



Complementary and Alternative Medicine Use in Rheumatoid Arthritis

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Published online: 26 August 2020

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Abstract

Purpose of Review Despite advances in pharmacologic management of rheumatoid arthritis (RA), complementary and alternative medicine (CAM) remains popular adjuncts to therapy among patients for ongoing symptomatology.

Recent Findings Mind-body interventions are becoming increasingly popular, including yoga and meditation. Randomized controlled trials have found these interventions to be helpful regarding pain, mood, and energy in RA patients. Other CAM modalities, such as natural products, special diets, acupuncture, and body-based therapies, also continue to be used by RA patients with limited evidence for efficacy and safety.

Summary While there are numerous CAM interventions available, the data is very limited at this time with only low-quality evidence supporting various therapies. Medical providers are more open to the addition of CAM in their patients and require increased education on the topic. Additional research needs to be conducted in order to provide evidence-based recommendations to our patients.

Keywords Complementary and alternative medicine · Rheumatoid arthritis · Integrative medicine · Mind-body practices

Introduction

Over the past two decades, there have been major advances in the pharmacologic management of rheumatoid arthritis (RA) and implementation of treat-to-target approaches [1]. Despite this, the use of complementary and alternative medicine (CAM) remains prevalent and may even delay time to initiation of DMARD therapy [2]. Major CAM modalities include alternative medical systems (traditional Chinese medicine, Ayurveda, homeopathic treatment, naturopathy, acupuncture), biologically based therapies (chelation therapies, folk medicine, herbs, and supplements), diet-based therapies, megavitamin therapies, body-based and manipulative medicines (chiropractic use, massage), and mind-body feedback (biofeedback, yoga, tai chi, qigong, mindfulness, meditation, healing rituals, Reiki), among others [3, 4].

Specifically, in arthritis, a survey of primary care clinics found that 90% of patients had “ever use” of CAM and about 70% were using CAM therapy at the time of the survey [5]. More broadly, the economic impact of CAM use is substantial and estimated to be \$28.3 billion–\$30.2 billion for all adults based on a 2016 analysis of the National Health Interview Survey (NHIS) [6]. These amounts represent 9.2% of total out-of-pocket expenditure by Americans on healthcare and 1.1% of all healthcare expenditure in the USA.

For patients with arthritis, preferences for CAM modalities have shifted between the last two decades. Data from the 2002 and 2007 NHIS, which included patients with RA, found that natural products were the most commonly used CAM modality and taken by 20% of individuals. Subsequently, the 2017 survey found that there was increased use of yoga, meditation, and chiropractors in adults aged 18 and over compared with 2012 [7]. Yoga was noted to be the most commonly used CAM in both 2012 and 2017.

Patients with pain or limited mobility are more likely to use CAM [8]. Among patients with arthritis, joint pain and poor functional status were the most common predictors of CAM use according to the NHIS [9]. Additional reasons for CAM use in RA include inadequate response to treatment, high symptom burden, and avoidance of real and perceived side

This article is part of the Topical Collection on *Complementary & Alternative Medicine*

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effects from RA treatments [10]. Other qualitative studies have suggested that CAM use may stem from the patient perception of increased control over one's treatment plan [11].

Despite the large number of patients using CAM therapies, patients often neglect to disclose use of these therapies to their medical provider. A systematic review of patient reporting of CAM use found that only 33% of patients disclosed the use of biologically based CAMs [12•]. Current literature highlights a number of reasons for this including lack of knowledge and unsupportive attitude from the healthcare provider as well as time-limited clinic visits [10]. In regard to rheumatologists' perception of CAM use, a 2010 survey found that body work (i.e., massage) had the highest perceived benefit at 70% of respondents followed by meditation, acupuncture, and spinal manipulation [13]. For CAM therapies with highly perceived benefit, the likelihood of recommendation by the rheumatologist was also higher in their patients with chronic back pain or joint pain. Additionally, female providers and rheumatologists not born in North America were more likely to perceive benefit in CAMs. This survey shows a favorable opinion among rheumatologists regarding many types of CAM. A recent study suggests that if rheumatologists use more participatory styles of decision-making, patients are more likely to disclose their CAM use [14].

The goal of this review is to provide an abbreviated summary of the current literature on the most commonly used CAM modalities by patients with RA (Table 1). There are numerous CAM therapies accessible to patients; however,

for this review, we focused on the most prominent modalities with available literature [4].

