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Complementary and alternative treatment in functional dyspepsia

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Abstract

Introduction and aim: The popularity of complementary and alternative medicine (CAM) in treating functional gastrointestinal disorders (FGIDs) has steadily increased in Western countries. We aimed at analyzing available data on CAM effectiveness in functional dyspepsia (FD) patients.

Methods: A bibliographical search was performed in PubMed using the following keywords: ''complementary/alternative medicine,'' ''hypnosis,'' ''acupuncture'' and/or ''functional dyspepsia.''

Results: In community settings, almost 50% of patients with FGIDs used CAM therapies. Herbal remedies consist of multi-component preparations, whose mechanisms of action have not been systematically clarified. Few studies analyzed the effectiveness of acupuncture in Western countries, yielding conflicting results and possibly reflecting a population bias of this treatment. Hypnosis has been extensively used in irritable bowel syndrome, but few data support its role in treating FD.

Conclusions: Although some supporting well-designed studies have been recently performed, additional randomized, controlled trials are needed before stating any recommendation on CAM effectiveness in treating FD.

Keywords

Functional dyspepsia, hypnosis, herbal supplements, acupuncture, complementary treatment

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Introduction

Patients' requests for a ''holistic'' treatment to functional gastrointestinal disorders (FGID) have been steadily increasing in recent years.[1] Nonetheless, this approach is often dismissed by physicians, based on the perception of a lack of scientific back-up to complementary and alternative treatment (CAM).[2] The available literature on CAM has been historically limited by a poor research approach in terms of sample size, randomization, outcome parameters and statistical evaluation.[1,2] However, a number of randomized, controlled trials (RCTs) have recently provided sound evidence of CAM effectiveness in FGIDs.[3] CAM is broadly defined as ''Medical practices neither taught widely in medical schools nor generally available in public hospitals''[4] (Figure 1). Recent United States (US) reports suggest that CAM therapies to treat GI disorders have been increasingly employed all over the world.[4] In a Canadian community setting, almost 50% of gastroenterology outpatients were found to implement treatments with supportive CAM therapies.[5] More recently, a multicenter study of 199 FGID patients found that 64% were using diet/herbal remedies and 49% CAM as supportive treatment options.[6] Women and whites tend to use CAM more than men and African Americans do, respectively.[6] Higher levels of education, higher annual incomes and comorbid

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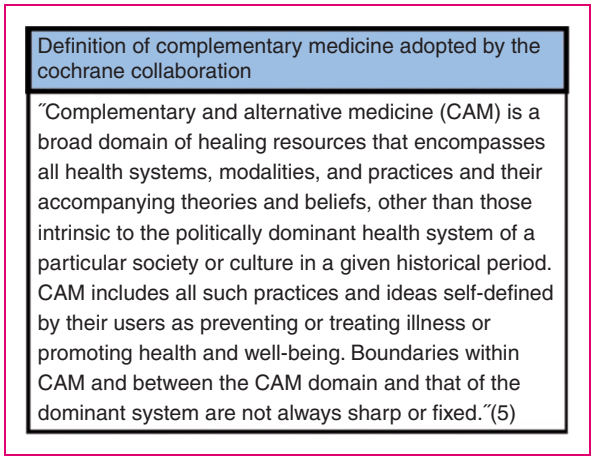

Figure 1. Definition of complementary and alternative medicine (CAM) therapy according to the Cochrane Collaboration.

medical conditions also correlate with CAM usage.[4,6] This information might be useful to gastroenterologists to determine which patients are likely to use these therapies. Regardless of the therapies employed, CAM modality is intended by patients to restore balance and to facilitate the body's own healing responses, thereby ameliorating troublesome symptoms.[6]

According to the Rome IV criteria, functional dyspepsia (FD) refers to a heterogeneous group of symptoms arising from the epigastric region in the absence of organic disease that are likely to explain the symptoms.[7] FD pathophysiology is still uncertain but seems to be related to multiple mechanisms[8] and despite current guidelines, the treatment of FD remains unsatisfactory.[7,8] Studies suggest that patients often look for person-centered care and personal physician-patient interactions. This search for a ''holistic'' approach might explain patients' choice to implement prescription treatment with CAM in FD.[1] This review will focus on the efficacy, safety and clinical data of CAM in FD to improve the physician approach to this appealing therapeutic option. Consideration is mostly limited to randomized or quasi-randomized trials to avoid emphasizing the magical allure still clouding some CAM approaches.

