AHC Media

Integrative Medicine

Evidence-based summaries and critical reviews on the latest developments in integrative therapies [ALERT]

Vol. 18, Issue 7, July 2015
www.AHCMedia.com

FIBROMYALGIA

Integrative Therapies for Fibromyalgia – What News?

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Dr. Selfridge reports no financial relationships relevant to this field of study.

Although fibromyalgia (FM) remains a challenging management problem in clinical medicine, significant progress has been made in the last 5 years in terms of identifying underlying neurobiological abnormalities, which may one day elucidate the pathophysiology of the disorder. Diagnostic criteria continue to be refined and debated. Wolfe's 2010 preliminary criteria were modified in 2011 (2011modcr).[1] These modified criteria have been validated repeatedly, and Bennett et al recently formulated a set of alternative criteria that compare favorably with the 2011modcr tool.[2] Both have demonstrated excellent sensitivity and specificity compared to the "gold standard" 1990 American College of Rheumatology (ACR) criteria. Both are also better suited for identifying patients for clinical and epidemiological research. They can be administered via patient survey and do not require a tender point count, which was difficult for physicians to perform reliably. Although these newer tools can be helpful in identifying patients with fibromyalgia, both Wolf and Bennett stress that an accurate clinical diagnosis should never be made on the basis of these sets of criteria alone. Patients deserve a thorough medical history and physical examination, a process that also forms the foundation of relationship-centered care. The three sets of diagnostic criteria are compared in Table 1.[2,3,4,5]

PATHOPHYSIOLOGY

The past 5 years have yielded a plethora of translational research concerning neurobiological mechanisms of chronic pain. The underlying pathology of FM is now acknowledged to be central pain sensitization, and many abnormalities in functional connectivity have been documented in areas of the brain associated with pain processing.[6-11] Of particular interest is the fact

Financial Disclosure: *Integrative Medicine Alert*'s executive editor David Kiefer, MD, reports he is a consultant for WebMD. Peer reviewer J. Adam Rindfleisch, MD, MPhil, AHC Media executive editor Leslie Coplin, and associate managing editor Jonathan Springston report no financial relationships relevant to this field of study.

Integrative Medicine [ALERT]

Integrative Medicine Alert,
Integrative Medicine Alert (ISSN 1096-942X) is published monthly by AHC Media LLC, One Atlanta Plaza, 950 East Paces Ferry Road NE, Suite 2850, Atlanta, GA 30326.

Periodicals Postage Paid at Atlanta, GA, and at additional mailing offices.

GST Registration Number: R128870672.
POSTMASTER: Send address changes to *Integrative Medicine Alert*, P.O. Box 550669, Atlanta, GA 30355.

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Summary Points

- Fibromyalgia diagnosis may be aided by newer criteria screening tools, but accurate diagnosis continues to require a thorough clinical evaluation beginning with a medical history and physical examination.
- Multiple neurobiological, endocrine, and immunologic abnormalities have been documented in fibromyalgia patients, indicating that it is not merely a psychological or psychosomatic disorder.
- Integrative interventions with best evidence of efficacy in systematic reviews are alternative exercise, hydrotherapy and balneotherapy, massage therapies, and repetitive transcranial magnetic stimulation. Treatment plans must be highly individualized and balance efficacy with safety, cost, accessibility, and patient preference.

that many of these areas have also been associated with difficult emotional states and emotional regulation (amygdala, anterior cingulate cortex, hippocampus). Thus, we have some rudimentary explanations for observations that FM patients often struggle with the affective dimensions of their pain condition, even when they are not co-morbidly depressed. In about 20% of FM patients, there is biopsy evidence of small fiber neuropathy.[12] Although routine biopsy is not considered standard care, clinicians would be wise to follow the evolution of clinical guidelines for changes concerning FM assessment in this regard.

Multiple neuroendocrine and immunological abnormalities have been reported in FM.[13-20] Although the precise etiology and pathophysiologic mechanism of FM remains obscure, there is currently so much evidence supporting neurobiological and hormonal derangements in FM patients that it is no longer tenable for physicians to be dismissive of FM as a "real" condition or to believe that it is of purely psychological origins. A 2010 survey of Canadian primary care physicians and specialists found that 23% and 12% of these practitioners, respectively, characterized FM patients as malingers.[21] Patients experience these attitudes as invalidating, and these messages generate mistrust; invalidation by and mistrust in the physician are associated with poorer quality of life for patients.[22] Table 2 provides examples of some of the pathological findings recently discovered in FM patients.

FM MANAGEMENT

As no single intervention is effective for all FM patients, treatment plans are best tailored to individual patients based on preferences and responses to treatments. Mainstays of conventional therapy include treatment of comorbid depression (present in up to 30% of patients) and disordered sleep, regular exercise, and judicious trials of medications, starting with a tricyclic agent and progressing to serotonin and norepinephrine reuptake inhibitors and anticonvulsants, some of which have been shown to be beneficial for managing FM symptoms. Medication efficacy is disappointing: 50% of patients improve by 30%.[3,23] Although statistically better than placebo, side effects from pharmacotherapy are common and any improvement in FM symptoms must be weighed against side effects causing reduced quality of life. Thus, prescription medication is not absolutely necessary to manage FM; non-pharmacological therapies, including some integrative medicine modalities, can work as well or better.[24] Recent research on integrative modalities will be reviewed here, focusing on systematic reviews and meta-analyses.

