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Review

Non-pharmacological Approach in the Management of Functional Dyspepsia

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Functional dyspepsia (FD) is a common functional gastrointestinal disease which bears a significant burden on society and individuals. Despite the high prevalence of FD, its pathophysiology remains poorly understood and the treatment options are limited and unsatisfactory. In the absence of effective pharmacological treatments for FD, non-pharmacological approaches, including: reassurance, lifestyle modification, psychotherapy, dietary interventions, medical food, acupuncture, and electrical stimulation and modulation are sought after by many physicians and FD patients. In this article, we review clinical studies which investigate non-pharmacological therapies for FD. We will also discuss potential mechanisms involved in the therapeutic effects of these non-pharmacological approaches. Though the evidences to support the routine use of the non-pharmacological management is still lacking, the non-invasive nature and potentially minimal side-effects of these therapies may be attractive in the FD management. In order to confirm the clinical effectiveness of these non-pharmacological approaches, more well-conducted, methodologically rigorous, and large-scaled clinical trials are required.
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Key Words
Complementary therapies; Dyspepsia; Electrical stimulation

Introduction

Functional dyspepsia (FD) refers to a group of symptoms arising from the epigastric region that do not originate from an organic disease.[1] FD is divided into 2 diagnostic categories of meal-related dyspeptic symptoms in the Rome IV criteria; they include: postprandial distress syndrome (PDS), characterized by postprandial fullness and early satiation, and epigastric pain syndrome (EPS), characterized by epigastric pain and burning.[2] The prevalence of FD in Asia ranges from 8% to 23%.[3] Though it is not a life-threatening disease, it significantly impairs patients' quality of life and bears a significant economic burden on society and individuals.[4] Despite its high prevalence and disease burden, the pathophysiology of FD remains poorly understood. However, several mechanisms have been proposed, including: impaired gastric accommodation,[5] delayed gastric emptying,[6] visceral hypersensitivity,[7] *Helicobacter pylori* infection,[8] hypersensitivity to duodenal lipid or acid exposure,[9,10] genetic factors,[11] social and psychological factors,[12] history of infectious colitis,[13] and duodenal eosinophilia.[14] Current guidelines for the treatment of FD suggest the use of proton pump inhibitors, the eradication of *H. pylori*, prokinetic drugs, and

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psychotropic agents.[15] Nonetheless, the efficacy of these pharmacological therapies remains unsatisfactory and a considerable number of FD patients are refractory to conventional pharmacological treatments. Furthermore, low compliance of the traditional therapy can be observed in some FD patients as they would opt out from these pharmacological options because of the concerns on the side effects.[16,17] In the absence of an approved drug to treat FD,[18] many patients seek person-centered, non-pharmacological approaches.[19] These therapies include reassurance, lifestyle modification, psychotherapy, dietary interventions, medical food, acupuncture, or electrical stimulation and modulation. This review will discuss the efficacy, potential mechanisms, and opportunities for the improvement of non-pharmacological therapies for FD.

We performed a systematic approach in the collection and review of relevant literature. PubMed was searched from 1994 through to December 2018 with a combination of the following basic and MeSH (medical subject headings) terms: "functional dyspepsia" or "functional gastrointestinal disorder" as the population; "medical food," "acupuncture," "psychotherapy," "electrical stimulation" or "non-pharmacological" as the intervention; "placebo" or "control" as the comparison; and "placebo controlled" or "randomized" as the study design. Reference lists of included studies were then manually searched for relevant studies.

Placebo Effect and Its Clinical Application in Functional Dyspepsia Patients

A number of clinical trials have shown that patients with functional bowel disorders (eg, FD, irritable bowel syndrome [IBS], etc) benefit from a greater placebo response when compared to patients with organic gastrointestinal diseases.[20] One meta-analysis including 45 FD trials showed a placebo response rate of 31% to 45%.[21] A 2006 Cochrane review found an average 56% placebo response among FD patients.[22] The underlying mechanisms behind the high placebo response rate among FD patients are still unclear, however, no studies have found a significant difference in the personality traits between placebo responders and non-responders. To date, the only factors predictive of a lower placebo response rate are a body mass index of lesser than 25 and a consistent predominant symptom pattern.[20] Talley et al[20] suggested that the placebo response to treatment can be maximized by a firm diagnosis that must be followed by explanation and reassurance. In daily practice, clinicians may take advantage of the placebo effect by reassuring the FD patient by explaining the pathophysiology of FD and the unlikelihood of cancer in order to relieve patients' anxiety and lead to symptomatic improvement.