Herbal supplements

An overview of the herbal supplements' trial is summarized in Table 1. Most of these herbal supplements are multi-component preparations with a wide variety of effects on GI function that have not been fully clarified so far.[9] The supposed inhibition of smooth muscle contractility has provided the rationale to study the efficacy of peppermint oil (*Mentha piperita*) and caraway oil (*Carum carvi*), as single supplements or in combination.[10,11] Also, an allosteric effect of menthol and peppermint oil on the 5-HT 3 receptor has been proposed to explain its antiemetic action; however, the effect was weak and may not be clinically relevant.[12] Furthermore, peppermint oil has been used traditionally in the management of gallstones, as a choleretic action of the oil has been described.[13] Finally, peppermint oil seemed also to exert a significant spasmolytic effect in the esophagus, lower stomach and duodenal bulb when orally administered in dyspepsia patients prior to barium meal and follow-through.[14] In several trials, peppermint and caraway oil were found to be more effective than placebo in improving dyspeptic symptoms.[3,15] In the most recent RCT, 96 FD patients were treated with either a fixed combination of peppermint oil and caraway oil (PCC; Enteroplant) or placebo for four weeks. The average intensity of epigastric pain was decreased by 40% in the herbal group compared to 22% of the placebo recipients.[15] Capsaicin has been traditionally used to treat various pain syndromes for its ability of selectively impair the action of nociceptive fibers.[16–18] Red pepper powder (*Capsicum annuum*) was more effective than placebo in improving dyspeptic symptoms in a small-sized (30 participants) RCT. The authors speculated a potential action on gastric visceral nociception, but no additional studies have replicated these data. Ginger (*Zingiber officinale*) has been traditionally used to treat dyspepsia.[19,20] Recently, the effect of ginger on gastric sensorimotor function was investigated in 11 FD patients. In this small-sized open study, ginger displayed prokinetic effects, but had no impact on gastric sensation, dyspeptic symptoms or gut peptides/hormones.[21] Artichoke (*Cynara scolymus*) leaf extracts have been commonly used to treat dyspeptic symptoms as its bitter compounds (cynaropicrin) are believed to increase bile flow exerting hepatoprotective, antioxidant and antispasmodic effects.[22–24] In a multicenter, double-blind RCT, 247 FD patients were treated with either a commercial artichoke leaf extract (ALE) preparation or placebo. After six weeks, the ALE preparation was significantly more effective, by intention-to-treat analysis, than placebo in alleviating symptoms ($p < 0.001$) and improving quality of life (QoL) index in FD patients. Interestingly, patients reporting symptom improvement on ALE observed it since the first week of therapy.[25] Finally, the best investigated herbal supplement to treat functional dyspepsia is STW5, known as Iberogast, a combination of herbal supplements empirically used in treating GI symptoms in German-speaking countries. Iberogast is an alcoholic extract of nine herbal supplements whose proposed mechanism of action is to modulate most of the potential alterations underlying FD. Four studies evaluated STW5 versus placebo and one study tested the non-inferiority of STW5 over the prokinetic drug cisapride. Von Arnim et al. performed

Table 1. Randomized trial of herbal supplement therapies in functional dyspepsia (FD) patients.

