7% rosmarinic acid and greater than 15% hydroxycinnamic acid derivatives. The study showed 18% improvement in anxiety manifestation, 15% improvement in anxiety-associated symptoms, and 42% improvement in insomnia (Cases et al 2011).

A very cursory study investigating MO benefit in stress found 600mg versus 300mg or placebo effectively improved mood assessed using the Defined Intensity Stressor Simulation (DISS)

battery. MO at 600mg per day also increased self-ratings of calmness yet reduced self-ratings of alertness (Kennedy et al 2004).

Sleep

Multiple human studies have investigated the use of MO for sleep, either solo or in combination with a variety of other natural substances. A Polish open-label study gave 40 participants Novanuit® Triple Action (a combo of classic soporifics melatonin, vitamin B6, *Eschscholzia* extract, *Passiflora incarnata* extract, and MO extract) capsules daily for two weeks noting reported benefit in sleep onset latency, total sleep duration, and sleep-related daytime parameters (Lemoine et al 2019). Another RCT investigated a combination of MO and *Valeriana officinalis* (VO) in 100 peri-menopausal or menopausal women ages 50-60 with diagnosed sleep disturbance. Significant improvement was seen in the treatment group using the PSQI (Taavoni et al 2013).

One interesting preliminary study looked at homeopathic preparations of MO, *Phytolacca decandra* (PD), MO + PD, or placebo for the treatment of sleep bruxism (SB) in 52 children (6.62 ± 1.79 years old). Visual Analogue Scale (VAS) was used as the primary outcome measure with the additional measurements of subjective parental/guardian sleep diary and the trait of anxiety scale (TAS). MO and MO + PD both showed improvement on SB via VAS scores. Other markers were not influenced. There were no adverse effects observed in any of the four groups (Tavares-Silva et al 2019).

Stress

MO has been used historically for stress and anxiety management both as a simple and in combination (Sarris et al 2013). One RCT using men only to evaluate a multi-herb product called Ze-185 (containing VO, MO, *Passiflora incarnata*, and *Petasites hybridus*) found the product significantly reduced the subjective emotional stress response during an acute stressor. This was measured via salivary cortisol and self-report (Meier et al 2018). The same preparation, Ze-185, was assessed via a retrospective case-control study in 3,252 psychiatric in-house patients analyzed over a 3.5-year period. Findings revealed that significantly fewer benzodiazepine prescriptions were required in the treatment group over the course of the study (Keck et al 2020).

Another trial combined MO and VO in twenty-four healthy volunteers comparing three doses (600mg, 1200mg, 1800mg) of the combo, or a placebo, on separate days with seven-day interval between dosing with assessment at one, three and six-hours post on treatment days. The 600mg dose showed reduced anxiety scores via DISS battery, but at 1800mg the anxiety scores seemed to mildly increase (Kennedy et al 2006).

A lozenge comprised of MO, *Lavandula* essential oil, and extracts from *Humulus lupulus* and *Aveena sativa* or matching placebo was given to sixteen healthy volunteers. Those receiving the lozenge exhibited increases in alpha-1 (associated with relaxation), alpha-2 (associated with

working memory) and beta-1 (associated with anxiolytic intervention) electrical activity via electrode measurement (Dimpfel et al 2004).

Cardiovascular/Metabolic

There exists historical and empirical literature for the usage of MO for a variety of cardiovascular conditions including congestive heart failure, hypertension, angina pectoris, atherosclerosis, cerebral insufficiency, venous insufficiency, and arrhythmia. There is also a decent amount of animal data regarding MO for cardio-protective benefits. One 2021 study claims that the only symptomatology confirmed for human clinical use of MO is heart palpitations (Draginic et al 2021), however, the studies detailed below suggest more possible markers for cardiovascular and metabolic application.

A RCT examining MO for palpitation was conducted using 500mg twice a day of lyophilized aqueous extract of MO leaves for 14 days. Mean frequency of episodes and somatic symptomology were significantly decreased (Alijaniha et al 2015).

A 12-week RCT by Asadi et al (2019) (62 participants) utilized 700mg twice daily of MO extract capsules and found the intervention safe and beneficial on lipid profile, glycemic control, and reduction of inflammation. Measures used in the study were fasting blood glucose, HbA1c, hs-CRP, TG, HDL-C, and systolic blood pressure. However, total cholesterol, LDL-C, insulin, and HOMA-IR showed no significant changes between the groups.

A 2019 RCT was conducted in 37 patients with a diagnosis of type II Diabetes Mellitus (DMII) utilizing a 500mg capsule twice daily of MO for three months and showed that MO decreases TG levels in dyslipidemic diabetic patients. Beneficial results were greatest in those with TG>200mg/dl pre-trial. The same study showed significant decreases in both systolic (SBP) and diastolic blood pressure (DBP) in those with greatest measures at the beginning of the trial (SBP>130/DBP>85) (Nayebi et al 2019).

Another study used 1000mg MO or placebo in 58 hyperlipidemic patients and evaluated pre/post study with measures of fasting blood glucose, HDL, LDL, TG, Creatinine, AST and ALT. MO significantly reduced levels of LDL and AST (Jandaghi et al 2016).

A follow-up study regarding MO use in DMII recruited seventy diagnosed diabetic patients aged 20-65. Participants were randomly assigned to receive a hydro-alcoholic extract of MO at 700mg/day or placebo twice-daily for 12 weeks. Multiple markers were gathered; improvement of Apo A-I, Apo B/Apo A-I, and lipid ratios were reported (Asadi et al 2018).

Eighty patients diagnosed with coronary artery disease and chronic stable angina were randomized to receive 3g MO/day or placebo for eight weeks. Among individuals with stable angina, MO improved lipid levels, malondialdehyde, hs-CRP, and paraxonase-1 (Javid et al 2018).

A less-than-glowing 2020 systematic review and meta-analysis of RCTs utilizing MO for cardiovascular concerns found that MO was not associated with statistically significant changes in triglycerides, low-density lipoprotein, diastolic blood pressure, high sensitivity c-reactive protein levels, fasting blood sugar, HbA1c, insulin or high-density lipoprotein levels. While there were no serious adverse events reported, the study opined that bias was high in a considerable number of studies. The study did acknowledge safety and beneficial effects on TC and SBP, and concluded that higher-quality trials are needed (Heshmati et al 2020). One consideration in weighing this conclusion is that most of the RCTs reviewed are of relatively short duration; it would be interesting to see what prolonged use of a gentle intervention such as MO might provide given that cardiovascular diseases are certainly chronic in origin.

Menstruation

One double blind RCT recruited ninety students (ages 18-26) experiencing symptoms of moderate to severe dysmenorrhea (evaluated via McGill system). Participants were randomized to receive either 330mg MO or placebo capsules containing corn starch. Doses were given to both groups for three days from the beginning of menstruation, three times daily for two cycles. The group taking MO experienced reduced neurological symptoms, fatigue and lethargy. Menstrual headache was not significantly impacted in either group (Mirabi et al 2018).

Childhood Concerns

MO is a frequently used herb in childhood complaints (Gurol et al 2019), which attests to its safety profile. One 28-day infantile colic (IC) study in 176 babies found a combination of *Matricaria chamomilla*, MO and tyndallized *L. acidophilus* (HA122) and *L. reuteri* DSM 17938 is significantly more effective than simethicone in IC (Martinelli et al 2017). Another study of 93 breastfed infants found improvement in colic within seven days of treatment with a combination of *Matricaria, Foeniculum vulgare* and MO (Savino et al 2005).

Nine hundred eighteen children under the age of 12 were given a combination of MO/VO for sleep. Dyssomnia was improved in 80.9% of patients, and restlessness was improved in 70.4% of patients. The intervention was well tolerated (Muller and Klement 2006).

A combination of proprietary extracts of MO/VO was given to 169 primary school-age children assessed with concentration and hyperactivity issues. The children were given a daily dose (640mg VO root extract and 320mg MO extract) and assessed at two and seven weeks by parents and pediatricians via questionnaire. Findings revealed that strong/very strong symptoms of poor ability to focus decreased from 75% to 14%, hyperactivity from 61% to 13%, and impulsiveness from 59% to 22%. There were also improvements in parent rated social behavior, sleep and overall symptom burden. Only two of the 169 children had reported adverse effects (Gromball et al 2014, Ross 2015).

Miscellaneous

One very interesting clinical trial investigated the benefit of MO prepared as tea twice daily (1.5g/100 mL) for 30 days upon the lab measured effects of ionizing radiation in 55 radiology department staff. There were significant improvements in plasma levels of catalase, superoxide dismutase, and glutathione peroxidase and a marked reduction in plasma DNA damage, myeloperoxidase, and lipid peroxidation. These outcomes were interpreted as improvements in oxidative stress and reduced DNA damage among individuals occupationally exposed to radiation (Zeraatpishe et al 2011).

In another study 24 patients diagnosed with chronic non-specific colitis were treated with a combination of *Taraxacum officinale*, *Hypericum perforatum*, MO, *Calendula officinalis* and *Foeniculum vulgare*. Spontaneous and palpable pains along the large intestine disappeared in 95.83 percent of participants by the 15th day of treatment (Chakurski et al 1981).

Viral Considerations

Topical treatments of prepared MO cream have given relief from oral herpes simplex in two double-blinded trials (Gaby 2006, Nelson et al 2020). While there are a lot of studies that show efficacy for inhibition of herpetic viruses *in vitro*, *in vivo* findings also indicate that *M. officinalis L*. extract inhibits HSV-2 replication at non-toxic doses (100mg/mL) (Mahendra and Kateryna 2013) and that topical preparations including MO are beneficial for prodromal/acute HSV1 outbreak (Nelson et al 2020).

Traditional Applications with no Human Data

Though lemon balm is used traditionally as an anti-viral, only the above two studies confirmed this usage. Only one review alluded to the common usage of MO in influenza and not specifically (Sargin 2021). No literature could be found for use of MO as a febrifuge, though this too is a classic application in historical herbal medicine (alone or in combo). What about contraindication with sluggish thyroid? Many of us (NDs/herbalists) learned that MO is contraindicated for use in a person with diagnosed hypothyroidism. Are there any data to back this up? No research data could be found in PubMed regarding MO contraindication in hypothyroidism though this is well established for use in mild hyperthyroidism historically (usually in combination with *Lycopus virginicus* and *Leonorus cardiaca*).

Areas of Promise for Future Research

Of course, we would all like to see more exploration of all of the above applications. As of now, there are numerous cell-line studies of MO extract inhibition of various human cancer cell lines (colon cancer cells, glioblastoma multiforme cells, etc); this will be an area to watch. Another positive retinal cell line study shows promise for macular degeneration. Likewise, cell studies of MO (and other *Lamiaciae* plants) for anti-viral (HSV, HIV) and anti-bacterial application are promising for further human study (Allahverdiyev et al 2004, Mikus et al 2000, Schnitzler and

Reichling 2011, Yamasaki et al 1998). Exciting things are possible, especially given MO is such an inexpensive, sustainable, and accessible medicinal plant.