Alternative Medical Systems

Traditional Chinese Medicine: Acupuncture

Acupuncture is the insertion of needles into the skin and underlying tissues at particular points for therapeutic purposes [15]. These points can be stimulated with electricity, lasers, heat, or ultrasound waves.

In 1999, a randomized placebo-controlled, crossover study looked at the effect of acupuncture in patients with RA [16]. Single point acupuncture or placebo was given with an intervening 6-week washout period. The placebo treatment consisted of the needle introducer being held at the acupuncture point without skin puncture for the same amount of time as the treatment arm. In both groups, the lower extremities were shielded from patient view. Outcome measures included inflammatory markers, visual analog scale of pain, global patient assessment, 28 swollen and tender joint count, and a general health questionnaire. The results demonstrated no significant effect of treatment and no significant interaction between treatment and period for any outcome variable. There were no adverse effects reported. Therefore, the investigators concluded that acupuncture could not be used as a useful adjunct therapy in patients with RA.

Table 1 Selected summary of commonly used CAM modalities in RA

CAM category	Level of evidence in RA	Side effect profile*
Alternative medical systems		
Acupuncture	Low	Low
Ayurveda	Low	Moderate
Biologically based therapies		
Omega-3 fatty acids	Moderate	Low-Mod
Gamma-linolenic acid	Low	Low
Probiotics	Low	Low
Thunder god vine	Low	High
Body-based therapies		
Massage	Low	Low
Balneotherapy	Low	Low
Chiropractic manipulation		Mod-High
Mind-body feedback		
Yoga	Moderate	Low
Tai chi	Low	Low
Meditation/mindfulness	Moderate	Low
Special diets		
Mediterranean diet	Moderate	Low
Intermittent fasting	Moderate	Low

*Based on reported adverse events in RCTs and systematic reviews

The most recent systematic review of acupuncture in RA was published in 2008 [17]. There were eight randomized controlled trials (RCTs) included. The trials that compared acupuncture versus sham acupuncture showed no difference between the groups. Several trials compared acupuncture versus conventional drugs which included diclofenac or methotrexate. There was no statistical significance suggesting superiority of acupuncture treatments over these medications either.

While there is no clear evidence of beneficial effect, acupuncture is largely thought to be safe when performed by an experienced practitioner using sterile needles.

Ayurvedic Medicine

Ayurveda is a 3000-year-old medicine system practiced in India and recognized by the World Health Organization as a complete system of natural medicine [18]. It includes complex herbal-mineral combinations, dietary and lifestyle modifications, oil therapies, and detoxification routines.

There was a 2011 double-blind, randomized, controlled, pilot study comparing classic ayurvedic medicine to methotrexate and a combination of both approaches [19]. This was the first ever study to compare Ayurveda to DMARD therapy. Forty-three patients completed the trial at 36 weeks. All met ACR criteria for a diagnosis of RA and had either a positive rheumatoid factor (RF) or positive anti-cyclic citrullinated protein (anti-CCP). There was no statistically significant difference between the three groups in terms of the DAS28-CRP score or the HAQ-DI. Only the ACR70 results at 24 weeks were superior for methotrexate alone compared with the other two groups. While conclusions regarding effectiveness of Ayurveda cannot be made based on this single, small study, this research demonstrates that blinded, randomized, and placebo-controlled trials are possible despite the complexity of this CAM intervention.

There were no adverse events reported in the previously mentioned study, but it is important to note that mineral and metals are common ingredients in ayurvedic preparations [20]. Studies on lead, mercury, and/or arsenic levels in these products have found that they have exceeded US Environmental Protection Agency and WHO limits for daily acceptable intake. Additionally, lead poisoning with long-term ayurvedic medication use has been documented as well as arsenic poisoning, although less commonly.

The first RCT using polyherbal ayurvedic medicine was published in 2000 [21]. A standardized formulation was compared with a placebo group. At the end of 4 months, responses to the intervention were indistinguishable from placebo for most measures. The proportion of patients with a 50% reduction in swollen joint count was higher in the intervention group. There were no significant changes in ACR20 or ACR50 responses. In 2012, patients with moderate to severe

RA were randomized to receive either one of two ayurvedic treatments or hydroxychloroquine [22]. One of the ayurvedic treatments, termed formulation B, was a polyherbal preparation and the other was a monoherb. There was a reduction in the physician global score noted in both the B formulation group and the hydroxychloroquine group compared with baseline. There was no difference in ESR, joint counts, visual analog pain scale, or HAQ scores. The authors concluded that B formulation was comparable with hydroxychloroquine in moderately severe RA.