Lifestyle Modification

Lifestyle factors are linked with the development of dyspeptic symptoms. For example, life stress, anxiety, and the use of inadequate coping strategies are predictors of FD.[23] Furthermore, anxiety was associated with PDS, but not with the EPS in a Swedish population study.[24] A Taiwanese FD study showed that PDS was independently associated with dimensions of somatization, depression, and phobia.[25] In addition, we and Miwa et al[26] both found that FD patients have a higher prevalence of sleep difficulties.[4] A large United States-based community study demonstrated that difficulty falling asleep is an independent risk factor for dyspepsia.[27] Though the studies evaluating the beneficial effect of adjustments in lifestyle are lacking, measurements to improve lifestyle may relieve dyspeptic symptoms. FD patients with refractory and persistent symptoms after conventional treatment may attempt lifestyle modification.

Psychotherapy

Numerous studies have evaluated psychological therapy in the treatment of IBS,[28] however, the body of evidence in support of psychological therapies for FD is rather limited. Nonetheless, patients who suffer from psychiatric comorbidities or who are otherwise non-responsive to pharmacological interventions may be suitable candidates for psychological therapy. Various methods of psychotherapy in the treatment of FD have been evaluated, including hypnotherapy,[29] cognitive behavioral therapy,[30-34] and psychoanalytic psychotherapy,[35,36] as summarized in Table 1. The American College of Gastroenterologists and the Canadian Association of Gastroenterologists recently reviewed psychotherapy among other interventions in the treatment of FD. Each of the 12 trials reviewed indicated a significant benefit from psychological therapies compared to control (relative risk [RR], 0.53; 95% confidence interval [CI], 0.44-0.65) with a number needed to treat of 3. Despite these positive results, the reviewers stated that the evidential basis for psychotherapy in the treatment of FD is weak. This is because the research to date has been far too heterogeneous—both in terms of the study populations and type of psychotherapeutic intervention—for any definitive support favoring the use of psychotherapy in the treatment of FD.[37] It can be difficult to judge the therapeutic effect objectively due to the heterogeneity in psychological treatment methods. The studied patients also ranged in their duration of illness and varied in the symptoms of FD that they had reported. The included studies also lacked methodological rigor; the study interventions were neither blinded nor were various interventions directly compared with each other. In addition, unlike the current standards for pharmaceutical

Table 1. Summary of Studies on Psychotherapy for the Treatment of Functional Dyspepsia

References	Trial design	Patient	Treatment groups	Main finding
Calvert et al[29]	Randomized controlled trial	FD patients (n = 93)	16 weeks of hypnotherapy (n = 27), supportive therapy plus placebo medication (n = 32), or ranitidine 150 mg bid (n = 34)	Hypnotherapy is more effective than medical treatment or supportive therapy plus placebo medication in both the short- and long-term management of FD.
Dehghanizade et al[30]	Pre-test, post-test and follow-up with a control group	FD patients (n=30)	10 sessions of cognitive behavioral stress management (n=15) or no intervention (n=15)	Cognitive-behavioral stress management strategies are effective in reducing symptoms in patients with FD compared with control.
Cheng et al[31]	Randomized controlled trial	FD patients (n = 75)	12 weeks with 6 sessions of flexible coping psychotherapy (n = 33) or supportive psychotherapy (n = 31)	Both flexible coping psychotherapy and supportive psychotherapy effectively reduced FD symptoms.
Hamilton et al[36]	Randomized controlled trial	FD patients (n = 73)	12 weeks of PI (n = 37) or supportive therapy (n = 36)	One year after treatment, the symptomatic scores were similar. After excluding patients with severe heartburn, PI therapy was superior to the control condition at 1 year.
Haug et al[33]	Randomized controlled trial	FD patients (n = 100)	4 months of cognitive psychotherapy (n = 50) or control treatment (n = 50)	Psychotherapy significantly reduce epigastric pain, nausea, heartburn, diarrhea, and constipation.
Orive et al[32]	Randomized controlled trial	FD patients (n = 158)	10 weeks of medical therapy plus psychotherapy (n = 76) or medical therapy alone(n=82)	Adding psychotherapy to medical therapy improves short-term outcomes in FD patients.
Haag et al[34]	Randomized controlled trial	FD patients (n = 100)	4 months of standardized symptom-oriented therapy (n = 24) or intensive medical therapy with either progressive-muscle relaxation (n = 20) or (n = 28), or intensive medical therapy only (n = 28)	Intensified medical therapy involving sensory-motor function tests and psychological intervention yields superior long-term outcomes.
Faramarzi et al[35]	Randomized controlled trial	FD patients (n = 49)	18 weeks of core conflict relationship themed psychoanalytic psychotherapy (n = 24) or standard medication treatment (n = 25)	Core conflict relationship themed psychotherapy can serve as an effective intervention for gastrointestinal and psychiatric symptoms in FD patients.