MO is easy to grow, has a wide array of beneficial applications in humans (both proven and empirical), and is safe for babies, elders, and everyone in between. It tastes good. In an age when Alzheimer's, neurodegenerative conditions, cardiovascular disease, and all chronic inflammatory conditions are on the rise this plant could easily be incorporated in a variety of ways from the home kitchen. More technical extractions of *Melissa officinalis* also show promise. The essential oils smell clean and bright and are soothing. We could likely all benefit from having this lovely garden herb in our lives.

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Canadian Journal of Naturopathic Medicine

Critical Appraisal of Approved Chemotherapy Regimens for Advanced Colon Cancer in Ontario, Canada

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Acknowledgements
None

Conflicts of Interest
The Author declares no conflicts of interest

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Abstract

Evidence-based medicine (EBM) is a term often used to describe allopathic medical therapies. Best evidence for a therapy was felt to be obtained by randomized clinical trials which remain the “gold standard” today. Many well-established chemotherapy regimens for metastatic colon cancer claim to be evidence-based, and are government approved and funded in Ontario, Canada. Conversely, natural therapies, off-label non-toxic therapies, and metabolic therapies for cancer remain unproven due to lack of large-scale clinical trials. Many such therapies are backed by lower levels of evidence that suggests they prolong life or enhance quality of life, yet they are not considered evidence-based by the oncology community. A careful analysis of the actual evidence underlying approved regimens for metastatic colorectal cancer raises important questions about the application of EBM in reference to cytotoxic chemotherapy.

Introduction

Evidence based medicine (EBM) is a term often used to describe allopathic medical therapies. This term originated from the work of Sackett and Guyatt and was first described in the medical literature in the Journal of the American Medical Association in 1992 (Evidence-Based Medicine Working Group 1992). Sackett clarified EBM succinctly as "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients." (Sackett 1996). Best evidence for a therapy was felt to be obtained by randomized clinical trials (RCT). The RCT remains the "gold standard" to define whether a therapy has clinical benefit that outweighs the harm.

EBM is of critical importance in cancer, as most available allopathic therapies are associated with significant toxicity. It is especially vital to know if maximum tolerated dose cytotoxic chemotherapy is beneficial for patients because death, disability, and reduced quality of life are known side effects of this form of therapy.

In Ontario, Canada, drug regimens are recommended for government funding and approved by the arms-length organization Cancer Care Ontario (CCO). As of this writing, for primary treatment of stage four colorectal cancer, frontline or recurrent, there are 19 approved government-funded chemotherapy-based regimens (Cancer Care Ontario 2021).

1. CAPE (capecitabine)
2. CAPE + BEVA (capecitabine + bevacizumab)
3. FLOX (fluorouracil + leucovorin + oxaliplatin)
4. FOLFIRI (fluorouracil + leucovorin + irinotecan)
5. FOLFIRI + BEVA (fluorouracil + leucovorin + irinotecan + bevacizumab)
6. FOLFIRI + PNTM (fluorouracil + leucovorin + irinotecan + panitumumab)
7. FOLFOXIRI (fluorouracil + leucovorin + oxaliplatin + irinotecan)
8. FU (fluorouracil bolus)
9. FU-CIV (fluorouracil continuous iv)
10. FU (IV-CIV) LCVR (fluorouracil + leucovorin, modified DeGramont regimen)
11. FULCV (DEGRAMONT) (fluorouracil + leucovorin, DeGramont regimen)
12. FULCVR(W) (fluorouracil weekly + leucovorin)
13. FU(W) (fluorouracil weekly)
14. IRIN (irinotecan)
15. IRIN+CETU (irinotecan + cetuximab)
16. IROX (irinotecan + oxaliplatin)
17. MFOLFOX6 (fluorouracil + leucovorin + oxaliplatin)
18. MFOLFOX6+BEVA (fluorouracil + leucovorin + oxaliplatin + bevacizumab)
19. XELOX (capecitabine + oxaliplatin)

Adjuvant post-operative regimens were not explored for the purpose of this review. For all the frontline regimens for stage four colon cancer, the CCO monographs state:

"Evidence Informed: Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to

alternatives…recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial."

This statement implies that a systematic analysis of the approved regimens would confirm that they are in fact superior to so-called "alternative" therapies and superior to best supportive care (i.e. no active therapy) based on available clinical evidence. In this situation it would be justifiable for the regimens to receive government-funding and for oncologists to regularly prescribe them despite their substantial risks, with informed patient consent.

All referenced evidence is the best evidence available according to the CCO monograph for the chemotherapy regimen under review. An independent search for further evidence was not carried out. Non-chemo regimens were not reviewed and combination regimens with non-chemo targeted drugs were not reviewed for the purpose of this analysis.

Capecitabine

There are three phase III trials supporting capecitabine, one with 605 patients (Hoff et all 2001), one with 602 patients (Van Cutsem et al 2001), and one with 1987 patients (Twelves et al 2005). All trials compare capecitabine against fluorouracil. Therefore, none of the trials referred to in the CCO regimen monograph establish whether capecitabine improves survival or quality of life.

FLOX - Fluorouracil + Leucovorin + Oxaliplatin

There is a single phase II trial supporting this regimen which enrolled 52 patients (Kato et al 2011). It was a single arm trial (no comparison arm) which looked at response rates and toxicity. Therefore, no conclusion could be drawn whether FLOX improves survival or quality of life.

FOLFIRI - Fluorouracil + Leucovorin + Irinotecan (+/- Bevacizumab)

Several clinical trials supporting this regimen were published. A phase three trial with 387 patients containing a chemo-to-chemo comparison (Douillard et al. 2000), a phase three trial with 813 patients containing a chemo-to-chemo + bevacizumab comparison (Hurwitz et al 2004), a phase three trial with 220 patients containing a chemo-to-chemo comparison (Tournigand et al 2004), and a phase three trial with 1914 patients containing a chemo-to-chemo comparison (Van Cutsem et al 2009). Therefore, none of the trials referred to in the CCO regimen monograph establish whether this regimen improves survival or quality of life.

FOLFOXIRI - Fluorouracil + Leucovorin + Oxaliplatin + Irinotecan

There is a single phase III trial supporting this regimen which enrolled 244 patients. The trial compared the full regimen against the same regimen without oxaliplatin (Falcone et al 2007).

There was no placebo arm. Therefore, no conclusion could be drawn whether this regimen improves overall survival or quality of life.

Fluorouracil

Several clinical trials supporting different variations of this regimen were published. A clinical trial of 86 patients in which continuous infusions were compared to bolus doses (Rougier et al 1992), a clinical trial of 184 patients in which continuous infusions were compared to bolus doses (Weinerman et al 1992), a clinical trial of 125 patients in which two dosage schedules of fluorouracil were compared (Budd et al 1987), a clinical trial of 122 patients in which continuous infusion of fluorouracil was compared against fluorouracil + cisplatin (Kemeny, N et al 1990), a randomized trial of 2135 patients in three treatment arms with a control group that received fluorouracil followed by irinotecan (Seymour et al 2007), a phase III trial of 420 patients in which fluorouracil/leucovorin +/- oxaliplatin were compared and quality of life was measured (deGramont et al 2000), a randomized phase III trial of 448 patients comparing two different schedules of fluorouracil combined with leucovorin (deGramont et al 1997), a randomized trial of 372 patients with two arms of different protocols of fluorouracil and leucovorin (Buroker et al 1994), a randomized trial of 291 patients examining fluorouracil + high dose vs. fluorouracil + low dose leucovorin (Jäger et al 1996) and a randomized trial of 148 patients comparing fluorouracil alone against fluorouracil combined with leucovorin (Nobile et al 1992).

Fluorouracil is one of the oldest chemotherapy drugs approved for treatment of colorectal cancer and is the drug against which many newer drugs are compared. Despite multiple available trials, no conclusion could be drawn whether this regimen improves overall survival or quality of life.

Irinotecan

Several clinical trials of irinotecan were published. Of all the trials, a single trial compared irinotecan chemo against best supportive care (i.e. no active treatment). In this randomized trial of 279 patients who had failed prior fluorouracil, one-year overall survival was evaluated and found to be improved in the chemo arm (36.2%) compared to the supportive care arm (13.8%). The difference was statistically significant. Quality of life was assessed and also favoured the irinotecan arm (Cunningham et al 1998).

IROX - Irinotecan + Oxaliplatin

A clinical trial of 383 patients examined the response rates and survival of patients treated with IROX compared against FOLFOX (Ashley et al 2007). A phase III randomized clinical trial of 628 patients comparing IROX against irinotecan alone found a 2.3 month survival benefit favouring IROX (Haller et al 2008). Since irinotecan alone has been demonstrated to improve survival compared against no treatment, there is a suggestion that IROX may improve overall survival. However, such a comparison is not scientifically rigorous since patients in different trials conducted in different time periods may have separate characteristics (age, race,

comorbidities, performance status, drug resistance etc). Therefore, no definite conclusion can be drawn about whether this regimen improves overall survival or quality of life.

mFOLFOX6 - Fluorouracil + Leucovorin + Oxaliplatin followed by Fluorouracil infusion

A phase II trial of 56 patients was conducted with a single chemo arm only (Braun et al. 2003). A phase III trial of 2034 patients was conducted in which FOLFOX was compared against XELOX with no placebo group (Cassidy et al 2011). A randomized trial of 223 patients was conducted in which the patients were divided into three different chemo arms (Hochster et al 2008). A phase II single arm study of 70 patients was conducted of chemo alone (Ryan et al 2003). This regimen is one of the most commonly prescribed regimens for advanced colon cancer. Yet no conclusion can be drawn whether this regimen improves overall survival or quality of life.

XELOX (capecitabine + oxaliplatin)

A phase III trial of 2034 patients was conducted in which FOLFOX was compared against XELOX (Cassidy et al. 2008). A clinical trial of 96 patients was conducted with XELOX alone (Cassidy et al 2004). A randomized phase III trial of 627 patients was conducted in which XELOX was compared to FOLFOX4 (Rothenberg et al 2008). Since there was no placebo arm in any of these trials, no conclusion could be drawn whether the XELOX regimen improves survival or quality of life.

Natural and Metabolic Therapies for Colon Cancer

The author has previously published a case report documenting long-term disease stabilization of stage four colon cancer (liver metastases) using the metabolic therapy dichloroacetate (Khan et al 2016). Dichloroacetate (DCA) induces apoptosis in cancer cells and can act as a cytostatic agent. As of this writing, the patient remains alive and well over 8 years after conventional chemotherapy was stopped. Since life-threatening side effects of DCA have never been documented (Stacpoole et al 1998) in stark contrast to cytotoxic chemotherapy drugs, and since it is inconsistent with the natural history of stage for four colon cancer to spontaneously stabilize for years, it is very plausible that DCA prolonged the survival of this colon cancer patient.