Herbal supplement	*n.*	Type of study	Treatment response rate	Placebo response rate	Conventional therapy response rate	*p* value	Outcome measures	Ref.	Proposed mechanisms of action
Dried banana powder	46	Randomized trial over standard care	75%	–	20%	$p < 0.05$	Symptom improvement	9	Antiulcerogenic activity Promotes gastric mucus secretion
Curcuma Longa	116	Randomized, double-blind, multicenter trial over placebo	87%	53%	–	$p = 0.003$	Symptom improvement	10	Increased biliary secretion Spasmolytic action
Ginger	11	Randomized, double-blind, trial over placebo	No difference over placebo			$p =$ NS	Gastric emptying rates	22	Increased gastric emptying rate, no effects on gut hormones[b]
Mentha piperita and *Carum carvi*	96	Randomized, controlled trial	40%	22%	–	$p < 0.05$	Intensity of epigastric pain	15	Choleretic and antimeteoric action
Capsicum annuum	30	Randomized, controlled trial	60%	30%	–	$p < 0.05$	Symptom improvement	19	Reduced gastric visceral nociception via desensitization of C-type neural fibers
Cynara scolymus	247	Randomized, double-blind, multicenter trial over placebo	[a]	[a]	–	$p < 0.001$	Overall change in dyspeptic symptoms and QoL (Nepean Dyspepsia Index)	26	Increased bile flow and exerts hepatoprotective, antioxidant and antispasmodic effects
Iberogast	315	Randomized, double-blind, placebo-controlled	[a]	[a]	No differences against herbal therapy group	$p < 0.05$	GIS	27–32	Modulation of gastric sensorimotor function, nociception, bile clearance and gastric acid clearance[b]
Rikkunshito	247	Randomized, double-blind, multicenter trial over placebo	33.6%	23.8%	–	$p = 0.04$	Global Patient Assessment (GPA)	39–41	Acceleration of gastric emptying by increasing ghrelin plasma concentration[c] Potential modulation of visceral afferents

[a]Results expressed as change in symptoms from baseline rather than response rate, by intention-to-treat analysis. [b]No relationship between symptom improvement and acceleration of gastric emptying could be demonstrated in vivo. [c]In animals, not confirmed in humans.
QoL: quality of life; GIS: gastrointestinal symptom score.

a double-blind, placebo-controlled RCT on 315 FD patients (Rome II criteria).[26] After seven days of washout, the patients were randomized to an eight-week treatment with either STW5 or placebo.[26] After four and eight weeks of treatment, the improvement in GI symptom score (GIS) was significantly higher in the STW5 group compared to placebo ($p < 0.05$). As secondary outcome measures, investigators' and patients' global symptom assessments confirmed the superiority of STW5 over placebo. At follow-up consultation, patients treated with STW5 remained recurrence free longer than patients who had received placebo. The overall tolerability of STW5 and placebo were comparable, though five patients reported adverse events potentially related to STW5 (abdominal pain, pruritus, sore throat, alopecia, hypersensitivity, hypertension, GI pain). The other three studies, two published in German,[27–29] replicated the data of a statistically significant superiority of STW5 versus placebo. One of these studies considered gastric emptying as a secondary outcome in patients with dyspepsia and gastroparesis.[30] However, no relationship between symptom improvement and acceleration of gastric emptying could be demonstrated. Furthermore, a double-blind, non-inferiority RCT had compared STW5 to cisapride in 186 FD patients showing analog effectiveness for both medications.[30] The effectiveness of Iberogast has also been confirmed by meta-analyses, the most recent of which included up to 637 patients showing a standardized mean difference of −1.1 over placebo, although there was statistically significant heterogeneity between studies.[31–34]

Traditional Chinese and Japanese medicine have been used for centuries to treat a number of symptoms, but only recently, the Kampo therapy has been systematically evaluated.[35] The ailment most studied is the rikkunshito treatment, which has been studied in Japanese scientific literature since 1500.[36] Rikkunshito is a complex herbal remedy composed of eight constituents. However, recent deeper chromatographic analysis showed that the rikkunshito formula was even more complex, revealing several additional ingredients.[35] In animal models, rikkunshito seems to accelerate gastric emptying by increasing ghrelin plasma concentration, but human studies are inconclusive.[36–39] However, a barostat study researching gastric response to environmental stress showed that rikkunshito improved gastric volume thresholds for generation of first sensation and epigastric discomfort, suggesting a potential modulation of visceral afferents.[38] A recent multicenter RCT has been run in Asia on 247 FD patients (Rome III) to compare the efficacy of rikkunshito or placebo for eight weeks.[36–40] Symptomatic improvement was recorded, as well as plasma ghrelin levels before and after treatment. Approximately one-third of patients in the rikkunshito group met the primary aim, without reaching statistical significance versus placebo ($p = 0.09$). On the contrary, epigastric pain was significantly improved by rikkunshito treatment compared to placebo while other dyspeptic symptoms and ghrelin concentration were not affected.[38,39]