NUTRITION, SUPPLEMENTS, AND BOTANICALS

In a recent systematic review of FM and nutrition, no single dietary intervention has been shown to be consistently effective for FM symptoms. However, patients with FM who are obese have more severe symptoms and lower quality of life; weight loss through energy-restricted diet and bariatric surgery have resulted in improvement in symptoms and quality of life.[25] No nutritional supplements or botanicals show consistent strong evidence of efficacy for improving FM symptoms. However, FM patients have been shown in some studies to have evidence of

Table 1: A Comparison of Fibromyalgia Diagnostic Criteria

	1990 ACR Criteria	2011 Modified Criteria	2013 Alternative Criteria
Assessment of tender areas	18 tender points assessed on physical exam by physician	WPI score (0-19): report of pain or tenderness at 19 different sites for > 3 months	PLI score (0-28): pain at 28 different sites for > 3 months
Assessment of key symptoms	Widespread pain > 3 months duration	SSS score (0-12): Sleep, fatigue, and cognition scored for severity (1-3) over past week; headache, depression, and abdominal pain scored for presence or absence (0-1) over past 6 months	SIQR score (0-50): Pain, energy, stiffness, sleep, depression, anxiety, memory problems tenderness to touch, balance, and environmental sensitivity all scored for severity (0-10) and total divided by 2
Source of data	Physician assessment	Patient survey	Patient survey
Qualifying criteria: FM likely§	History of widespread pain > 3 months' duration and 11/18 tender points on physical examination	WPI > 7; SSS ≥ 5 or WPI 3-6; SSS ≥ 9 or WPI + SSS ≥ 13	PLI ≥ 17; SIQR ≥ 21 or PLI + SIQR ≥ 44
Performance	Sensitivity 84.4% Specificity 81.1%	Sensitivity 83% Specificity 67%	Sensitivity 81% Specificity 80%

§For accurate clinical diagnosis, full clinical assessment is necessary to ensure that symptoms cannot be fully explained by another co-existing condition
WPI: Widespread Pain Index; SSS: Symptom Severity Score; PLI: Pain Location Inventory; SIQR: Revised Symptom Impact Questionnaire

increased oxidative stress, suggesting that investigating the impact of nutritional antioxidant strategies on FM symptoms would be valuable. Although research evidence is inconclusive, some studies suggest that gluten avoidance may be beneficial. Similarly, avoidance of excitotoxins (aspartame, monosodium glutamate) has demonstrated mixed results. These two dietary strategies require additional research to ascertain their efficacy in improving FM symptoms.

ALTERNATIVE EXERCISE

Although aerobic exercise is considered an essential component of FM treatment and has consistently shown sustained benefit for FM symptoms, studies have been plagued by high attrition. About 80% of research on exercise for FM has explored aerobic or mixed conventional exercise programs.[26] Patients often experience severe post-exercise pain even when exercise is appropriate for fitness level, likely manifestations of impaired growth hormone secretion and abnormal inflammatory mediator response noted in research. This is a significant management challenge facing the clinician trying to write an exercise prescription for the FM patient. Thus, alternative forms of exercise might be uniquely beneficial for this population.

Bidonde et al evaluated the efficacy of aquatic exercise for FM for a Cochrane review.[27] Sixteen studies involving 881 patients were included for analysis, and authors cited lack of confidence in outcomes due to poor study design and methodological flaws. Compared to non-exercising controls, aquatic exercisers reported improvements in multidimensional function (mean difference [MD] -5.97; 95% confidence interval [CI], -9.06 to -2.88); pain (MD -6.59; 95% CI, -10.71 to -2.48); and stiffness (MD -18.34; 95% CI, -35.75 to -0.93). Muscle strength improved, on average, to 0.63 standard deviations higher than the control group, a moderate effect size. Only stiffness and muscle strength met the 15% improvement threshold for clinical significance. Aquatic exercise compared favorably to land-based programs in five studies with no statistical differences in improvements in pain, stiffness, multidimensional function, or cardiorespiratory function. However, land-based programs resulted in slightly greater muscle strength measurements. None of the outcomes of either type of exercise reached the 15% threshold for clinical significance. Dropout rates were the same for both types of exercise programs.