High dose ascorbic acid (vitamin C) has been researched for decades and is supported by extensive pre-clinical data as an effective cancer therapy or adjuvant therapy (Ohno et al 2009). High dose intravenous vitamin C is also associated with tumour regression in advanced cases of colon cancer (El Halabi et al 2018). Survival benefit was also demonstrated in pancreatic cancer in a phase I trial when vitamin C was used as an adjuvant to gemcitabine chemo. Roughly double the survival was observed with added vitamin C compared to gemcitabine alone (Polireddy et al 2017). High dose ascorbic acid does not have life threatening side effects in contrast with

chemotherapy. Therefore, it is plausible that ascorbic acid can prolong survival in colon cancer patients.

Low dose naltrexone (LDN) is an unapproved therapy that induces an increase in endogenous levels of methionine-enkephalin, an opioid with demonstrated in vitro anti-cancer effects in colon cancer (Hytrek et al 1996). Schwartz et al (2014) published a case series demonstrating clinical efficacy of LDN combined with natural agents alpha lipoic acid and hydroxycitrate in various cancers including colon. One of the colon cancer patients in the series was reported to be alive and well four years after the diagnosis of widely metastatic disease (Schwartz et al 2014). Therefore, it is plausible that LDN can prolong survival in colon cancer patients.

Despite the limited but convincing evidence cited in these case reports of unapproved non-toxic therapies, they are all considered unproven by the oncology community and do not fall within the definition of evidence-based medicine.

Discussion

Of all the clinical trials of approved colon cancer drug regimens that were reviewed, only one clinical trial conducted in 1998 (single agent irinotecan) established an overall survival benefit compared to placebo/best supportive care. It may be argued that once a chemotherapy drug has been found to improve overall survival, it would only be ethical to design subsequent trials to compare newer drugs against this proven drug. In other words, using placebo would deny patients access to a drug with a known survival benefit. To determining whether this was in fact the justification for other chemo drugs not being compared against placebo, one may simply assess the dates of the trials. Examining the dates of the multiple 5-FU trials, for example, reveals that they were *all* conducted *before* the irinotecan trial in question (before it was known that irinotecan improved overall survival). Even so, none of these trials were conducted against placebo. This suggests the above-mentioned ethical dilemma was not the reason these trials were designed without placebo.

Despite limitation of lack of comparison to placebo/best supportive care for all the drug regimens discussed (aside from irinotecan), all are labelled as evidence-based or “evidence-informed”. Specifically, they are all labelled as demonstrating meaningfully improved outcomes including survival and quality of life. The author finds such an overtly contradictory statement deeply troubling. Lessons learned from the opioid crisis, and recent announcements of massive settlements to be paid by pharmaceutical companies to help repair the damage of industry overzealousness (CTV News 2021, USA Today 2021), should serve as an important reminder to sternly question who’s interests are served when suspect standards of care emerge.

Who sits on the expert panels that make the recommendations for chemo approval and government funding?

Is there any motivation to make questionable statements?

Are there undisclosed conflicts of interest among the expert panels?

Are oncologists generally aware that the chemo regimens they prescribe are largely unproven by the standard of demonstrating overall survival benefit?

Are patients unknowingly led to believe that these regimens are likely to help them survive longer?

Are patients truly giving informed consent when they agree to taking these powerful chemotherapy drugs?

Based on this review, a fresh analysis of all the chemo regimens for advanced colon cancer is urgently needed. Such an analysis must be conducted with full disclosure of any conflicts of interest of the expert panels, such as direct or indirect ties to the pharmaceutical industry or industry funding. Experts with conflicts of interest must not be permitted to advise government which drugs to fund or approve. This is of vital importance to enhance patient awareness of the expected outcomes of any proposed chemotherapy regimen. Only then will patients be able to provide truly informed consent in the selection of their chemotherapy regimens.

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Canadian Journal of Naturopathic Medicine

Grief and Sickness Behaviour in Naturopathic Practice: Standards of Care for Screening and Support

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Acknowledgements
None

Conflicts of Interest
The Author declares no conflicts of interest

Grief and Sickness Behaviour in Naturopathic Practice: Standards of Care for Screening and Support

Abstract

Lifestyle counselling is a part of practice scope for naturopathic doctors, however, the identification of grief management is not well reviewed or identified for screening in practice. Acute grief has many physical attributes that are similar to sickness behaviour, and when identified properly, can be supported as part of a general health care plan and are within naturopathic care strengths, including herbal medicine and lifestyle resources such as forest bathing, journaling, and creativity. In addition, complicated grief or prolonged grief disorder should be identified and referred to appropriate care as many individuals benefit from complicated grief therapy, and will also have numerous health concerns that will not improve when not getting adequate support. Standards of care for different aspects of grief therapy in therapeutic practice are reviewed, with a unique supportive role for care and referral in naturopathic outpatient settings.

Grief and Sickness Behaviour in Naturopathic Practice: Standards of Care for Screening and Support

Naturopathic doctors are trained to use lifestyle counselling in practice, which includes encouragement of healthy behaviour, listening, and providing therapeutic presence, supporting manageable change, and referring mental health support with licensed therapists as identified. While the mind-body connection is understood, the recent pandemic has highlighted the true relationship between physical conditions such as IBS, hypothyroidism, menopausal appearance or aggravation, and insomnia. The impact of stress through loss of societal norms, including loss of income, support network, life, and identity are now clear in their impact on the physical body.

Sickness behaviour and its relationship to the body's ability to process loss and grief are not always fully understood, being that time in which the body can be affected by emotional loss can be longer than is understood by a person struggling and their health professionals. Sickness behaviour is a state of being in which inflammation in the brain triggers a series of metabolic and behavioural adjustments in order for an organism to address an infection; the hypothalamic-pituitary-adrenal axis adjusts to increased temperature (fever) and increased circulation of cytokines IL-1, TNF-alpha, and IL-6 in the body which induce change in macrophages in the brain (Dantzer 2006). Outer behavioural changes include fatigue, social withdrawal, an inability to concentrate, and reduced motivation. In sickness behaviour, supporting infection through natural immune modulators such as chaga (Lu et al 2021), cordyceps (Das et al 2021), astragalus, codonopsis, and increased Vitamin C and zinc (Roxas and Jurenka 2007) are well-documented to improve the body's ability to reduce cytokine activation, decrease IL-1 and IL-6, and improve humoural immunity. Sickness behaviour that does not dissipate after six weeks of a viral or bacterial infection (often due to IL-1) is thought to contribute to mental health disorders such as major depressive disorder and anxiety (Viljoen and Panzer 2005).

Grief is seen primarily as the emotional reaction to the loss of a loved one through death, however bereavement grief is only one of many grief experiences. Ambiguous grief (e.g. a divorce, loss of person through mental illness or dementia, loss of job) (Nathanson and Rogers 2021), anticipatory grief (awaiting a loss such as supporting a loved one through long-term illness) (Coelho et al 2018), and disenfranchised grief (e.g. clinicians for their patients, secondary losses such as the loss of social title, self-identity) (Lathrop 2017) are three of many common grieving experiences, all of which have physical manifestations in the first two years of a loss or separation or beyond (Buckley et al 2012, Iglewicz et al 2020).

Rather than the five concrete stages of grief outlined by Elisabeth Kübler-Ross, grief is more associated with some predictable phases that have a lot of variability within and around them (Buckley et al 2012, Kübler-Ross 1969, Ong et al 2011). In acute stages of grief, similar shifts akin to sickness behaviour are physically seen within the first 12 months after a loss, with the first six months being the most pronounced in terms of increased cortisol, hypertension, decreased activity of NK cells, and increased IL-6 and IL-1 (Buckley et al 2012, Cankaya et al

2009, Holland et al 2014, Latham and Prigerson 2004, O'Connor 2019, Prigerson et al 1997). These changes shift naturally after six months in uncomplicated grief, in which the loss integrates into the person's life as the person learns to process their emotions, and to accept their loss. The addition of meaning from the experience, and creation of new and fulfilling habits or hobbies will then become known as integrated grief. The person may continue to feel sad, but they are no longer thinking as much about the loss and have learned to regulate intense emotion, confront challenging memories, and create new meaning in their lives (Shear 2010). Physically, cortisol and blood pressure are typically entering normal range between six and12 months, and insomnia has also stabilized (Buckley et al 2012, Iglewicz et al 2020). However, this again is not an absolute experience.

For some, acute grief elongates, and individuals develop complicated grief (CG) or prolonged grief disorder (PGD); a prolonged state of grieving in which grieving intensifies beyond six months and can last for many years after a loss (Iglewicz et al 2020, Shear 2010, Shear et al 2011, Shear et al 2007). Vulnerable individuals include those with intense longing or emotional pain, frequent preoccupying thoughts of the deceased person or inability to accept the loss and difficulty imagining a meaningful future without the deceased person (Nakajima 2018, Shear et al 2011). Dysfunctional thoughts, maladaptive behaviours and emotion dysregulation are hallmarks of the condition, yet also include significant physical manifestations of grief including high blood pressure, heart disease, cancer, headaches, insomnia, psychiatric symptoms, poor quality of life and reduced vitality (Ong et al 2011). Elevated cortisol is also a characteristic of CG and can be elevated for two years after a loss in individuals with CG and can influence cortisol indefinitely following a loss, most often seen in late life bereavement and children with parental loss and emotional abandonment (Luecken 1998, O'Connor 2019, Ong et al 2011, Saavedra et al 2017). It is understood that the nucleus accumbens, the region of the brain associated with reward, is what drives ongoing yearning in CG, and that in non-complicated grief the NA does not show activation with time and healing (O'Connor 2019). Screening for CG is done with professionals trained in the skill and with the PG-13 tool (Iglewicz et al 2020, Prigerson and Maciejewski 2021, Shear et al 2011).

Supporting loss and sickness behaviour for naturopathic medicine is a long process, but a worthwhile undertaking. Those with grief and loss most often need a compassionate ear, a willingness to listen, and the creation of trust (Joplin and Vrklevski 2017, Shear 2010, Shear et al 2011). Supporting physical manifestations of the condition, while encouraging new habits and therapy that confronts the loss with positive coping strategies is something that could be revolutionary for long-term physical ailments related to loss (Bower and Irwin 2016).

Treatment within Naturopathic Outpatient Facilities of Acute and Ongoing Grief

Acute grief, as it mimics (and often also has) sickness behaviour, benefits from improved quality and length of sleep, cortisol reduction, and incorporating easy lifestyle shifts that support these changes as there is often intense fatigue and memory lapses (Iglewicz et al 2020, O'Connor 2019). Creating an environment to develop integrative grief should continue to involve these strategies, while encouraging therapy to confront avoidance and introduce new meaning into life.

To support deeper and more effective sleep, a combination of herbal medicine and lifestyle interventions that address cortisol reduction and support anxiety reduction is most helpful. Entrainment of circadian cycles to support melatonin production will suppress cortisol, but it will also prevent immune inflammation that can occur with maligned circadian rhythms (Wright et al 2015).