Acupuncture

Acupuncture has been used to treat FD in Eastern countries for several millennia, although the underlying mechanism remains unclear. The practice of acupuncture consists of inserting fine, solid needles (32 to 36 gauge) into selected body locations (acupoints). More than 300 points located in systematic fashion on meridians or channels of energy flow are mapped onto the body surface. Key principles in traditional Chinese medicine are that both wellness and illness result from an imbalance of *yin* (the feminine aspect of life) and *yang* (its male counterpart). The movement between these opposite forces, named *Qi,* is considered to be the essential element in the healing system. In Western countries, acupuncture is being increasingly accepted as an alternative treatment for FGIDs.[41,42] Ma et al. have conducted an RCT to assess the efficacy of acupuncture in FD compared to Itopride.[43] In this trial, 712 FD patients were randomly assigned to receive acupuncture at specific and non-specific acupoints versus sham acupuncture and a drug control group for four weeks. Treatment efficacy was evaluated at the end of treatment and at 12 weeks' follow-up consultation. All groups had an improvement both in symptoms and QoL scores at the end of treatment that was sustained for the whole follow-up. The overall response rate was significantly higher in the acupuncture group on specific acupoints (70.69%) than in the other groups with the lowest response observed in the sham acupuncture group (34.75%). Also, the QoL scores improved significantly in the specific acupuncture group. These results showed that acupuncture at specific points of the stomach meridian was superior to acupuncture at points of other meridians and sham points, as well as oral administration of Itopride. These data have been recently replicated in a small-sized study evaluating 30 FD patients treated according to a cross-over design by acupuncture at specific points, acupuncture at non-specific points and standard care.[44] Recently, Zeng et al. studied brain responses to acupuncture in FD.[45] Seventy-two FD patients were randomly assigned to receive either sham or classic acupuncture on four specific acupoints: ST34 (*Liangqiu*), ST36 (*Zusanli*), ST40 (*Fenglong*), and ST42 (*Chongyang*) (see Figure 2). Ten patients in each group were randomly selected for fluorine-18 fluorodeoxyglucose positron emission tomography-computed

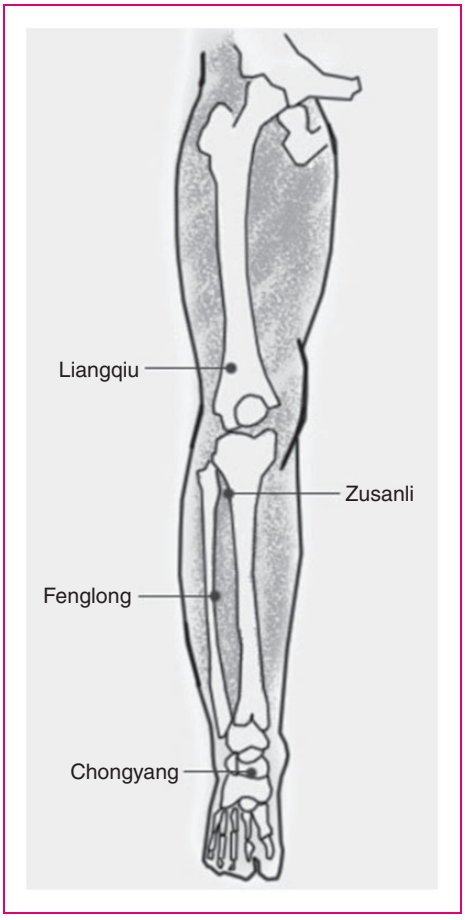

Figure 2. A schematic representation of the four classic acupuncture points for gastric disorders: ST34 (Liangqiu), ST36 (Zusanli), ST40 (Fenglong) and ST42 (Chongyang).

tomography (PET-CT) scans to detect cerebral glycometabolism changes. Neuroimaging indicated that the acupuncture group showed extensive deactivation in cerebral activities compared with the sham acupuncture group. This deactivation was associated with symptom improvement, suggesting the potential effectiveness of acupuncture at specific points in FD.[45] This assumption has been partially supported by a recent PET-CT scan study investigating similarities and differences in clinical and cerebral responses at different acupoints in 20 FD patients.[46] In this study, different acupoints showed similar clinical efficacy but relatively different cerebral responses. The authors speculated that the influence on the sensory transduction regions and visceral modulation regions might be the common mechanism of different acupoint treatment.[46] Nevertheless, a Cochrane review concluded that "It remains unknown whether manual acupuncture or electroacupuncture is more effective or safer than other treatments" in FD patients.[47] More recently, a meta-analysis including almost the same studies as the Cochrane's review reached opposite conclusions stating that "Acupuncture appears to be efficacious in relieving FD symptoms and improving quality of life."[48] It should be acknowledged that the few studies run in Western countries did not provide positive outcome data, reinforcing the population bias of this intriguing treatment.[47,48]