Alternative forms of exercise were the subject of a recent review by Mist et al.[28] Sixteen studies of 832 participants were included in their meta-analysis. Interventions included yoga, tai chi, Qigong, Pilates, Biodanza, and a "body movement and perception" intervention. Several of these studies had no control group. The dropout rate was 81%, but when a control group was present, dropout rate in the treatment group did not differ from dropout rate in the control group. Study strength was considered moderately low by Jadad and modified Jadad scores. In the meta-analysis of study results, standard difference in means (effect size) was moderate to high at

Table 2: Examples of Pathological Findings in Fibromyalgia Patients

Neurophysiological
- Reduced levels of hippocampal n-acetyl aspartate
- Elevated levels of glutamate:
  - posterior insula
  - amygdala,
  - posterior cingulate
  - ventral lateral prefrontal cortex
- Reduced levels of GABA
  - Anterior insula
- Altered functional connectivity between
  - Insula
  - DMN€
  - EAN§
- Reduced resting connectivity within somatosensory cortex
- Increased functional connectivity between
  - Somatosensory cortex
  - DMN€
- Small fiber neuropathy (20%)

Neuroendocrine
- Elevated CSF substance P
- Impaired growth hormone secretion in response to exercise
- Excessive sympathetic autonomic tone
- Reduced IGF-1 levels

Immunologic
- Elevated CFS Interleukin-8
- Altered lymphocyte corticosteroid receptors
- Decreased T cell activation marker expression

0.84 and standard error was 0.07, statistically significant positive outcomes for alternative exercise studies reviewed ($P = 0.00$). No significant adverse events were noted in any of these studies.

ACUPUNCTURE

Acupuncture was the subject of a systematic review by Deare et al for the Cochrane database.[29] Nine randomized, controlled trials were included, three using electroacupuncture and six using manual acupuncture (n = 395). All studies used "formula acupuncture" (a standard set of acupoints stimulated for each patient) except for one that used trigger points. Study quality was hampered by biases (selective reporting, attrition, performance, and detection), small sample sizes, and methodological flaws. Authors concluded from the pooled data that there is low to moderate level evidence that acupuncture improves pain compared with no treatment (MD, -22.40 points on a 100-point scale; 95% CI, -40.98 to -3.82; $P = 0.02$) or standard therapy (MD, -17.30 points on a 100-point scale; 95% CI, -24.13 to -10.47; $P < 0.00001$). Moderate level evidence suggests that acupuncture is no better than sham acupuncture in improving pain, fatigue, sleep, or overall well-being. Electroacupuncture showed slight nonsignificant improvement over manual acupuncture for all symptom outcomes reported. Limited evidence from two studies suggests that effects are not sustained. Acupuncture appears to be a safe, low-risk intervention. A different review on traditional Chinese medicine arrived at similar conclusions about acupuncture.[30]

BODY AWARENESS INTERVENTIONS

Courtois et al reviewed the efficacy of body awareness interventions for FM and for chronic fatigue syndrome, believed by some to be a similar clinical entity.[31] Of 29 studies meeting inclusion criteria included in the review, after reviewing reported data for completeness or usefulness, only eight were included in the meta-analysis. Interventions in these 29 studies were heterogeneous and included meditation, movement therapies, massage and other manual therapies, hypnotherapy, and breathing exercises. In some studies, the control intervention could be argued to increase body awareness (yoga, progressive relaxation, massage). Only one of the studies reported body awareness as an outcome, limiting interpretation for the others that body awareness is the factor in these interventions that is correlated with clinical symptom outcomes. The heterogeneity of the studies, hampered by small sample sizes and methodological flaws, limits applicability to clinical practice decision-making, although the authors concluded that body awareness interventions appear to have an overall positive effect on pain and quality-of-life measures.

MASSAGE

In a 2015 systematic review and meta-analysis by Yuan et al, 10 randomized and non-randomized controlled trials were included.[32] The six massage interventions included Swedish massage, manual lymphatic drainage, myofascial release, shiatsu, connective tissue massage, and combination technique massage. Strong evidence does not exist to support any form of massage for FM symptoms. Moderate to low evidence supports all styles of massage reviewed for improving FM pain and quality of life except for Swedish massage. Myofascial release appeared to have the best evidence of efficacy for multiple symptom outcomes. The studies reviewed were again hampered by small sample size, design, and methodological flaws, which, along with the small number of studies, limit confidence in these results for clinical application and decision making. However, massage is a low-risk intervention and is widely accessible.

MIND-BODY THERAPIES

Theadom et al conducted a review and analysis of mind-body therapies for the Cochrane database.[33] Sixty-one randomized, controlled trials with 4234 participants were included. Interventions assessed included psychological therapies, biofeedback, mindfulness, movement therapies, and relaxation. Quality of studies was low or very low and analysis was hampered by small numbers of trials for each intervention and by wide heterogeneity in the use

of outcome measures. Authors concluded that current research only supports psychological therapies as effective for improving pain, physical functioning, and mood.

SPA THERAPY

Spa therapy efficacy for FM symptoms was reviewed by Guidelli et al in 2012.[34] Spa therapy studies encompassed not only thermal mineral baths (balneotherapy), but also mud packs, massage, relaxation, and exercise therapies. In this review, studies were of low sample size, and the trials were hampered by design and methodology flaws, such as absence of double-blinding and failure to include intention-to-treat analysis. Further, the high heterogeneity of the treatment programs and differences in the study populations made it difficult to compare studies. However, balneotherapy appeared to have lasting positive effects on FM pain and quality of life, although the authors felt that definitive conclusions were not possible.