Baicalin scullcap inhibits IL-1, decreases NF-kB, and enhances GABA (A) receptor activity to sleep-waking cycles (Bone 2003, Chang et al 2011). In animal models, baicalin scullcap has anti-hypertensive action and shows reduced inflammation at the intestinal lumen (Wu et al 2019, Zhao et al 2016). *Skullcap laterifolia* is long known for its nervine properties and to support insomnia and anxiety, as is piper methysticum which is a potent anxiolytic (Brock et al 2014, Sarris et al 2011, Zhao et al 2016). Phosphatidylserine also supports cortisol dampening. Phosphatidylserine complex and phosphatidic acid given to students to support stress resulted in blunting of both serum ACTH and cortisol with 400 mg, and a positive emotional response to the Trial Social Stress Test (TSST) (Hellhammer et al 2004). It has also been seen to blunt cortisol with respect to exercise-induced stress in multiple doses (Monteleone et al 1990, Starks et al 2008).

Motherwort, a herb most often affiliated with female reproductive disorders, is known best for its cardiovascular affinity (hence its Latin name, *Leonurus cardiaca*) (Romm 2010). Being that hypertension is a hallmark of physical grief recovery (and the broken heart phenomenon it is most often associated with), motherwort is an ideal herb to add to a protocol as it relaxes vascular tone, slows tachyarrhythmias, lowers lipids, improves insomnia, improves depression and is used as a nervine (Boyd and Sohl 2020, Fierascu et al 2019, Rauwald et al 2015, Romm 2010, Zou et al 1989). It is also thought to cross the blood-brain barrier to influence cortisol and has multiple antiinflammatory and immunomodulatory properties (Altinterim 2014, Fierascu et al 2019, Reul et al 2014).

It has also been documented that deeper REM sleep is possible when emotions are released before bed. While this may indeed be triggering or initially worsen sleep latency, it will eventually lead to deeper REM, increased length of REM cycles, and generally better mood the following day (Baglioni et al 2010). This can be achieved with journaling about one's emotional state; tracking one's moods and their abilities to change and improve is a key component of CGT

(Nakajima 2018, Shear 2010, Shear et al 2011). Emotional freedom technique, or tapping, can also ameliorate the worries that may be prone to keeping individuals up at night or releasing intense emotion to promote sleep. Individuals with PTSD were given tapping as an approach to release intense emotion and had significant progress releasing obsessive thoughts and repetitive thoughts associated with relapse and recall of traumatic memories (Church et al 2013). It may also be useful to recommend a funny or joyful television program or book as a daily or alternate day practice, as laughing also reduces cortisol and can be used as a tool after a difficult experience (Berk et al 2008). Laughter and a sense of humour are still present in grief, while often grievers may forget this is okay, it should be encouraged.

Forest bathing, or Shirin-Yoku, the act of being in the forest for health and medicinal practices, is now emerging to be a powerful practice for health and well-being, mentally and physically (Hansen et al 2017). Forest bathing involves either walking or sitting for varying lengths (from 10-90 minutes), and indices of immunity, heart rhythm and volume, stress hormones, and depression and anxiety have been studied (Park et al 2010). With respect to cortisol specifically, forest watching and bathing decreases cortisol in comparison to placebo both in anticipation of visiting the forest, and immediately after being in the forest (Antonelli et al 2019), especially in comparison to walking or watching in an urban area (Park et al 2010). Breathing forest air reduces NK cell activity (Li 2010) due to phynocides in forest air. Lymphocytes are also known to be reduced in mental stress, as is experienced with PTSD and grief, and as such could be supported in this very simple practice, on a daily or weekly basis (Buckley et al 2012, Glover et al 2005).

Immunomodulation can be an important target to modify the inflammatory response, notably elevated IL-1 and heightened NK reactions, that are typical in both sickness behaviour and acute grief. Immunomodulation can be achieved using herbs such as chaga (Peng and Shahidi 2020), rehmannia glutinosa (Kim et al 1999) (which is also used to support cortisol), and rosemarinic acid (which has both immunomodulatory and anti-inflammatory properties), thus supporting many diseases of prolonged immune activation (Friedman 2015, Luo et al 2020). Astragalus, with evidence of immune support and a role in acute MI rehabilitation, can also be considered (Zhang et al 2019).

Lifestyle-based recommendations such as encouraging positive community interaction (in-person or virtual) supports reaching out, creating new neural pathways, and new healthy memories (Iglewicz et al 2020). Music used to “express, experience, or understand emotions” in those with depression and low mood improves depressive outcomes and gives the listener a way to channel and release emotions in a productive way. From painting to doodling, art therapy in structure and unstructured formats all show improved positive affect and protection against CG, caregiver burnout and compassion fatigue (Kaimal et al 2019, Xiu et al 2020).

To summarize, there are many interventions that are effective, easy to find and prescribe, and have multiple cross-linking benefits (e.g. antihypertensive, antidepressant, immunomodulating

and cortisol reducing) for support of acute and integrative loss and sickness behaviour within naturopathic practice. Clinicians should use their knowledge of their patients to use other interventions that are evidence-based and beneficial that have not been listed in this paper. As we may meet many people with different losses experienced within the last calendar year and beyond, we need to meet our fellow humans with compassion, humility, and curiosity to support their physical and emotional well-being.

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Canadian Journal of Naturopathic Medicine

The Thyroid - SIBO Connection

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Acknowledgements
None

Conflicts of Interest
The Author declares no conflicts of interest

The Thyroid - SIBO Connection

Abstract

The purpose of this review is to explore the evidence for a causal link between hypothyroidism and Small Intestinal Bacterial Overgrowth (SIBO). Upon reading the paper, the clinician will have a good understanding of when to assess a hypothyroid patient for Small Intestinal Bacterial Overgrowth (SIBO) and the hypothesized pathophysiology behind this link.

Introduction

Hypothyroidism, prevalent in women, the elderly, and certain ethnic groups, is the result of inadequate production of thyroid hormone or the inadequate action of thyroid hormone in target tissues. Primary hypothyroidism is the principal manifestation of hypothyroidism, but other causes include central deficiency of thyrotropin-releasing hormone (TRH) or thyroid-stimulating hormone (TSH), or consumptive hypothyroidism from excessive inactivation of thyroid hormone. Hypothyroidism is defined as either clinical (elevation in the TSH and low levels of FT4) or subclinical (primary hypothyroidism with levels of FT_4 are normal with an elevated serum TSH) in nature (Almandoz and Gharib 2012). The wide array of symptoms of hypothyroidism indicates an effect on metabolism and dysfunction in multiple organ systems. Treatment in most cases involves oral administration of exogenous synthetic thyroid hormone.

When a patient presents with hypothyroid symptoms, clinicians may not consider the significant risk for Small Intestinal Bacterial Overgrowth (SIBO) as a consequence of reduced intestinal motility and constipation. However, this is an important underlying pathology to investigate especially if other abdominal symptoms are present such as bloating and abdominal pain, even if mild. The clinical manifestations of SIBO depend upon the severity of disease. While one would assume that the greater the quantity of bacteria, the greater the symptom, this has not been well studied (Sachdev and Pimentel 2013). SIBO can be asymptomatic yet present itself in other conditions outside the gut such as hypothyroidism and autoimmunity (Gasbarrini et al 2007, Patil 2014, Pimentel et al 2002). Today, SIBO is perceived as a condition underlying a wide range of intestinal and even extraintestinal diseases (Quigley et al 2020). Indeed, the pathogenesis of SIBO is still not completely understood.

The most up to date definition of SIBO is an increase in the number of bacteria in the upper gastrointestinal tract, specifically a jejunal aspirate culture exceeding 10^3 CFU/mL (Takakura and Pimentel 2020). Normally, fewer than 10^3 organisms/mL are found in the upper small intestine and they consist of Gram-positive bacteria (Dukowicz et al 2007). In a clinical setting, an alternative method for SIBO diagnosis is used; namely a breath test after the ingestion of either 75g of glucose or 10g of lactulose substrate. Hydrogen (H2) and Methane (CH4) gases are measured thereafter, which are produced as a result of microbial metabolism. The North American consensus defines a rise in H2 gas ≥ 20ppm from baseline within 90 minutes of substrate ingestion or a CH4 gas level ≥ 10ppm at any time to be diagnostic for SIBO (Takakura and Pimentel 2020). A third type of gas, hydrogen sulfide (H_2S), has recently been explored as another marker of bacterial overgrowth in novel breath testing (the trio-Smart breath test) but needs further investigation. This type of SIBO is sometimes deduced clinically.

SIBO is associated with a variety of symptoms including bloating, abdominal pain, flatulence, abdominal cramping, nausea, constipation, and diarrhea. The type of microbial flora present will play an important role in the manifestation of signs and symptoms of SIBO. Many pathogenic microorganisms can contribute to intestinal overgrowth, including *E. coli*, *Enterococcus*,

Klebsiella, and *Methanobrevibacter smithii* (Chojnacki et al 2021). Gram-negative coliforms release toxins called Lipopolysaccharides (LPS), such as *Klebsiella* species, that damage the intestinal villi and mucosa, creating an inflammation cascade and interfering with the absorptive function of the gut, in turn increasing one's risk for gut dysbiosis and autoimmunity. This presentation may sometimes be confused for and mimic tropical sprue.

It has been recently proposed that, as *M. smithii* can overgrow in areas of the gut outside of the small intestine and is not technically characterised as a bacterium, the term intestinal methanogen overgrowth (IMO) is a more appropriate term in cases of methane-positive breath testing (Takakura and Pimentel 2020). Although measurement of CH4 is not always included, the North American consensus and the recent SIBO guidelines both recommend that CH4 be measured concurrently with H2 during breath testing.

The signs and symptoms of SIBO can also arise from the malabsorption of nutrients, alteration in intestinal permeability, inflammation, and/or immune activation that arises from the pathologic bacterial fermentation within the small bowel. A positive H2 breath test has been associated with diarrhea-dominant IBS (IBS-D) and IBS with mixed bowel habits (IBS-M). A predominance of bacteria that metabolize bile salts to unconjugated or insoluble compounds may lead to fat malabsorption or bile acid diarrhea. A positive CH4 breath test is indicative of methanogen overgrowth, which has been associated with constipation-dominant IBS (IBS-C). Microorganisms that preferentially metabolize carbohydrates to short-chain fatty acids and gas may produce bloating without diarrhea because the metabolic products can be absorbed. SIBO could be one of the possible causes of irritable bowel syndrome (IBS) and is more common in females (Chojnacki et al 2021), just like hypothyroidism (Dunn and Turner 2016). The prevalence of SIBO in IBS varies from 30 to 85% depending on the source used (Pimentel et al 2000). High recurrence rates after successful antibiotic treatment emphasise the need to identify aetiological factors (Lauritano et al 2014). It is still unclear if SIBO is a cause, a consequence, or just a phenomenon in relation to the other GI tract disorders (Quigley et al 2020).