Hypnosis

Hypnosis can be defined as an altered state of consciousness, different both from sleep and normal wakefulness, characterized by highly focused attention and heightened compliance with suggestion.[49] Clinical hypnosis relies on deliberately inducing the state of hypnosis in a patient through verbal guidance, and making use of its properties for targeted therapeutic purposes. Hypnotherapy delivered as a structured, multi-session, focused intervention has been extensively used to treat irritable bowel syndrome according to the gut-focused protocols of the Manchester or the North Carolina group.[50] Recently, the Manchester group has also provided experimental evidence to support the use of hypnotherapy in FD. Calvert et al.[50] randomized 126 FD patients to hypnosis, supportive therapy plus placebo medication, or medical treatment (ranitidine 300 mg/day) for 16 weeks. Change in symptoms from baseline was assessed both short term (16 weeks) and long term (56 weeks). QoL was also measured as a secondary outcome. Hypnosis was induced using eye fixation followed by progressive muscular relaxation and deepened by standard procedures. Suggestions of improvement in gastric motor function, sensitivity and gut secretion activity were also given. At the short-term follow-up, hypnotherapy was significantly more effective than both the supportive and the medical treatment in ameliorating symptoms and QoL scores, even at long-term follow-up. In addition, general practitioner consultations for dyspeptic symptoms were dramatically decreased. The authors concluded that hypnotherapy is both an effective and cost-effective treatment for FD, but the mechanism(s) of action remained speculative.[50]

Chiarioni et al.[51] studied gastric emptying by ultrasonography and epigastric sensations in 11 healthy individuals and in 15 FD patients under three conditions: (a) basal, (b) after cisapride 10 mg and (c) during 90 minutes of a gut-oriented hypnotic trance. Eight healthy individuals repeated an emptying study listening to relaxing music. Hypnosis was significantly more effective than cisapride and relaxing music in decreasing gastric emptying duration both in dyspeptics and healthy volunteers ($p < 0.005$). Symptoms were significantly improved by hypnosis in FD patients, but no correlation with gastric emptying time could be found.

Therefore, a single session of hypnosis is as effective as prokinetic treatment in FD, but the mechanism underlying symptom improvement remains unclear. One can speculate that since FD pathophysiology is multifactorial and involves many components of the brain/gut axis, hypnosis might target different pathophysiological mechanisms in FD. The state of profound relaxation achieved during hypnosis is associated with a sustained and generalized reduction of the sympathetic activity, lasting even after the actual hypnosis interval. Furthermore, hypnosis might decrease visceral hypersensitivity, a hallmark feature of all functional syndromes. Brain imaging studies in FD are consistent with a disproportionate activation of the anterior cingulated cortex, responsible for the affective response to pain. Hypnosis has been shown to decrease reported pain sensation in response to painful stimuli, by likely reducing the activity of the anterior cingulated cortex.[49] Although these conceptual premises imply that hypnotherapy might represent an appealing therapeutic option, dedicated expertise is a must and additional RCTs in FD are needed before stating recommendation.[51,52]

Conclusions

CAM therapies offer the potential to be considered in alternate and mainstream treatment of FD. An increasing body of literature provides sound evidence of effectiveness of herbal supplements in FD, although supporting well-designed studies aimed at identifying the active components, the potential receptors and the mechanism of action involved in symptom relief are needed. However, the overriding lesson seems to be that the clinical efficacy of these multi-component preparations relies on a multi-targeted approach to multifactorial disorders. Acupuncture is a traditionally accepted therapy in Asia, but its use in Western countries is far from being considered by the general population for the lack of scientific background. In the future, hypnosis might be an appealing treatment option, but studies supporting its therapeutic efficacy are eagerly awaited.

Declaration of conflicting interests

G.S., A.F. and M.P. have nothing to declare.
G.C. is a consultant/member of the speaker's board for: Alfa Wassermann, Allergan, Malesci and Takeda, and is a member of the Rome Foundation Anorectal Committee.

Ethics approval

Not aplicable, being this paper a review, non involving subjects or patients

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Informed consent

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