A meta-analysis and review of balneotherapy and hydrotherapy (treatments with normal tap water) interventions in 2014 attempted to isolate the effects of these therapies for FM symptoms.[35] For hydrotherapies, there was moderate-to-strong evidence for a small reduction in pain (effect size -0.42; 95% CI, -0.61 to -0.24; $P < 0.00001$; $I^2 = 0\%$) and moderate-to-strong evidence for a small improvement in health-related quality of life at the end of treatment (effect size -0.40; 95% CI, -0.62 to -0.18; $P = 0.0004$). Heterogeneity in these study analyses, as measured by I^2 calculation, was low (0-15%). Five studies (n = 177) on balneotherapy showed moderate evidence for a medium-to-large size reduction in pain (effect size, -0.84; 95% CI, -1.36 to -0.31; $P = 0.002$). I^2 analysis indicated moderate heterogeneity in these studies for this outcome. Moderate evidence was demonstrated for a medium improvement of health-related quality of life (effect size -0.78; 95% CI, -1.13 to -0.43]; $P < 0.0001$) with low calculated heterogeneity. The improvements for pain were maintained at 3- to 6-month follow-up, though with smaller effects.

OTHER THERAPIES

Repetitive transcranial magnetic stimulation (rTMS) was the subject of two recent reviews. This intervention involves the use of an electromagnetic field generator on the scalp to stimulate neurons in deeper brain regions with the small electrical currents produced. Galhardoni et al evaluated rTMS for several chronic pain conditions in a descriptive review of 33 randomized trials (n = 843, 166 of whom had FM).[36] The FM studies all involved multiple rTMS sessions for patients and were double-blind, placebo-controlled or sham-controlled trials. Several positive outcomes were described: reductions in daily pain, improvement in quality of life, and improvement in cognition as measured by neuropsychiatric testing. One study found that positive outcomes were associated with regional brain metabolic changes.

Table 3: Integrative Modalities Demonstrating at Least Moderate Positive Effect on FM Symptoms

Intervention	Symptom Improvement
Balneotherapy and hydrotherapy	Pain and quality of life
Massage (all styles except Swedish)	Pain and quality of life
Repetitive transcranial magnetic stimulation (rTMS)	Pain and quality of life
Alternative exercise (e.g., Tai Chi, Yoga, Pilates)	Multiple symptoms

Knijnik et al performed a meta-analysis on five studies reported on FM, which they determined were of moderate to high quality and which included four of the studies reviewed by Galhardoni above.[37] Results of their analysis indicated that rTMS improved quality of life with a moderate effect size (pooled SMD = 0.472; 95% CI, 0.80-0.14). There was a trend toward reducing pain intensity, again with a moderate effect size (SMD = 0.64; 95% CI, 0.31-0.017). Depressive symptoms were not affected.

In a review of cannabinoids for the treatment of non-cancer pain, Lynch and Campbell found one randomized, placebo-controlled trial of nabilone (a synthetic cannabinoid) for FM that met inclusion criteria. This study reported statistically significant reductions in visual analog scale for pain ratings ($P < 0.02$) and improvements in the fibromyalgia impact questionnaire ($P < 0.02$) and anxiety ($P < 0.02$).[38] Many side effects were reported. Further, nabilone can have toxic effects when abused. Another study compared FM cannabis users (n = 28) to non-users (n = 28) and noted improvement in pain scores, increased relaxation, and increased sense of well-being in cannabis users ($P < 0.001$).[39] Because of the recent increase in states legalizing cannabis for medical and recreational use, patients may ask about these potential treatments.

CONCLUSIONS AND RECOMMENDATIONS

Confident interpretation of research on complementary and alternative interventions for FM is still hampered by the overall low amount and quality of research. Based on recent reviews, the following therapies have demonstrated at least moderate positive effect on FM symptoms: balneotherapy and hydrotherapy for pain and quality of life, rTMS for pain and quality of life, massage (all styles studied except for Swedish) for pain and quality of life, and alternative exercise for multiple symptoms

(*see Table 3*). All of these interventions are low risk. No optimum treatment protocols have been developed for any of these interventions for FM. Repetitive transcranial magnetic stimulation is costly ($6000-$10,000 for a 4- to 6-week treatment regimen). Patients should be encouraged to exercise and may try alternative exercise forms such as Tai Chi and yoga, which are accessible in terms of availability and cost. Patients with access to mineral springs can be encouraged to try balneotherapy. Massage is also widely accessible; many massage schools offer discounts to clients to allow their students sufficient practice toward certification, thus making this intervention less costly for patients. Acupuncture remains a popular and commonly used intervention for patients with chronic pain, including fibromyalgia. Despite the lack of evidence of efficacy, patients may wish to try a short series of treatments to assess their own individual response. In the end, however, we will have to await more and higher quality research on both conventional and alternative treatments, and patient treatment plans will have to remain highly individualized, consisting of trials of multiple modalities, balancing evidence of efficacy and safety, to arrive at optimum management of symptoms. ■

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ABSTRACT & COMMENTARY

Spiritual Interventions for Patients with Cancer

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Dr. Pantuso reports no financial relationships relevant to this field of study.

SYNOPSIS: A systematic meta-analysis investigating the effects of spiritual intervention in patients with cancer found that spiritual interventions had significant moderate effects on spiritual well-being, meaning of life, and depression.