The SIBO - Hypothyroid Connection

It has been shown that intestinal dysmotility is one of the risk factors for the development of SIBO (Bohm et al 2013). Gastrointestinal system disorders are often ignored in hypothyroidism because of other systemic symptoms of cardiovascular, neuromuscular, and ocular disorders with thyroid dysfunctions. However, there are reports of disorders of motility and transport functions in the digestive system resulting from hypothyroidism (Yaylali et al 2009). A reduction in the motor activity of the stomach, small intestine, and colon has been reported as well as delayed intestinal transit time in hypothyroid patients. The most probable pathological reason is the intestinal edema due to mucopolysaccharide accumulation in gastrointestinal tissue (Yaylali et al 2009). As a result, changes in the motor activity of the digestive system may result in gastric distension and constipation in hypothyroidism.

Yaylali et al (2009) indeed showed that hypothyroidism significantly decreased gastroesophageal motility in their study of 30 female patients with primary hypothyroidism. Patients with primary hypothyroidism, without any systemic disorder, were followed for two to four months and were all suffering from minor dyspeptic problems; however, none of them suffered from severe gastrointestinal system complaints such as nausea, vomiting, abdominal pain, or constipation. They were examined via gastroesophageal endoscopy. The goal of the research was to determine if there was atrophic gastritis and/or other probable gastric pathologies affecting esophagogastric motor parameters.

Motility disturbances in the form of significantly higher mean esophageal transit time and gastric emptying time were seen in patients with hypothyroidism compared with the control group, showing that motility disturbances in hypothyroidism can lead to gastrointestinal dysfunction overall (Yaylali et al 2009).

Comparing the esophagogastric scintigraphic parameters in the patients with those of healthy cases, Yaylali et al (2009) found a significant reduction in both gastric and esophageal motor functions. These results were similar to previous published studies showing that hypothyroidism affects gastrointestinal system motility (Brechmann et al 2017, Patil 2014, Wang et al 2021). Esophageal transit time and gastric emptying half-time values were found to be significantly higher, while the esophageal emptying value was significantly lower in hypothyroid patients. Therefore, hypothyroid patients show significant reduction in gastric emptying, potentially predisposing them to SIBO as bacteria would have more time to ferment carbohydrates from the diet in one's stomach/small intestine.

Furthermore, it was proposed that thyroid autoantibodies arising from autoimmune thyroid diseases may lead to atrophic gastritis and mucosal atrophy of the fundus can occur without symptoms. Frequently, there is autoimmune pathogenesis, and it may even develop into pernicious anemia and gastric malignancy in the following years. In the case of hypothyroidism, mucinous material (mucopolysaccharide/hyaluronic acid) may accumulate in gastrointestinal system mucosa, which may lead to dysmotility – more likely in chronic cases (Yaylali et al 2009).

A subset of patients with SIBO show reduced motility with fewer phase III contractions of the migrating motor complexes (Pimentel et al 2002). Brechmann et al (2017) studied 1809 patients who underwent H2 breath testing. It was found that impairment of the gastric acid barrier, impairment of intestinal clearance, immunological factors (drug-induced immunosuppression), altered thyroid gland metabolism (hypothyroidism/levothyroxine therapy) and diabetes mellitus were associated with SIBO. Further analysis revealed that gastric surgery, stenoses, medical immunosuppression, and levothyroxine were the strongest predictors of SIBO, with levothyroxine therapy being the strongest contributor. Therefore, it appears that patients with hypothyroidism and substitution of levothyroxine show a higher risk of SIBO.

A case control study by Lauritano et al (2008) has already revealed a high prevalence of SIBO in patients with autoimmune thyroiditis and hypothyroidism. Multivariate analysis confirmed that levothyroxine therapy is a stronger predictor of SIBO than hypothyroidism. The underlying mechanism is unclear. One might speculate that hypothyroidism leads to hypomotility, but, surprisingly, levothyroxine therapy is even more powerfully correlated with SIBO than hypothyroidism, and does not reverse the hypomotility effects of hypothyroidism.

It has been reported that SIBO may be present in more than half of patients with hypothyroidism (Almandoz and Gharib 2012). One study (Lauritano et al 2007) looked at 50 patients with a history of overt hypothyroidism due to autoimmune thyroiditis. Diagnosis of bacterial overgrowth was based on a positive hydrogen glucose breath test. Bacterial overgrowth positive patients were treated with 1,200mg rifaximin/day for one week. A glucose breath test, gastrointestinal symptoms, and thyroid hormone plasma levels were reassessed one month after treatment. A total of 27 patients with a history of hypothyroidism demonstrated a positive result to the breath test (54%), compared with only two individuals in the control group (5%). The difference was statistically significant. Moreover, abdominal discomfort, flatulence, and bloating were significantly more prevalent in the bacterial overgrowth positive group, so this needs to be paid careful attention to as well when assessing a patient's risk.

Conclusion

In summary, hypothyroid patients with abdominal discomfort, flatulence or bloating should be assessed for SIBO. Based on the research reviewed in this paper, a history of hypothyroidism is indeed associated with the development of bacterial overgrowth in the small intestine. Breath testing is useful to diagnose SIBO before antibiotic treatment. The cause of SIBO is varied, and this may need to be determined in order to prevent the common recurrence of this condition. A focus on prevention in SIBO is also important in order to avoid repeated courses of antibiotics. Treatment of the underlying cause such as hypothyroidism is the primary mode of prevention.

Studies evaluated above found that impaired immune response, impaired intestinal clearance, and hypothyroidism are the key pathways for the development of small intestinal bacterial overgrowth. The strongest effects derive from levothyroxine treatment and/or the presence of hypothyroidism, although the relevant mechanism of action remains unclear. Intestinal motor dysfunction associated with hypothyroidism could be a strong predisposing factor to bacterial overgrowth in the small intestine.

Impairment of intestinal clearance and levothyroxine use are among the most important contributors for the development of SIBO (Brechmann et al 2017). The pathogenesis of SIBO and underlying predisposing conditions are insufficiently understood, yet three main pathogenetic pathways have been hypothesised: hypo or achlorhydria, impaired intestinal clearance, and immunosuppression.

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Canadian Journal of Naturopathic Medicine

Intraarticular Injection of Hyaluronic Acid for Osteoarthritis of the Knee: A Review

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Acknowledgements
None

Conflicts of Interest
PR and SE declare no conflicts of interest
RO, JM, MJA, and ADD declare use of the specific preparation discussed within this manuscript in their respective private practices

Manuscript Contributions by Author
RO, JM, MJA, and ADD prepared the "Administration" section of the manuscript
PR and SE prepared the remainder of the manuscript

Intraarticular Injection of Hyaluronic Acid for Osteoarthritis of the Knee: A Review

Abstract

Hyaluronic acid (HA) represents a safe, minimally invasive intervention known to provide significant symptomatic relief for individuals suffering with osteoarthritis. Naturopathic doctors (NDs) practicing in several jurisdictions across North America are provided scope of practice that allows for clinical application of this important tool. The goal of this review is two-fold; to familiarize ND's with this intervention in regions where its use is permitted, and to encourage ND's in regions currently excluded from this medicine to pursue its inclusion as an allowed substance for administration by injection. There are several hundred human intervention trials of injectable HA. To establish an evidence base manageable for the scope of this review, authors Rouchotas and Egan reached out to a team of NDs actively using the substance in British Columbia, Canada. We chose to cover the specific agent Durolane, also known as NASHA (Non-Animal Stabilized Hyaluronic Acid), due to our colleagues' familiarity with the agent. We acknowledge the existence of several other specific forms of the substance and suggest future reviewers endeavour to systematically assimilate all available evidence of this important agent. Other available forms of injectable HA include Euflexxa, Orthovisc, Synvisc-One, Synvisc, Supartz, Monovisc, Gelsyn-3, Hyalgan, Hymovis, and Supartz FX. Hyaluronic acid proves safe and effective for knee OA. Use across a broader range of applications is reasonable and should be further explored.

Introduction

Osteoarthritis (OA) is the most prevalent form of arthritis, characterized by the degeneration of the joint lining, ligaments, cartilage, bone within the affected joint, as well as the presence of osteophytes (Menkes 1991). OA targets joints of the hands and spine, as well as weight-bearing joints such as the knee and hip. Impacting an estimated 4% of the global population, OA is classified as one of the 50 most common diseases and injuries, with OA of the knee contributing to 83% of reported cases (Vos et al 2012). The number of individuals impacted is expected to rise to 78.4 million by the year 2040 as a result of the aging populace born between the 1940s-1960s, combined with the current obesity epidemic (Osteoarthritis Action Alliance 2021). In 2010, Canada saw an OA prevalence of 13.8% with an average cost of $2.9 billion, which is projected to increase to 18.6% with a cost of $7.6 billion in 2031 (Sharif et al 2015). Signs and symptoms include pain, stiffness, a decrease in joint range of motion (ROM), and swelling. OA proves to significantly reduce the overall quality of life in those impacted (Centre for Disease Control and Prevention 2021). Fifty-four percent of individuals diagnosed with knee OA will undergo total knee arthroplasty (TKA) at some point in their life with a direct $140,300 discounted per person lifetime cost (Losina et al 2015).

Hyaluronic acid (HA) belongs to a family of molecules known as glycosaminoglycans. Glycosaminoglycans are complex polysaccharides containing amino groups principally occurring as components of connective tissue. Molecules belonging to the glycosaminoglycan class include HA, chondroitin, keratin, and heparin. HA is a linear chain of repeating disaccharide units. Each disaccharide unit contains N-acetyl-D-glucosamine and D-glucuronic acid. At physiological pH, HA is negatively charged and attracts a variety of positively charged cations. The resulting hydrophilic salts are referred to as hyaluronan or hyaluronate and result in a hydration shell (Fallacara et al 2018). These complex long chains of hydrophilic polysaccharides possess qualities ideal for increasing viscosity in situations of compromised joint integrity, providing joint lubrication and shock absorbency, as well as restoring the rheological properties of synovial fluid (Filardo et al 2012, Maia et al 2019).

The use of HA as treatment for knee OA results in substantial cost savings. Out of 2,030,497 knee OA patients, only 15.9% of those treated with HA required TKA within two years, however, the HA treatment then contributed to 1.7% of total OA related costs, saving an average of $20,740 per patient (Ong et al 2019).

Human Intervention Trials of NASHA (Non-Animal Stabilized Hyaluronic Acid)

A superficial PubMed search of “intraarticular injection hyaluronic acid” with “clinical trial” as limits produced over 400 results in April of 2021. Similar to subcutaneous injection of mistletoe for patients with cancer, intraarticular injection of HA has expanded to the level of requirement for evaluation of each individual preparation available, as opposed to a scoping review of all

evidence. As such, the decision was made to focus on evidence relating to the use of Durolane, manufactured by Bioventus, headquartered in North Carolina, USA. The basis for covering this specific preparation stemmed from colleagues in British Columbia choosing to use this material in their private practices and the goal of partnering with these colleagues to include accurate and concise guidance on administration of the substance within this review.

Nineteen human trials of intraarticular injection of HA were identified for this review. Thirteen of them focused on knee osteoarthritis, as summarized in Table 1. Six of them evaluated HA use for sites other than the knee and are included for completeness, as found in Table 2.