There have been limited studies in this area, but they have indicated that some ayurvedic preparations can have comparable effectiveness to conventional RA drugs. However, given the side effect profile, improper use of these medications can be harmful.

Biologically Based Therapies

Omega-3 Fatty Acids

These are a key family of polyunsaturated fatty acids and are primarily derived from marine-based sources [23]. They are also sold as dietary supplements. Animal studies in the 1990s have shown a direct relationship between these fatty acids and the ability to modulate pro-inflammatory mediators [24, 25]. Clinical trials in humans have shown that supplementation with these fatty acids can have a beneficial outcome in reduction of triglycerides, reduction blood pressure, and inflammation, thereby becoming important in coronary heart disease, obesity-related diseases, and rheumatic diseases [26].

A 2017 review evaluated clinical trials of omega-3 fatty acids in RA, systemic lupus erythematosus (SLE), lupus nephritis, and osteoarthritis (OA) [27]. They reported 20 double-blinded, placebo-controlled trials (ranging from 1980 to 2016) published on the role of fish oil supplementation in RA. The majority of studies showed that increased dietary intake of omega-3 fatty acids resulted in improvement of at least two clinical measures such as duration of early morning stiffness, hand grip strength, patient global assessment, physician's global assessment, physician's pain index, Ritchie's articular index, swollen joint account, tender joint account, and joint pain intensity. The most common improved outcome for the intervention group was a decrease in tender joint count. One of the more recent studies showed a 70% improvement in tender joints in 77% of patients receiving omega-3-fatty acids. Notably, several of the studies found a reduction in the usage of nonsteroidal anti-inflammatory drugs (NSAID). The most recent study included was in 2015 that showed a 72% reduction versus 8.33% in the control group of concomitant analgesic drug reduction. There were no reported adverse events in these studies.

Thus, studies on omega-3 fatty acids have shown a modest favorable effect on pain in RA patients, and no adverse effects were reported in the above studies. Patients who are on anti-coagulants should discuss the use of omega-3 fatty acids with their primary medical provider.

Gamma-Linolenic Acid

GLA is an essential fatty acid found in certain plant seed oils, most commonly marketed as borage, black currant seed, and evening primrose oil preparations. It is metabolized to dihomo-gamma-linolenic acid which is the immediate precursor of prostaglandin E1, with potential for autoinflammatory and immunoregulatory properties [28].

There have been various studies throughout the 1990s in regard to the efficacy of GLA in RA patients. Two studies evaluated the effects of blackcurrant seed oil [29, 30]. One showed a significant difference in the tender joint count. The second study found morning stiffness, measured in minutes, to be statistically significantly reduced. There were nonsignificant trends to improvement in Ritchie index, pain, improved grip strength, and improved patient global assessment. Two studies evaluated borage seed oil, and both showed some differences in areas of tender joint scores as well as swollen joint counts [31, 32]. The first study had a statistically significant reduction in tender joint count and swollen joint count, and the second study showed statistically significant improvement in swollen joint count, tender joint count, duration of morning stiffness, patient global assessment, patient assessment of pain, and HAQ score compared with baseline. Two evening primrose oil studies were also completed [33, 34]. In the first, there was statistically significant reduction in morning stiffness, measured in minutes. In the second study, the results favored the intervention group for reduction in pain and NSAID use but no disease modifying effects.

Data for GLA is limited and shows a possible mild improvement in RA symptoms such as morning stiffness, tender joints, and swollen joint count. The side effect profile is low with rare side effects that are mild, but it is unknown what the long-term side effects are for GLA supplementation.

Probiotics

Probiotics are live microbiota that are used to balance the gastrointestinal microbiome by favoring beneficial bacteria and preventing colonization by pathogenic bacteria through competition for nutrients, production of inhibitory compounds, upregulation of gut mucin genes, and stimulating the immune system [35]. A reported advantage of probiotics is the regulation of immune system function by either stimulating immune function or regulating overexpressed immune responses. Animal models of arthritis have shown an improvement in clinical manifestations (clinical arthritis score was

obtained by scoring paw changes and measuring ankle thickness), reduced pro-inflammatory cytokines, and increased regulatory cytokines with the administration of probiotics [36, 37].