FD, functional dyspepsia; PI, psychodynamic-interpersonal.

drug trials, the lack of a placebo arm in the clinical trials involving psychotherapy also weakens the evidence for such therapy. Furthermore, the use of psychotherapy in FD patients is lessened by a lack of familiarity among gastroenterologists with such interventions, as well as patients who do not recognize or are unwilling to accept the influence of psychological symptoms on the severity of gastrointestinal symptoms. Future studies should address these limitations in order to convince patients and healthcare providers to introduce psychotherapy for the treatment of FD.

Dietary Management and Medical Food

Starting from the Rome III consensus, FD, and in particular PDS, has been considered a disorder related to food ingestion.[38] Avoiding foods which trigger indigestion may be of benefit. Several studies and systemic reviews have indicated that wheat-containing foods, fatty or spicy foods, and carbonated drinks can trigger dyspeptic symptoms,[39] as summarized in Table 2. However, it is not yet understood exactly how these foods trigger FD symptoms.

Another dietary intervention for the treatment of FD is medical food; defined by the United States Food and Drug Administration as foods which are formulated to be consumed or administered enterally under the supervision of a physician which is intended for the specific dietary management of a disease or condition.[40,41] Medical foods, unlike food supplements, require safety reviews by panels of toxicologists and must be generally recognized as safe for consumption, although phase 1, 2, and 3 trials are not required.[42]

Table 2. Food and Food Components Reported in Association With Dyspeptic Symtpoms[39]

Category	Ingredients
Grains, nuts, and seeds	Grains, wheat containing food, nuts
Meats	Sausage, bologna, bacon, fish
Vegetables	Pickles/vinegar, red pepper, bell pepper, cucumber onions, beans, horseradish
Dairy	Milk, cheese, some mayonnaise, cream
Sweets and fats	Chocolate, high fat yogurt, sweets, cake
Fruits	Watermelon, banana, pineapple, citrus fruits
Drinks	Carbonated drinks, tea, coffee, wine, beer
Others	Fatty food, fried food, fumed food, baked food, pizza, pasta, spices

Medical foods can affect several pathophysiological mechanisms in FGIDs, such as functioning as an anti-inflammatory, causing smooth muscle relaxation, analgesia, mitigation of gut barrier dysfunction, and stimulation or inhibition of gastrointestinal receptors.[41] Several medical foods are available in Europe and United States for the treatment of FD. In Western countries, caraway oil (CO) has often been combined with peppermint oil (PO) in order to treat abdominal discomfort and pain. Two randomized controlled trials have demonstrated that this PO + CO combination improves FD patients' global symptom impressions in a manner comparable with cisapride[43] and superior to placebo.[44] A separate randomized controlled trial (RCT) compared the efficacy of CO + L-menthol (FDgard) or a placebo as adjuvants to conventional medications in the treatment of FD. After 4 weeks of treatment, the CO + L-menthol group showed improved clinical global impressions to a greater extent than placebo (61.2% vs 48.9%, respectively), however, the difference was not statistically significant. CO is thought to produce its therapeutic effect through a prokinetic effect whereas PO produces its therapeutic effect via kappa-opioid-receptor dependent anti-nociception, anti-inflammatory properties, and TRPM8-receptor dependent smooth muscle relaxation.[41]