Knee Osteoarthritis

Two of the 13 studies examining knee OA focused on determining impact of NASHA relative to control (saline) (Altman et al 2004, Arden et al 2014). Both were robust, well-controlled, and long-term. Altman and colleagues (2004) conducted their trial across 18 centres from the USA, Canada, and Sweden, and appears to be the most well-controlled of the trials reviewed. While the outcomes for NASHA-treated patients were impressive, saline-treated patients achieved significant benefit, and therefore between group comparisons for several outcomes were non-significant. The study was confounded by including participants with OA of multiple sites as opposed to focusing on knee OA. Sub-analysis did reveal statistically significant superiority for NASHA across several important parameters, notably among patients with specifically knee OA, and even stronger outcomes among individuals with unilateral knee OA.

Several studies compared NASHA to other treatments, notably platelet-rich plasma (PRP) (Buendia-Lopez et al 2018, Louis et al 2018), platelet-rich growth factor (PRGF) (Vaquerizo et al 2013), allogeneic bone marrow mesenchymal stem cells (Vega et al 2015), umbilical cord-derived mesenchymal stromal cells (Matas et al 2019), and various steroids (Leighton et al 2014, Skwara et al 2009). These papers appeared to be set up in a manner focused on establishing superiority of the comparator treatment, yet NASHA was reproducibly found to deliver meaningful clinical outcomes.

Lastly, several studies compared NASHA to other available HA preparations (Estades-Rubio et al 2017, McGrath et al 2013, Zhang et al 2015). All three papers demonstrate significant superiority of NASHA relative to other forms of HA. Of note, Estades-Rubio and colleagues (2017), as well as McGrath and colleagues (2013) declare no conflicts of interest, while Zhang and colleagues (2015) disclose funding and manuscript review from Bioventus, the manufacturer of Durolane (NASHA).

Jurado and colleagues (2013) conducted a retrospective case analysis of 224 patients referred for knee prosthesis to evaluate factors that delay requirement for surgery. The paper has been omitted from Table 1 based on the lack of intervention trial design. The authors represent the Specialty Clinic of Knee Osteoarthritis (SCKO) of the Rheumatology department of the Hospital of Jaen, Spain. The team relies heavily on the use of NASHA, as 90.2% of cases reviewed

received the treatment. The mean time to surgery for patients not receiving NASHA was 694 days, compared to 1093 days for patients receiving the therapy.

Osteoarthritis of Sites Other than the Knee

Six studies have evaluated intraarticular injection of NASHA for sites other than the knee (see Table 2). Shoulder (McKee et al 2019), ankle (Younger et al 2019), and thumb (Velasco et al 2017) have each been evaluated by one human trial. All three of these studies are open-label in design. Hip OA has been evaluated by two open-label trials (Berg and Olsson 2004, Conrozier et al 2009) and one controlled study (Atchia et al 2011). The controlled trial by Atchia and colleagues has concerns, notably that it was presented as a symposium supplement, and differences appear in outcomes as presented in the supplement versus its presentation in PubMed. While this preliminary body of evidence of NASHA administration for sites other than the knee is encouraging, it would be desirable to see the evidence in the area further developed.

Pharmacokinetics

Lindqvist and colleagues (2002) undertook an investigation of single administration of ^{131}I-labeled NASHA to the knee of six healthy participants with the goal of evaluating elimination of the substance from the knee following injection. Elimination is described as conforming to a "three-exponential-function model", suggesting a rapid elimination immediately following injection (1.5-hour half-life), followed by a period of delayed elimination (1.5-day half-life), then followed by a period of very slow elimination (four-week half-life).

Administration

Successful HA therapy is accomplished when the substance is safely and accurately injected into the joint capsule. It is for this reason that providers must undergo adequate training in orthopedic injections to ensure the success of this therapy. When delivering intraarticular joint injections, aseptic technique is recommended to decrease the risk of in-office infection and post-injection complications (Suvikas-Peltonen et al 2017).

Considerations for injection technique regarding in-office HA are broadly divided into two main categories: Use of image-guided injections and blind injections. Current literature supports the use of image-guidance for intraarticular knee injections (Bum Park et al 2012) when compared to blind injection success rate. When examining skilled injectors, blind approach to intraarticular needle placement resulted in an 83.7% success rate, while ultrasound-guided intraarticular injection resulted in a 96% success rate (Hashemi et al 2016).

While competency to deliver both Point Of Care Ultrasound and ultrasound guided injections will take a physician years to master, current Canadian courses exist for physicians to learn injection techniques via ultrasound guidance that can be completed in a series of weekend courses. Physicians may seek a formal designation from the Alliance for Physician Certification

& Advancement (APCA) under the Musculoskeletal Sonography Certification (RMSK). Currently, British Columbia is the only legislated provincial jurisdiction in Canada where Naturopathic Physicians can use ultrasound for both attaining information towards a diagnosis and injection procedure in a clinical setting.

When performing a sterile tray setup for aseptic ultrasound-guided knee injections, the following tools are needed to successfully complete the in-office procedure.

Sterile drape sheet plain 18”x26”
Aquasonic ultrasound gel, sterile, 20g packets
OR towel, huck 17”x26” sterile
Sterile sauze 4”x4” 4-ply non-woven
NitriDerm nitrile sterile exam gloves
IV extension set 6"
Sterile ultrasound probe cover
ChloraPrep clear, 1mL Appl, CA
2-inch 22G Luer lock needle

When performing an ultrasound-guided intraarticular knee injection, the recommended injection site is superolateral to the patella, with the knee in 30° of flexion, in order to access the joint capsule. For those with limited amounts of synovium, aka “dry knee,” the medial mid-patellar approach may be utilized. Blind anterolateral patella injections can be completed with the patient in a seated position with the knee in 90° of flexion.

Upon entering the capsule, a distinctive “popping” can be felt in the form of needle reverberation. After ensuring against vascular placement, little to no resistance should be felt upon injecting the substance. Clinicians would benefit from repeated procedural experience to understand the resistance feedback of non-articular placement of HA.

Discussion

Associations establishing guidelines for OA management present mixed opinions on use of HA, yet it is not difficult to find reputable authorities showcasing robust recommendations for HA administration. The Osteoarthritis Research Society International (OARSI) showcases intraarticular HA as a Level 1B/2 recommendation (Bannuru et al 2019). To achieve a Level 1A recommendation, 75-100% of the advisory panel must vote in favour of the intervention’s inclusion. A Level 2 recommendation requires 60-74% of the advisory panel to approve the intervention.

Similarly, the OARSI recognizes intraarticular corticosteroids (IACS) as a Level 1B/2 recommendation. Yet, when comparing IACS with HA, the team showcases that while IACS provides short-term relief, HA delivers relief at and beyond week 12, and also delivers a more favorable long-term safety profile (Bannuru et al 2019).

All intervention trials reviewed objectively documented adverse events. In 10-15% of patients, a worsening of pain is reported following HA treatment, yet this worsening is short-lived, transient, and resolves quickly on its own or with the assistance of basic analgesics. Beyond this acute treatment-related event, the intervention appears devoid of adverse effects.

Given this impressive safety profile, and important magnitude of efficacy reproducibly delivered, it is not surprising that clinicians utilizing this intervention push beyond the peer-reviewed applications of the intervention. It is not unreasonable to consider administering more than a single treatment, nor is it unreasonable to consider the treatment for sites other than the knee. Furthermore, it is also not unreasonable to consider the treatment for situations of chronic pain not defined by OA, notably sport-related injuries or joint pain from other chronic inflammatory diseases.

Table 1: Human Intervention Trials of NASHA Injection for Osteoarthritis of the Knee

Methods	Outcomes	Reference
Multicentre trial across USA, Canada, and Sweden. Patients with osteoarthritis (OA) at various sites (346) assigned to receive a single injection of NASHA vs saline placebo, with 26-week follow-up. WOMAC served as the primary endpoint measure, with at least a 40% improvement or 5-point reduction in WOMAC considered a “responder”. ITT outcomes reported.	WOMAC scores improved significantly in both groups with no significant differences between groups. Among responders at week two, most remained responders at week 26. Among a subset of individuals only presenting with knee OA (216), NASHA was significantly superior to saline. NASHA demonstrated superior efficacy for individuals with OA isolated to one knee vs individuals with bilateral OA.	Altman et al 2004
RCT of intraarticular NASHA vs saline, single injection, in 218 patients with six-week follow-up. WOMAC absolute reduction of >/= five points, or >/= 40%	No difference in responder rate at six weeks (NASHA 30.6% vs saline 26.4%). Subgroup analysis among individuals without clinical effusion showed superiority of NASHA	Arden et al 2014

improvement from baseline criteria for "response". ITT outcomes reported.	(responder rate 40.6% vs 19.7%). The team notes image guidance for injection was intended to be used but was not.	
Patients were randomized to a single injection of PRP (N=33), NASHA (N=32), or daily NSAID (N=33). Follow-up at 26 and 52 weeks. Primary outcome: 20% decrease in WOMAC pain subscale. Secondary outcomes: 20% decrease in WOMAC physical function scale and VAS.	PRP outperformed NASHA and NSAID significantly by 30% at 26 and 52 weeks in primary and secondary outcomes. NASHA outperformed NSAID at 26 and 52 weeks, yet the differences were not significant.	Buendia-Lopez et al 2018
Comparative investigation of two different HA preparations; single injection of NASHA vs five injections of Go-ON. Fifty-four patients were randomized and followed for 26 weeks. WOMAC and analgesic use served as endpoint measures.	NASHA significantly outperformed Go-ON by week four, and continued to outperform through week 26. NASHA-treated patients consumed significantly less analgesic medication relative to Go-ON treated patients over the 26-week treatment period.	Estades-Rubio et al 2017
Knee OA patients (N=442) were randomly assigned to single injection of NASHA vs methylprednisolone acetate (MPA) for 26 weeks. WOMAC responder rate as endpoint measure. In open-label fashion, NASHA was offered to all participants after week 26.	No difference between WOMAC responder rate at week 26 (44.6% NASHA, 46.2% MPA). WOMAC subscales of pain, physical function, and stiffness favoured NASHA vs MPA from weeks 12-26. Further improvement among participants who received a NASHA after week 26, regardless of initial treatment received.	Leighton et al 2014
Fifty-four patients with knee OA were randomized to receive one-time injections of PRP or NASHA, and were followed for six months. Forty-eight patients (24 in each group) were available for final analysis. WOMAC	PRP achieved a higher percentage of WOMAC responders relative to NASHA, yet the difference was not significant. The satisfaction rate was 82% in the PRP group and 79% in the NASHA group.	Louis et al 2018