A 2017 systematic review and meta-analysis evaluated the therapeutic effect of probiotics on RA [38]. Six studies were included in the meta-analysis. There was no difference between probiotic group and the placebo group in terms of disease activity score (DAS). Other values such as the health assessment questionnaire (HAQ), swollen joint count (SJC), and C-reactive protein (CRP) were not different either. Four of the studies evaluated IL-6 levels and noted a significant reduction in levels in the probiotic group compared with placebo.

The current data shows that there is no efficacy of probiotics on RA symptoms. However, in people who are healthy, probiotics have a good safety record [39]. Serious complications are extremely rare but have included endocarditis, liver abscess, sepsis, and fungemia. These events occurred in elderly people with intravenous catheters and immunocompromised patients.

Thunder God Vine

Tripterygium wilfordii Hook F (TWHF), also known as thunder god vine, is native to China and is used for swelling in traditional Chinese medicine [40]. The active ingredient is unknown, but there are components thought to have immunosuppressive and anti-inflammatory properties. However, this herb can be extremely poisonous if the extract is not prepared properly.

In 2011, there was an update to a Cochrane systematic review of herbal therapies in RA including thunder god vine [41]. Three studies compared thunder god vine with placebo and one with sulfasalazine. These studies indicated improvements in some outcomes with statistically significant improvement in joint tenderness, swollen joint count, ACR20 response, and ACR50 response. However, data from these studies could not be combined due to differing interventions, comparisons, and outcomes. The reported severe adverse outcomes associated with thunder god vine included fever and aplastic anemia.

A more recent systematic review in 2018 focused solely on TWHF efficacy and safety in RA patients [42]. Compared with the control groups, TWHF preparations were noted to be more effective than treatment by conventional western medicine and Chinese medicine or placebo. Conventional western medicine included leflunomide, methotrexate, or NSAID.

A 2018 randomized, non-blinded, controlled study evaluated the impact of TWHF and methotrexate treatment on radiologic progression in active rheumatoid arthritis with a 2-year follow-up [43]. Patients were randomly allocated to three arms, TWHF, methotrexate, or a combination of the two.

They found that TWHF monotherapy was noninferior to methotrexate monotherapy in controlling disease activity. Additionally, there was no statistically significant difference in terms of radiographic progression among the groups. The most common adverse events were in regard to nausea and liver function abnormalities. Other side effects include decreased bone mineral content (with long-term use), infertility, menstrual cycle changes, rashes, diarrhea, headache, and hair loss. Although TWHF has some efficacy in RA, risks outweigh benefits for most patients given the frequency and severity of potential side effects.

Special Considerations Regarding Dietary Supplements

The FDA has warned about several dietary supplements that are marketed for arthritis and pain that are contaminated with prescription drugs [44]. These can have side effects or interact with other prescribed medications. It is important for patients to discuss any supplements or herbs they are taking in conjunction with prescription medications with their medical providers.

Body-Based Therapies

Massage

Massage therapy (MT) can also be beneficial for patients with RA and is sometimes covered by medical insurance. MT decreases stress and anxiety, which are known correlates of pain [45]. Reduction in these symptoms leads to a decrease in sympathetic activity and an increase in parasympathetic activity which could lead to pain reduction [46]. Others have proposed that mechanical pressure from MT can lead to decreased motor unit firing rates by stimulation of mechanoreceptors within muscles which thereby reduces tensions across joints affected by arthritis [47].

There was a 2013 study comparing moderate pressure or light pressure massage in 42 RA patients [48]. The patients were randomly assigned into either group and underwent massage of the affected arm and shoulder once a week for 4 weeks and were also taught self-massage to be done once daily. The moderate pressure group had less pain and perceived greater grip strength following the first and last massage sessions. At the end of the 4-week period, the moderate pressure group had less pain, greater grip strength, and greater range of motion in the wrist and large upper joints.

A systematic review published in 2017 evaluated seven randomized controlled trials that included 352 participants [49]. The quality of evidence was found to be low to moderate and was in favor of massage therapy compared with nonactive

therapies in reducing pain and improving certain functional outcomes for those with RA.