SOURCE: Oh PJ, Kim SH. The effects of spiritual interventions in patients with cancer: A meta-analysis. *Oncol Nurs Forum* 2014;41:E290-E301.

To evaluate the effects of spiritual interventions in patients with cancer, the authors performed a meta-analysis that included 15 studies and 889 patients. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was used as a guide for the systematic review. The participants, interventions, controls, outcomes, and studies (PICOS) framework was followed to determine which studies were eligible. Participants were 18 years or older and had a diagnosis of any type of tumor at any stage with any type of treatment and any time since diagnosis.

Summary Points

- Spirituality is related to better quality of life, lower anxiety, and depression.
- Spiritual interventions demonstrated statistically significant effects on spiritual well-being, meaning of life, and depression in patients with cancer.

Spiritual interventions were defined as having two components: 1) religious, which was defined as achieving harmony with God, and 2) existential aspects, such as finding meaning and purpose in one's life. Spiritual interventions could occur in a number of different formats, including Internet-based modalities, telephone, individual, or group types. The primary outcomes measured were spiritual well-being and meaning of life. Secondary outcomes included measures of psychological distress, including levels depression and anxiety.

Randomized controlled trials (RCTs) and non-RCTs were included. Studies where an effect size could not be calculated were excluded. Statistical analysis was performed using the Cochrane Review Manager and RevMan Analyses software.

Of the 15 studies, eight studies were conducted in Korea, five studies were conducted in the United States, one study was conducted in Canada, and one in Hong Kong. Seven studies were RCTs and eight studies, which were the Korean studies, were non-RCT. Eleven of the studies analyzed were conducted in a mixed cancer diagnosis population (*see Table 1*). The range of participant numbers in studies was from 23-118 and the duration of the studies ranged from 2 days to 16 weeks (*see Table 2*).

Ten of the studies applied religious interventions and five applied existential interventions. One of the existential interventions was logotherapy, a technique developed by Viktor Frankl that is rooted in the belief that the search for meaning in life is a motivational force. The most frequent format was an individual approach, although one study combined individual and group approaches (*see Table 3*). Nurses were the most frequent intervention providers (n = 10), followed by clinical psychologists (n = 4), dieticians (n = 1), and oncologists (n = 1).

Table 1: Cancer Diagnoses in the Analyzed Studies

Populations of patients	Eleven studies were in a mixed cancer diagnosis population	Two of the studies were in gynecologic cancer populations	One study was in breast cancer patients	One study was in melanoma patients

Table 2: Range and Mean of Participant Number, Duration, and Sessions in Studies Analyzed

	Range	Mean
Participant number in studies	23-118	59
Duration of study	2 days to 16 weeks	6.4 weeks
Number of sessions	1-12 sessions	7 sessions
Time per session	15-60 minutes	46.3 minutes

Fourteen of the 15 studies had a control condition, while one study compared the spiritual intervention to secular meditation. Usual care control groups were the most common (n = 12). Counseling for weight loss (n = 1), therapeutic massage (n = 1), and supportive group psychotherapy (n = 1) were the other control groups used in three studies.

Eight studies evaluated spiritual well-being as a primary outcome and six studies evaluated meaning of life as a primary outcome using various assessment tools (*see Table 4*). Depression and anxiety were measured as secondary outcomes for this review and also used various assessments (*see Table 4*). There was a large amount of heterogeneity with an I^2 range between 65-87%.

The weighted average effect size for spiritual well-being (n = 8) was d = -0.48 (95% confidence interval [CI], -0.82 to -0.14) with $P = 0.006$ and $I^2 = 65\%$, which the authors consider a significant moderate effect size (*see Table 5*). The meaning of life (n = 6) weighted average effect size d = -0.58, (95% CI, -1.05 to -0.11; $P = 0.02$; $I^2 = 70\%$) (*see Table 4*). For anxiety (n = 6), the weighted average effect size was d = -0.87, (95% CI, -1.59 to -0.16; $P = 0.02$; $I^2 = 87\%$) (*see Table 5*). The weighted average effect size for depression (n = 9) was moderate (d = -0.62; 95% CI, -1 to -0.25; $P = 0.001$; $I^2 = 73\%$) (*see Table 4*). The authors considered a Cohen's d of 0.2 as a small effect size, 0.5 was medium and 0.8 was large, and the –d is the direction of the effect of the intervention.

To assess for publication bias, the authors used funnel plot analysis, which demonstrated no evidence of publication bias for anxiety and depression; however, there was uneven distribution with meaning of life and spiritual well-being.

In the studies that applied religious interventions, a significant moderate-to-large effect on spiritual well-being and depression was found. This subgroup was highly heterogeneous, although existential intervention demonstrated significant and moderate effects on meaning of life and significant and small effect on anxiety.