responder rate served as a primary endpoint measure.		
Twenty-nine patients were randomized to two-time injection of NASHA, single injection of UC-MSCs, or repeat injection of UC-MCSs for knee OA and followed for 12 months. WOMAC and VAS as endpoint measures.	NASHA reduced total WOMAC 13.7 points (28.9 to 15.2) and total VAS 10.7 points (38.7 to 28.0) at six months, with further improvement through 12 months. Multiple UC-MCSs achieved superior outcomes to NASHA at both the six-month and 12-month assessments.	Matas et al 2019
A comparative investigation of patients receiving a single injection of NASHA vs Synvisc for knee OA, followed for 12 months. One hundred sixty-eight patients participated in the final assessment. VAS, SF-36, and the Oxford knee scores served as endpoint measures.	Both groups achieved significant reductions in joint pain by three months, with the impact of NASHA superior to Synvisc. Reduction in pain remained significant at six months in the NASHA group, yet was no longer significant in the Synvisc group.	McGrath et al 2013
Sixty patients were randomly assigned to single injection of NASHA or triamcinolone for treatment of knee OA, with 50 patients available for final analysis. Follow-up was conducted 12 weeks following treatment. Gait was assessed using the Helen-Heyes marker set. VAS and KSS also served as endpoint measures.	NASHA led to significant improvements in gait, notably for stride strength, walking speed, and range of motion. Likewise, VAS significantly improved, as did total knee and function scores of the KSS. Triamcinolone treatment achieved similar outcomes, with no differences between groups.	Skwara et al 2009
Ninety-six patients with knee OA were randomly assigned to a single injection of NASHA vs three injections per two weeks of PRGF for 48 weeks. WOMAC, OMERACT-OARSI, and Lequesne scores served as endpoint measures.	The study focused on comparing NASHA to PRGF. PRGF outperformed NASHA on all evaluated endpoint measures. Three treatments per two weeks with PRGF vs a single treatment with NASHA is relevant. NASHA appeared to deliver benefit across assessed endpoints, yet statistical analysis was	Vaquerizo et al 2013

	not performed comparing NASHA to baseline.	
Thirty patients were randomly assigned to receive single injection of NASHA or allogeneic bone marrow mesenchymal stem cells and followed for 12 months. VAS, WOMAC, and Lequesne scales served as endpoint measures.	VAS and pain subscale of WOMAC were significantly reduced in both groups at 12 months, and not significantly different from each other. Allogeneic bone marrow mesenchymal stem cells outperformed NASHA regarding the Lequesne scale and general subscales of WOMAC.	Vega et al 2015
Patients with knee OA (N=349) were randomized to a single injection of NASHA or five (once weekly) injections of sodium hyaluronate (Artz). WOMAC and global self-assessment served as endpoint measures. Patients were followed for 26 weeks.	Single injection of NASHA and five injections of Artz significantly improved endpoint measures over the 26-week observation period. There were no significant differences between the two treatment arms.	Zhang et al 2015
In open-label fashion, fifty patients with knee pain received a single injection of NASHA. Patients were followed for 26 weeks. VAS served as the primary endpoint measure.	At 26 weeks of follow-up, significant improvements were observed for pain, range of motion, and quality of life and activity.	Krocker et al 2006. Abstract.

Abbreviations

ITT = Intention To Treat
KSS = Knee Society Score
N = Number of participants
NASHA = Non-Animal Stabilized Hyaluronic Acid
NSAID = Non-Steroidal Anti-inflammatory Drug
OMERACT-OARSI = Outcome Measures for Rheumatology Committee and Osteoarthritis Research Society International Standing Committee for Clinical Trials Response Criteria Initiative
PRGF = Platelet Rich Growth Factor
PRP = Platelet Rich Plasma
RCT = Randomized Controlled Trial
SF-36 = Short Form Survey-36
UC-MSC's = Umbilical Cord-Derived Mesenchymal Stromal Cells
VAS = Visual Analogue Scale

WOMAC = Western Ontario McMaster Universities osteoarthritis index

Table 2: Human Intervention Trials of NASHA Injection for Sites Other than the Knee

Methods	Outcomes	Reference
Forty consecutive patients referred for single injection of NASHA therapy for hip OA. Six-month follow-up. Investigators administered the following endpoint measures: OMERACT-OARSI, PASS, MCII. Patients were asked to complete the VAS walking pain subscale, WOMAC, and the PGA.	VAS walking pain, PGA, and WOMAC were reduced 40%, 36%, and 25% respectively. Mean reduction in NSAID use was 32%, ranging from 0-97%. 76% of patients achieved PASS. 71% were OMERACT-OARSI responders. 61% achieved MCII.	Conrozier et al 2009
Open-label trial in 31 patients with hip OA administered single injection of NASHA, followed for three months. WOMAC response rate and patient global assessment served as endpoint measures.	WOMAC response rate was 50% at two weeks and 54% at three months. 68% of patients reported improved global assessment of pain.	Berg and Olsson 2004
Seventy-seven patients with hip OA were randomized to one of four groups: standard care (no injection), saline, NASHA, and methylprednisolone acetate. WOMAC, "worst pain" (rated 0-10), and OMERACT-OARSI served as endpoint measures. Follow-up spanned eight weeks.	Methylprednisolone acetate outperformed all other interventions. At week one, responders based on the OMERACT-OARSI scale were 74% in the methylprednisolone group, 21% in the NASHA group, 11% in the saline group, and 10% in the no injection group. Data was not provided for the eight-week assessment.	Atchia et al 2011
Open-label trial in 41 patients administered a single injection of NASHA for shoulder OA, followed for 26 weeks. VAS as primary endpoint measure.	Intervention significantly reduced total VAS score 20.1mm, for a mean VAS reduction of 29.5%. Patient global assessment scores also improved significantly.	McKee et al 2019
Open-label study in 35 patients with thumb OA. Patients received a single	Over the six-month treatment period, a significant 2.0-point	Velasco et al 2017

injection of NASHA and were followed for six months. VAS served as the main endpoint measure.	reduction in VAS was observed, corresponding to a mean 27.8% improvement.	
Open-label study in 37 patients with ankle OA received a single injection of NASHA and were followed for 26 weeks. VAS served as the main endpoint measure.	VAS pain score improved a significant 40%, and the VAS disability score improved a significant 34% over the 26-week observation period.	Younger et al 2019

Abbreviations

MCII = Minimal Clinically Important Improvement
NASHA = Non-Animal Stabilized Hyaluronic Acid
OMERACT-OARSI = Outcome Measures for Rheumatology Committee and Osteoarthritis Research Society International Standing Committee for Clinical Trials Response Criteria Initiative
PASS = Patient Acceptable Symptom State
PGA = Patient's Global Assessment
VAS = Visual Analogue Scale
WOMAC = Western Ontario McMaster Universities osteoarthritis index

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Canadian Journal of Naturopathic Medicine

Drawing Attention to Omega-3 Supplements in Attention Deficit Hyperactivity Disorder (ADHD)

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Acknowledgements
None

Conflicts of Interest
The Author declares no conflicts of interest

Drawing Attention to Omega-3 Supplements in Attention Deficit Hyperactivity Disorder (ADHD)

Abstract

Attention deficit hyperactive disorder (ADHD) is a common challenge among children, adolescents, and adults. Parents, especially, remain cautious in utilizing medications as a first line therapy for their young children who have been diagnosed with ADHD, hence creating an expanding need for natural therapeutics. Omega-3 polyunsaturated fatty acids (PUFAs) have been effective at alleviating symptoms in various diagnoses (neurological, cardiovascular, endocrine and more) due to their anti-inflammatory nature. Omega-3 PUFAs would be a good option for children with ADHD due to their moderate efficacy and lower level of side effects. This article comments on studies that address this efficacy by focusing on which subtype of ADHD patients would benefit the most, as well as the best dosage, duration, age range, and symptom profile that show clinical benefits. This article also comments on mechanisms of action that are relevant and that underlie the logic of utilizing omega-3 PUFAs in a clinical setting. Overall, based on a review of a collection of studies in ADHD, omega-3 PUFAs are promising natural therapeutic agents alone or in combination with conventional medications in children age six to 15, at a dose >500mg EPA/DHA and in those with the hyperactive/impulsive subtype of ADHD.

Introduction

Attention deficit hyperactive disorder (ADHD) can be a challenging diagnosis for children and a worrisome one for their parents. It has been noted that 6.1 million children in the United States of America between the ages of two and 17 are thought to have ever been diagnosed (CDC 2020). Parents are often careful in pursuing conventional medications for children, especially younger ones. Therefore, the pressing need for natural interventions in this niche has been growing immensely over recent decades for young children and those who wish to pursue natural means before seeking medication.

ADHD can often be diagnosed in childhood, as early as three years of age. The primary features of ADHD include inattention and hyperactive-impulsive behavior. The symptoms can be mild, moderate or severe. If unresolved, these can make their way into adult life. ADHD is more prevalent in males than in females. Moreover, the expression of the array of behaviours can be different in boys and girls. There are three types of ADHD: a) inattentive, b) hyperactive/impulsive, and c) mixed (Mayo Clinic 2019). Most common treatments include psychostimulant drugs and behaviour therapy. Among the drugs, there are three main types that are available in either short or longer acting forms. The first is the Amphetamine class. This includes but is not limited to dextroamphetamine (Dexedrine), dextroamphetamine-amphetamine (Adderall XR) and lisdexamfetamine (Vyvanse). The second is the Methylphenidate class. This includes but is not limited to methylphenidate (Concerta, Ritalin) (Mayo Clinic 2019). The third class is slower acting and is classified as being in the antidepressant category, such as bupropion (Wellbutrin). Key side effects of concern are cardiovascular in nature and include elevated blood pressure and increased pulse rate. Additional side effects of further behaviour alterations can occur, such as hallucinations, psychoses, and manic expression. These worrisome side effects and pharmaceutical hesitancy create an immense need for efficacious alternatives to conventional medication or a need to improve the outcomes of conventional therapies.

There have been several natural therapeutic options that have been examined for mental health diagnoses such as ADHD. One promising natural option has been omega-3 PUFAs. Deficiencies in omega-3 PUFAs have been found, more specifically DHA, in children diagnosed with ADHD (Hawkey and Nigg 2014, Stevens et al 1995). This concept is extended clinically as well. Lower levels of EPA and DHA were found in the blood of those with symptoms of ADHD (Colter et al 2008, Crippa et al 2018). These and other studies have been monumental in creating an interest in the use of omega-3 supplements alone or with medication for ADHD.

Background

Prior to appreciating the clinical usefulness of omega-3 PUFAs in the neurological system and more specifically to ADHD, the structure, function, and mechanisms of action of these crucial players should be revisited. Omega-3 fatty acids are PUFAs; there is a double bond at the third carbon atom from the end of the carbon chain. PUFAs are a part of the phospholipid structure of

the cell membrane. They also create eicosanoids that participate in cell signalling for processes in neurological, cardiovascular, pulmonary, and immune systems. There are three types of omega-3 fatty acids that are clinically relevant to this article: α-linolenic acid (ALA) (found in plant oils), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) (found in fish oils).

Omega-3 fatty acids are broken apart into smaller fatty acid units. Therefore, products are vital to downstream processes, such as the construction/disruption of lipid rafts, promotion of optimal signalling mechanisms, formation of changes in gene expression, and regulation of lipid/peptide mediators (Calder 2013). An important concept to note is the following: unlike plants, humans/animals do not have the delta-15 desaturase enzyme that enables the construction of ALA. Humans are able to metabolize it via processes of desaturation and elongation. ALA forms stearidonic acid via delta 6 desaturase and then stearidonic acid is worked on to create EPA (Calder 2013). It is important to note that the conversion of α-linolenic acid to EPA is in competition with the conversion of linoleic acid to arachidonic acid (AA), thus swaying the outcomes of inflammatory versus anti-inflammatory actions.