There is evidence of benefit in RA patients with moderate pressure massage. The risk of adverse effects from massage is low. According to the arthritis foundation, deep tissue massages are recommended against in some people with RA given the possibility of lingering soreness. This would be a reasonable recommendation for patients interested in mind and body approaches in their treatment plan.

Balneotherapy

Balneotherapy employs soaking in different types of mineral water compositions in thermal baths or with the application of mudpacks.

A 2016 systematic review evaluated eight RCTs using balneotherapy as an intervention [50]. They found that the majority of the studies had poor methodological quality, and therefore, it was not possible to draw sufficient evidence of the benefits of spa therapy.

Based on the current data, no conclusion can be drawn about the efficacy of this intervention. However, the safety record is good with no adverse events reported within RCTs [51].

Chiropractic Manipulation

Chiropractic manipulation entails adjustment of the spine to improve pain and mobility with more than a hundred various techniques and approaches. As noted previously, the use of chiropractic care by US adults increased from 2012 to 2017, and its use was highest in those aged 45 to 64 years old [7].

Although spinal manipulation has been shown to be somewhat helpful in chronic pain conditions such as non-inflammatory back pain [52], no RCTs evaluating chiropractic manipulation have been carried out in RA. Furthermore, the World Health Organization (WHO) has stated that joint manipulation is contraindicated in anatomic regions of RA involvement [53]. In addition, cervical spinal manipulations should not be done in RA patients given the potential of atlanto-axial joint instability and the possibility of transverse ligament rupture [54].

Mind-Body Feedback

Yoga

Yoga combines physical exercise with relaxation techniques. Originating in India, it includes physical postures, breathing techniques, and meditation in North America and Europe [55]. It has been shown to improve pain and function in a broad range of musculoskeletal disorders that include RA,

osteoarthritis, fibromyalgia, and low back pain. Additionally, practicing yoga has been found to be an acceptable and safe intervention in a range of musculoskeletal disorders including RA [56].

In 2015, an RCT evaluated the effect of integral-based hatha yoga in sedentary people with RA compared with wait-list controls [57]. Integral-based yoga synthesizes the six branches of yoga philosophy and includes yoga postures, breathing exercises, and meditation. There were significant improvements in SF-36 role physical, pain, general health, vitality, and mental health scales in the intervention group. Of all yoga participants, there is a significant improvement in physical component summary (PCS), flexibility, 6-min walk, and most SF-36 health-related quality of life. There were no associated worsening joint symptoms or adverse events with regular yoga practice. Additionally, a large-scale RCT in early RA patients receiving standard medical therapy plus yoga ($n = 83$) vs standard medical therapy alone ($n = 83$) found that the DAS28 significantly improved after 12 weeks as well as a statistically significant reduction of baseline levels of IL-1 α and cortisol [58]. Of note, baseline mean \pm standard deviations of cortisol levels were within the normal range.

A 2018 review of tai chi and yoga in RA and spondyloarthropathies [59] included eight studies evaluating the benefit of yoga in RA patients. Overall, it was felt that yoga was effective in decreasing pain and inflammation as some studies showed a reduction in inflammatory mediators (i.e., IL-6 levels) while also increasing quality of life in RA measured by HAQ and SF-36 in a majority of the studies. However, the literature was lacking in long-term studies and larger patient groups.

There are various types of yoga practices, and some are felt to be more appropriate than others for arthritis patients. The following are recommended for most arthritis patients: Anusara yoga, which is anatomically-based, with an emphasis on opening the heart; integral and Sivananda yoga, which are both gentle practices that include poses, breathing, chants, and meditation; and Iyengar yoga, which has a strong anatomical basis and uses props to individualize poses.

Tai Chi

Tai chi has been practiced in China for centuries as an art form, religious ritual, relaxation technique, exercise, and a self-defense method since the thirteenth century [60]. Various health benefits of tai chi have since been documented including stress reduction, improved agility and balance, posture control, and lower extremity strength [61–64].