Table 3: Intervention Used and Number of Studies

Type of Intervention	Intervention Used	Number of Studies
Spiritual intervention	Spiritual nursing care	7
	Spiritual counseling	1
	Oncologist-assisted spiritual intervention	1
	Spiritually focused meditation	1
Existential intervention	Meaning-centered psychotherapy	2
	Meaning-of-life intervention	1
	Meaning-making intervention	1
	Logotherapy-based resilience promotion program	1

The authors also looked at intervention length and found that studies with an intervention length of seven sessions showed a significant moderate-to-large effect on all study outcomes, except for meaning of life. Study intervention of less than seven sessions only showed a significant effect on depression.

The authors concluded from the results that spiritual interventions delivered with an individual approach in more than seven sessions in oncology patients may have beneficial effects on meaning of life, spiritual well-being, and depression.

■ COMMENTARY

This meta-analysis adds additional support for the benefit of spiritual interventions in oncology patients. This study indicated that spiritual interventions in cancer patients have an effect on spiritual well-being, meaning of life, and depression. One of the core domains for cancer patients in their quality of life is spirituality, and a lack of spiritual well-being can decrease the coping ability of the patient.[1-4] Increasing coping ability allows for improvement in psychosocial outcomes and may have various impacts on a patient's life both during and after treatment.[1-4] Spiritual care has been associated with fewer aggressive medical interventions, higher satisfaction with care, and improved quality of life among patients.[4] As reviewed in a recent *Integrative Medicine Alert* issue, spiritual needs cross over to people from all backgrounds, such as Latinas undergoing chemotherapy.[5]

There are a number of limitations to this study. Only 14 of the total 15 studies were controlled; seven used an RCT design while eight were not RCTs. The assessments that were used to assess spiritual well-being, meaning

Table 4: Assessment Tools Used to Evaluate Outcomes in Analyzed Studies

Outcome	Assessment Tools Used
Spiritual well-being measured in eight studies	Paloutzian and Ellison's conceptualization of spiritual well being (n = 3), the Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being (FACIT-SWB) scale (n = 2), FACIT-Spiritual (FACIT-Sp) subscale (n = 2), and the World Health Organization Quality of Life (WHOQOL) spiritual subscale (n = 1)
Meaning of life measured in six studies	FACIT-Sp meaning subscale (n = 1), the Quality of Life Concerns in the End of Life (QOLC-E) scale (n = 1), the Purpose in Life (PIL) scale (n = 1), the Life Orienetation Test (LOT) scale (n = 1), Crumbaugh's scale (n = 1), and the existential subscale from the McGill Quality of Life (MQOL) questionnaire (n = 1)
Depression measured in nine studies	Hospital Anxiety and Depression Scale (HADS) (n = 3), Zung's Depression Inventory (n = 2), the Center for Epidemiological Studies-Depression (CES-D) scale (n = 2), Symptom Checklist-90 revised (SCL-90R) (n=1), and Brief Symptom Inventory Depression (BSID) subscale (n = 1)
Anxiety measured in six studies	HADS (n = 3), SCL-90R (n = 1), and the State Trait Anxiety Inventory (STAI) (n = 2).

Table 5: Effect Sizes of Spiritual Interventions

Outcomes	Effect Sizes of Spiritual Interventions Standard Mean Difference = d (95% CI)
Spiritual well-being	-0.48 (0.082 to -0.14) *P* = 0.006*
Meaning of life	-0.58 (-1.05 to -0.11) *P* = 0.02*
Anxiety	-0.87 (-1.59 to -0.16) *P* = 0.02*
Depression	-0.62 (-1 to -0.25) *P* = 0.001*
*Statistically significant	

of life, depression, and anxiety were varied and not measured in all of the studies (*see Table 3*). The authors declare that the "evidence remains weak because of the mixed study design and substantial heterogeneity." The authors also investigated subgroup analysis that was not hypothesis driven, and these results are quite heterogeneous, making the results questionable.

Spiritual care is not commonly provided to cancer patients. In one study, 72% of patients with advanced cancer reported their spiritual needs were not adequately met.[4] The most frequent type of spiritual care is encouraging or affirming beliefs, which can begin with a spiritual history being taken in an initial evaluation.[4] Spiritual histories are infrequently taken by nurses and doctors, with one study reporting that only 10% of patients being asked to give a spiritual history.[4] Both spiritual history taking and chaplaincy referrals are underused.[4] In a number of studies, nurses are believed to be the provider responsible for spiritual counseling; however, studies have shown that nurses are unable to routinely provide this care within the current system.[2]

More quality research is required to understand how spiritual and or meaning-of-life interventions exert effects on quality of life and coping ability in patients dealing with cancer.[1-4] Understanding how to best implement these interventions into a patient's treatment will also require more research.

This study adds evidence that spiritual counseling increases quality of life and that discussing spiritual care with oncology patients has other important outcomes. ■

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SHORT REPORT

Sustainable 25(OH)D Levels? Choose Vitamin D3 over D2

By Donald Brown, ND

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Dr. Brown reports he is a retained consultant for Nature's Way.

SOURCE: Oliveri B, et al. Vitamin D3 seems more appropriate than D2 to sustain adequate levels of 25OHD: A pharmacokinetic approach. *Eur J Clin Nutr* 2015;doi:10.1038/ejcn.2015.16. [Epub ahead of print].