EPA and DHA acid are key players in cellular function and help with actions such as the reduction of platelet function and plasma fibrinogen. The anti-inflammatory effects of Omega-3 PUFAs are the reason they are used in clinical application. Higher levels of EPA or DHA have been shown to decrease levels of prostaglandin E2 (PGE2) and 4 series leukotrienes (LT). The anti-inflammatory effects are mainly a result of the fact that omega-3s and in turn EPA/DHA produce a different set of eicosanoids than AA, which then alters leukotriene synthesis. EPA, for instance, contends with AA for desaturation enzymes (Calder 2013). The anti-inflammatory aspect is due to the formation of 3 series prostaglandins (PGs) and 5 series thromboxanes (TXs), respectively.

EPA and DHA also demonstrate anti-inflammatory effects by producing molecules known as resolvins and protectins via cyclooxygenase and lipoxygenase molecular pathways. These molecules prevent transendothelial migration of neutrophils. They also prevent the formation of tumour necrosis factor (TNF) and interleukin (IL)-1β (Calder 2010). Omega-3 fatty acids also contribute to anti-inflammatory states by reducing adhesion molecule expression on leukocytes and on endothelial cells, which in turn reduces intercellular adhesive interactions. Omega-3 PUFAs are considered to be ligands for peroxisome proliferator activated receptor (PPAR) gamma that regulates nuclear factor (NF)κB activation and hence inflammatory gene expression (Calder 2010).

The analysis of mechanisms of action involved in the relationship between ADHD and omega 3s and other PUFAs have to do with neuroprotective effects mainly involving changes in the synaptic membranes (Mischoulon and Freeman 2013). Detailed mechanisms related to protection of neuromembranes include but are not limited to cell signalling within the brain, maintenance and regulation of monoamines, and receptor alterations related to signal transduction pathways (Assisi et al 2006, de la Presa and Innis 1999, Hallahan and Garland 2005, Ross et al 2007).

Additional findings of omega-3 PUFAs involved a role in alterations in the function of the dopamine transporter/dopamine production and dopamine/serotonin levels at the synapse (Foster et al 2008). The regulation of neurotransmitters and the sustenance of an anti-inflammatory state are the main mechanisms at play for omega-3 PUFAs and their neurological success.

Promising Evidence for the Use of Omega-3 PUFAs in ADHD

The clinical application of omega-3 PUFAs in ADHD is immense and worth examining. Chang et al (2018) provided a systematic review and meta-analysis to delve into this and have shown that children with ADHD had lower red blood cell levels of EPA and DHA, as well as that supplementation with omega-3 PUFAs in those with ADHD provided a significant clinical improvement in cognitive performance. Symptom assessment also echoed this improvement; a dose of EPA greater than 500mg/d improved symptoms in individuals with the hyperactivity/impulsivity subtype of ADHD.

Positive results were shown in a study that provided omega-3 PUFAs to children age six to 12 for 12 weeks, where higher concentrations of EPA/DHA were found in red blood cells (RBC) and correlated significantly with improvements in working memory. There was no effect seen in parent and teacher rated behaviour (Widenhorn-Müller et al 2014). A double-blind, randomized, placebo-controlled trial (DBRPCT) found that boys aged eight to 14 who were given 650mg EPA/DHA for 16 weeks had improved parent rated attention and symptoms of ADHD, however had no effect on cognitive control or functional MRI outcomes of brain activity (Bos et al 2015). Kidd (2007) also discussed a neuroprotective effect of EPA/DHA; for instance, a DBRCT that administered phosphatidylserine compounds with EPA/DHA showed improved symptoms of ADHD.

Conversely, several studies have shown no differences between omega-3 PUFA treatment groups versus placebo in those with ADHD. One example is a study that had a crossover design where children took EPA, DHA or linoleic acid and the study measured attention, cognition, literacy, and utilized the Conner's Parent Rating Scale (CPRS) (Milte et al 2015). Another review that assessed RCTs had looked at studies with omega-3 PUFAs in children and adolescents as measured by CPRS and showed no statistically significant changes between placebo and treatment groups (Abdullah et al 2019). One RCT administered Omega-3 and -6, methylphenidate (MPH), or both for one year to 90 individuals with ADHD, who were assessed via the ADHD Rating Scale and Clinical Global Impressions-Severity (CGI-S) scale. The findings showed that a combination of omega-3 and -6 with MPH had similar findings to the group with MPH alone (Barragán et al 2017). These studies with findings of no improvements in the treatment group are equally valuable, as they lead us to examine underlying reasons behind the lack of aimed result and strive to improve future efficacy, as will be further addressed in the discussion.

Overall, it seems that despite the group of aforementioned studies, there is compelling evidence to support the therapeutic use of omega-3 PUFAs in improving outcomes of ADHD. A randomized control trial with supplementation of 500mg per day of EPA and 2.7mg per day of DHA reduced inattentiveness but not hyperactivity (Gustafsson et al 2010). Other similar evidence was found in a study where restlessness and impulsive symptoms (parental rated input) improved in the treatment group when compared to placebo (Manor et al 2012). Another study with parent rated input demonstrated a reduced set of symptoms of hyperactivity, inattentiveness, and impulsive behaviour in the treatment group (Sinn et al 2008). One study used measurement outcomes of parental and teacher rated conduct/attention levels; the treatment group (480mg EPA, 80mg DHA, 40mg AA, and 96mg GLA) showed a significant reduction in symptoms when compared to placebo (Stevens et al 1995). One review showed that 13 of the 16 RCTs reviewed demonstrated improvement in a wide variety of symptoms including hyperactivity/impulsiveness, inattentiveness, working memory, and visual queued learning. Furthermore, a subset of these studies had a dosage of 9:3:1 of EPA/DHA/GLA that showed success alone or in combination with conventional medication (Derbyshire 2017).

Discussion

A large array of studies has supported the use of omega-3 PUFAs in ADHD; these effects depend on age, dosage regimen, length of treatment, and method of outcome measurement. Yet overall, there is still consistency that treatment groups with omega-3 PUFAs have improved clinical outcomes and that also reflect improved physiological findings (e.g. blood markers).

Although some studies have shown no difference between treatment (omega-3 PUFAs) and placebo groups in ADHD, there are several explanations and things to consider. Perhaps these findings could lead us to consider if this may be related to the half-life and metabolism of these molecules. One study showed that the half-life values of ALA is one hour, EPA is 39-67 hours and DHA is 30 hours (Braeckman et al 2014, Nguyen et al 2014). It may be possible that clinical usefulness might involve administration at the immediate onset of symptoms and for a shorter duration, rather than with long-term use, to maximize the half life.

Another thing to note in maximizing efficacy would be the ratios of EPA to DHA in the dosage administration in ADHD. Some studies used a nearly 1:1 ratio, while others used DHA alone. DHA tends to exist in high concentrations in the retina and brain and plays a large role in pre and postnatal brain development, whereas EPA is more important in regulating mood/behaviour. This is important when considering clinical usage of either one. Adjusting the regimen to incorporate higher ratios of DHA versus EPA or vice versa might be promising, depending on the ADHD subtype. Interestingly, the notion of levels of EPA/DHA versus AA are important in the context of cell exposure, accumulation and membrane fatty acid structure, as this will determine how those cells function from the standpoint of measuring cell inflammation. Additionally, it begs the question of whether an improved molecular profile of EPA/DHA influenced anti-inflammatory metabolites would translate clinically to improved symptoms.

From the evidence provided above, the answer confirms it mostly will. However, it should be noted that most studies did not do any baseline EPA/DHA blood/RBC measurements to compare to post treatment levels.

Consideration should also be given to what would be deemed a therapeutic dose. Calder reports that a minimum dose of 2g/d of omega-3 PUFAs appears to produce a significant anti-inflammatory effect (difficult to achieve through diet or normal over the counter supplements) (Calder 2010, Calder 2013). Moreover, it would be harder to get children to consume these higher levels of omega-3 PUFAs.

Another interesting notion is that most of the studies were performed in school-age children. Perhaps an effect may have been omitted that could have been observed in the younger age groups, given that ADHD can be diagnosed as early as three years of age. Another interesting perspective is to question whether certain severity subsets of ADHD benefit more from therapy with omega-3 PUFAs than others. For instance, one study showed that EPA/DHA given for three months to children aged six to 15 with ADHD did not benefit the treatment group as there was no measured benefit in symptom improvement in those with mild ADHD (Cornu et al 2018). Perhaps there could have been better efficacy in those with moderate or severe ADHD, either through measured symptoms or molecular markers. Another aspect to efficacy is the gender factor. A study noted that boys (12.9%) are more likely to have ever been diagnosed with ADHD than girls (5.6%) (CDC 2020). Girls may demonstrate a more muted symptom profile and manifest these symptoms differently, hence revealing an underlying bias.

It was also noticed that symptoms as measured by parent scores in studies were improved in the PUFA treated group, whereas this effect was less seen with teacher measured scores. Teachers assess children during the day in class and use different criteria to assess attentiveness, whereas parents might take a wholistic approach in assessing the child for a broader list of activities in the home. This may have impacted the findings in a lack of effect noted with teachers in the treatment group when compared to an effectiveness of PUFA in ADHD as reported by parents.

Conclusion

There is a strong body of evidence that supports the use of omega-3 PUFAs in ADHD. Patterns indicate that most studies in those with ADHD showed either a) a specific, deficient profile of cellular/molecular/bio markers, b) improvement in these same marker levels of PUFAs post supplementation (e.g. RBCs), and/or c) reduced symptoms in the treatment group. Overall, this was more specifically demonstrated by >500mg EPA/DHA, in the six to 15-year age group, for greater than three months duration, and with improvements mostly found in the hyperactive/impulsive subtypes and those with more severe ADHD, as measured by parent rated symptom assessment.

While some studies showed no improvement in treatment groups that were administered omega-3 PUFAs for ADHD, the dose, ratio of EPA/DHA, duration of treatment, age range, and type of

measurement outcome would need to be further examined to assess whether there was truly no benefit.

For combination treatments (conventional therapy and omega-3 PUFAs), no additional benefit was seen with the combination compared to either therapy alone. However, a systematic review by Bloch and Qawasmi suggests that omega-3 PUFAs, although less effective than psychostimulant medication, is still promising. Omega-3 therapy delivers reduced side effects compared to medication and still demonstrates moderate success in ADHD symptom relief. Therefore, omega-3 PUFAs can be used alongside conventional medication or alone (in those who are reluctant to use medication) (Bloch and Qawasimi 2011). Omega-3 supplementation is a safe intervention with solid evidence supporting a role in ADHD management, either to be attempted as a monotherapy, or alongside conventional treatments.

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