A 2018 review evaluated six studies of tai chi among RA patients [59]. An increase in range of motion and physical performance was noted in some studies. However, results for quality of life outcomes were contradictory, and the strength of evidence was judged to be weak due to the

inconsistency of outcome measurements. In September 2019, an update to a 2004 Cochrane review of tai chi for RA concluded that there was uncertain effect on clinical outcomes [65]. This review included seven trials with a total of 345 participants. A high risk of bias was noted due to a lack of blinding of participants and evaluators. There was uncertain effect on joint pain, activity limitations, and function in RA. Important effects could not be confirmed or excluded since all the outcomes had very low-quality evidence. It was felt that the adverse effects were unlikely, but the included studies failed to report such events. This updated review had minimal change in their conclusions as compared with 2004.

The current evidence has shown uncertain effect on clinical outcomes in RA patients. Again, the risk of adverse events is low with this therapy, and there has been no evidence that it makes RA symptoms worse. Traditional forms of tai chi would likely have to be adapted for safe participation by RA patients.

Mindfulness Meditation

Mindfulness is defined as a heightened attention to and awareness of one's present experience or the current moment without judgment [66]. It has been applied to psychological health issues including pain in the West since the 1970s [67].

A 2018 systematic review and meta-analysis evaluated mindfulness-based interventions for RA [68]. This included five trials and a post hoc analysis including 399 participants. The mindfulness techniques included in the analysis were mindfulness-based stress reduction (MBSR), vitality training program (VTP), internal family systems (IFS), and mindful awareness and acceptance therapy (MAAT). They concluded that based on limited evidence, mindfulness-based interventions may be effective for improving patient-reported outcomes and emotional disturbances related to RA.

More recently, evidence is emerging regarding the benefits of mindfulness meditation through smartphone-based applications. These findings show evidence for an association between immediate and long-term use of guided meditation applications and an improved emotional state [69].

For RA patients who engage in mindfulness, there is evidence for improvement in subjective symptoms such as pain and improved ability to cope with illness [70]. There are no significant adverse effects associated with this approach.

Relaxation Techniques

Relaxation response was coined by Dr. Herbert Benson and is meant to counter the stress or "fight or flight" response and thereby mitigate the effects of chronic stress by slow breathing, relaxing muscles, and reducing blood pressure [71]. These can be done with a variety of different methods including meditation.

A 2010 RCT evaluated cognitive behavioral therapy (CBT), relaxation response training, or arthritis education to assess their benefits in RA patients [72]. The relaxation response sessions consisted of diaphragmatic breathing, progressive muscle relaxation, and generalization of relaxation response skills to symptoms management. There was a significant improvement in pain among the relaxation response group at 12 months. Notably, depression and anxiety did not improve with any of the interventions.

There is only a small amount of literature regarding this technique, and no formal conclusions can be made. However, the risk of adverse events is low with this approach.

Special Diets

The Mediterranean diet has been regarded as a healthy and disease-preventing diet [73]. It is characterized by the high consumption of fruit, vegetables, cereals, and legumes. The primary source of fat is olive oil, and there is an emphasis on fish over red meat. A 2003 randomized, parallel study evaluated a Mediterranean diet versus a control diet in 56 patients [74]. The intervention group had a statistically significant difference in their DAS28 (28 joint count disease activity score) and HAQ score. Mediterranean diet patients also reported an increase in vitality that was significant. There were no differences in the control group. These differences became apparent in the second half of the 12-week trial.

Intermittent fasting is a more recently popularized diet that is characterized by either alternate-day fasting or daily time-restricted eating [75]. Animal models have shown that the lifespan can be increased significantly with this intervention. Clinical studies have been short term and have not shown the same benefits as animal models, but there were improvements in obesity, insulin resistance, dyslipidemia, hypertension, and inflammation. There is also evidence supporting its use in RA patients [76, 77, 78].

Conclusions

There is a high prevalence of CAM use among RA patients, and this will likely continue to increase in the future. Because of this and patient reluctance in reporting usage, it is important to understand the safety and efficacy of individual therapies in order to make educated recommendations to our patients especially given the potential side effects and interactions with conventional therapies. It is important to be able to provide evidence-based education material on CAMs to our patients and to acknowledge the current limitations in scientific evidence. It is also important for providers to acknowledge the role of chronic illness and pain contributing to stress, anxiety, and depression among our patients. Thus CAMs, such as

mind-body therapies, could be a helpful adjunct in stress management.

Funding Information Dr. DiRenzo is supported by the Jerome L. Greene Foundation.

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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