Completed by researchers in Buenos Aires, this single-blind, placebo-controlled, randomized study looked at both the short-term effect of a loading dose of either vitamin D3 or vitamin D2 on serum 25-hydroxycholecalciferol (25-hydroxyvitamin D [25(OH)D]) levels, as well as the effect of a smaller daily dose on 25(OH)D levels both during and after supplementation. Completed during the winter months in Buenos Aires, the study included 33 healthy volunteers, who were 24-46 years of age and had limited sun exposure (< 8 hrs/week). Following screening, subjects were randomized at baseline to a single loading dose of 100,000 IU of either D3 or D2 or a placebo. Vitamin D and placebo were delivered in oral drops. From days 7 to 20, subjects received either 4800 IU/day of D3 or D2 or placebo (all in liquid drops). From days 21 to 77, subjects stopped taking the oral supplements, and this period was used to evaluate the elimination phase. All subjects received an oral dose of 500 mg/day of calcium carbonate throughout the study. Fasting blood samples were collected at baseline (prior to the loading dose) and at days 3, 7, 14, 21, 35, 49, 63, and 77. Two-hour urine fasting samples were collected at baseline and at days 7, 21, and 77. Serum calcium and urinary calcium and creatinine were measured at baseline and days 7 and 21 to evaluate the safety of the loading dose and daily doses.

At baseline, the three groups had similarly low vitamin D intake from the diet (placebo group, 3.2 ± 2.0 mcg/day; 3.4 ± 2.0 mcg/d in the D3 group; and 4.3 ± 2.0 mcg/d in the D2 group). Fifteen subjects presented with 25(OH) D levels < 20 ng/mL and another 15 with levels 20-30 ng/dL. Only three subjects had 25(OH)D levels ≥ 30 ng/dL. After the loading dose of 100,000 IU, the 25(OH)D levels of both vitamin D groups had a rapid and similar rise that persisted to day 7 (D2, 36.6 ± 11.0 ng/mL; D3, 41.0 ± 4.9 ng/mL). The geometric mean of C_{max} was analyzed during the course of the study and the area under the curve (AUC) was for days 7 to 77 (based on the equivalent 25(OH)D levels in the vitamin D groups after the loading dose). The D3 AUC was 28.6% higher than the D2 AUC and both vitamin D groups were statistically significantly higher than placebo ($P < 0.04$ for D3 and $P < 0.01$ for D2). At day 77 (after 56 days of no supplementation), 25(OH)D levels in the D2 group were significantly lower compared to the D3 group (23.6 ng/mL vs 33.4 ng/mL, $P < 0.04$) and closer to those for the placebo group (22.5 ng/mL). Taking into account the presence of vitamin D independent of the loading dose, it was estimated that the elimination half-lives were 33 days of D2 and 82 days for D3. There were no reported treatment-related adverse events and no subject had hypercalciuria or hypercalcemia.

Summary Points

- Compared to vitamin D2, daily supplementation with vitamin D3 appears to sustain serum 25(OH)D levels even after discontinuation of supplementation in healthy adults.

The debate about the merits of vitamin D3 and D2 have largely landed on D3 as the preferred form of vitamin D for daily supplementation. This interesting study suggests that both forms are adequate to raise 25(OH) D levels when given in a large loading dose. However, the value of the study lies in evaluating which form has a more sustained effect on serum 25(OH)D when taken daily — in this case for 14 days — and what 25(OH)D levels look like after supplementation has been stopped. The results of the trial suggest that even 56 days after ceasing supplementation, vitamin D3 appears to be far superior in maintaining 25(OH)D levels above 32 ng/mL compared to vitamin D2. The 4800 IU/day dose is similar to the 4000 IU/day dose reported by Heaney and colleagues to maintain this level of 25(OH)D in young adults.[1] Finally, the results support the conclusions of a

2012 meta-analysis that showed a higher response to D3 compared to D2 in terms of increase and maintenance of 25(OH)D levels.[2] ■

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DIGESTIVE DISORDERS

SHORT REPORT

Prevention of Proton Pump Inhibitor-induced Bowel Symptoms with Probiotics

By Donald Brown, ND

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Dr. Brown reports he is a retained consultant for Nature's Way.

SOURCE: Compare D, et al. *Lactobacillus paracasei* F19 versus placebo for the prevention of proton pump inhibitor-induced bowel symptoms: A randomized clinical trial. *Digestive Liver Dis* 2015;47:273-279.

Proton pump inhibitors (PPIs) have been reported in some but not all studies to cause small intestine bacterial overgrowth[1] that may result in symptoms such as diarrhea, abdominal pain, and bloating. This randomized, double-blind, placebo-controlled trial included subjects ages 18 to 70 years with gastroesophageal reflux disease lasting more than 6 months and occurring at least three times weekly. Exclusion criteria included the use of PPIs or H2-antagonists for at least 2 consecutive weeks in the prior 3 months and the use of antibiotics or probiotics in the 4 weeks before the study.

Summary Points

- The administration of a *Lactobacillus paracasei* strain (F19) twice daily and 3 times per week for 6 months appears to reduce the incidence of bowel symptoms (bloating and flatulence) and reduce changes in bowel habits (increased stool frequency and loose stools) but not abdominal pain in patients taking proton pump inhibitors.

All subjects were treated with pantoprazole (40 mg/day) for 6 months. While taking pantoprazole, subjects were then randomized to one of the following groups: 1) *Lactobacillus paracasei* F19 (LP-F19) bid for 3 days/week for 6 months; 2) placebo bid for 6 months; 3) LP-F19 bid for 3 days/week for the first 3 months followed by placebo 3 days/week bid for the following 3 months; or 4) placebo bid for 3 days/week for 3 months followed by LP-F19 bid for 3 days/week for the following 3 months. LP-F19 and placebo were delivered in sachets that were dissolved in water and taken right before meals. The active sachets contained 12 x 10^9 colony forming units (cfu) of LP-F19. Bloating, flatulence, abdominal pain, and bowel habits were assessed monthly. The primary endpoint was the percentage of subjects who developed clinically relevant bloating, flatulence, and abdominal pain at each monthly check-up. The secondary endpoints were: 1) changes in the mean score of bloating, flatulence, and abdominal pain at each monthly check-up, and 2) changes in the mean stool frequency/week and mean stool form at each monthly check-up.

One hundred subjects were randomized for the study with 25 in each arm. Mean age was 39 ± 10.4 years with 56 men and 44 women. In the parallel groups, the percentage of subjects developing clinically relevant bowel symptoms during the 6-month study was lower in the LP-F19 group compared to placebo. With regards to bloating, there were no significant differences between groups up to month 3. However, bloating was significantly lower in the LP-F19 group compared to placebo at months 4 ($P = 0.038$), 5 ($P = 0.025$), and 6 ($P = 0.023$). The rate of subjects developing flatulence was significantly lower in the LP-F19 group compared to placebo at all time points ($P = 0.011$). There was no significant difference between groups in terms of abdominal pain ($P = 0.25$). In the crossover groups, the percentage of subjects who developed clinically relevant bowel symptoms was lower during the LP-F19 phase compared to placebo for all three measures, bloating, and abdominal pain measured at 3 months. On the secondary endpoints for the parallel groups, the mean score of each symptom was lower for the LP-F19 group compared

to placebo, and bowel habits (increased stool frequency and loose stools) changed significantly only in the placebo group. When the covariates time, LP-F19 treatment, and treatment by time interaction were considered, LP-F19 significantly affected the mean score of bloating ($P = 0.02$), flatulence ($P < 0.0001$), mean stool frequency/week ($P = 0.016$), and mean stool form ($P = 0.02$) compared to placebo. The mean abdominal pain score did not differ significantly over time. The same results were noted for the crossover groups. Adverse events are not reported in the paper.

The results of this multicenter trial suggest that concomitant use of probiotics (most likely lactobacilli strains) may reduce bowel symptoms such as bloating and flatulence but not abdominal pain in patients taking PPIs long-term. The four-arm design of the study was a bit of a head scratcher, and it is this reviewer's opinion that that a two-arm parallel design with a larger cohort in each group would have been sufficient. An interesting note is the fact that probiotics were only used twice daily for 3 days/week during the study. According to the researchers, this was based on data showing LP-F19 survives intestinal transit and colonizes the intestinal tract for "long periods" after ingestion.[2] It will be interesting in future clinical trials looking at probiotics for prevention of gastrointestinal symptoms consider not only probiotic potency (cfu/day) but also frequency of administration. Finally, clinicians should be asking if the rampant use of PPIs and subsequent small intestinal bacterial overgrowth might be one of the primary contributors to the rise in functional bowel disorders such as irritable bowel syndrome. ■

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CME QUESTIONS

1. **Which of the following best describes the purpose for developing the newer modified and alternative FM criteria described in this review?**
   a. To allow more accurate diagnosis
   b. To more easily identify patients for research
   c. To reduce gender discrepancies
   d. To improve on prior criteria sensitivity and specificity
   e. To increase clinician reliability
2. **Which of the following best describes balneotherapy?**
   a. Exposure to moist heat
   b. Spa treatments
   c. Warm mineral baths
   d. Mud packs and physiotherapy
3. **Which of the following is *not* true regarding spiritual interventions in oncology patients?**
   a. Spiritual interventions have an effect on meaning of life and spiritual well-being.
   b. Spiritual interventions have demonstrated effects on depression and anxiety.
   c. Most patients report that their spiritual care is appropriately addressed by their medical team.
   d. Spiritual interventions may help increase coping ability in oncology patient populations.
4. **In a pharmacokinetic study with healthy young adults, what daily dose of vitamin D3 for 2 weeks was found to maintain 25(OH) D levels over 32 ng/mL for 56 days after stopping supplementation?**
   a. 500 mg
   b. 1000 IU
   c. 4800 IU
   d. 100,000 IU
5. **The concomitant administration of a probiotic strain in persons taking a proton pump inhibitor daily was shown to significantly reduce the incidence of abdominal pain.**
   a. True
   b. False

[IN FUTURE ISSUES]

N-acetylcysteine for tobacco use disorder

Updates in acupuncture

Ginger and diabetes

Supplements and botanicals for diabetes