Another medical food of interest is STW 5—an herb composed of garden angelic root, milk thistle fruits, greater celandine, bitter candy tuft, caraway fruits, liquorice root, chamomile flowers, balm leaves, and peppermint leaves. STW 5 has been used to treat a variety of functional digestive symptoms.[45] In a meta-analysis of 3 RCTs evaluating STW 5 in the treatment of FD, Melzer et al[46] found treatment with STW 5 (n = 138) to be more effective than placebo (n = 135) with regard to the severity of the most bothersome gastrointestinal symptom ($P = 0.001$; OR, 0.22; 95% CI, 0.11-0.47). An RCT by von Arnim et al[47] found a similarly favorable result: statistically significant improvement in Gastrointestinal Symptom Score in the STW 5 arm (n = 158) as compared to the placebo arm (n = 157) (6.9 ± 4.8 vs 5.9 ± 4.3 at 56 days, $P < 0.05$). It has been suggested that the therapeutic mechanism of STW 5 includes a decrease in muscle tone within the gastric fundus that enhances antral contractility.[45] However, Braden et al[48] found that the clinical effects of STW 5 in FD patients with FD and gastroparesis were not directly mediated by an acceleration of gastric emptying. No serious adverse events have been reported in the RCTs evaluating STW 5 for FD.[46-48] Though STW 5 is thought to be a safe remedy and available without doctor's prescription in many countries including the United States, STW 5 is linked with drug-induced liver injury in recent 2 case reports, which might be the results from an idiosyncratic reaction.[49,50]

Another non-pharmacological avenue for the treatment of FD is probiotics. Probiotics are living microorganisms that (when consumed) have the potential to confer a beneficial health effect; they can be marketed as a medical food.[51] Probiotics containing *Lactobacillus gasseri* have demonstrated a beneficial effect on FD symptoms. A placebo-controlled study by Ohtsu et al[52] recruited 106 FD patients and found the elimination rate for PDS-like symptoms was 17.8% and 37.5% in the placebo and *L. gasseri* groups, respectively ($P = 0.040$). The elimination rate for EPS-like symptoms was not statistically significant. Nakae and colleagues[53] evaluated the effects of an *L. gasseri*-containing yogurt on the gastrointestinal symptoms and composition of enteric bacteria in FD patients vs healthy controls. They found that the abundance of the bacterial genus *Prevotella* was reduced in the gastric fluid of FD patients compared to healthy controls. Interestingly, there was a significant inverse correlation between *Prevotella* abundance and the severity of PDS-like symptoms in patients with FD that was nearly reversed by probiotic treatment. Their findings suggest that the gastric fluid's abundance of *Prevotella* may be used as a biomarker of the efficacy of *L. gasseri*-containing probiotics for the treatment of FD.[53]

Medical foods may appeal to those who have failed conventional therapies or who are seeking dietary management for their FD symptoms. Table 3 displays trials investigating medical food to treat FD. What is considered medical food varies between regions. Till now, there has not been enough evidence to warrant the clinical use of medical foods. Future large, well-controlled studies are needed to assess both the safety and efficacy of medical foods in the treatment of FD patients with different races and ethnicities.

Table 3. Summary of Studies on Medical Foods for the Treatment of Functional Dyspepsia

References	Trial design	Patient	Treatment groups	Main finding
May et al[44]	Randomized controlled trial	FD patients (n = 96)	4 weeks of 90 mg PO + 50 mg CO (n = 48) or placebo (n = 48)	PO + CO were superior to placebo in improving global symptom impression and pain intensity.
Madisch et al[43]	Randomized controlled trial	FD patients (n = 118)	90 mg PO + 50 mg CO per day (n = 60) or cisapride (3 × 10 mg/day) (n = 58)	PO + CO were comparable with cisapride and provides an effective means for treatment of FD.
Chey et al[54]	Randomized controlled trial	FD patients with PDS (n = 34) or EPS (n = 39)	4 weeks of 50 mg CO + 41.5 mg L-menthol twice/day (n = 37) or placebo (n = 36)	PO + CO group showed non-significantly improved clinical global impressions to a greater extent than placebo (61.2% vs 48.9%, $P > 0.05$).
von Arnim et al[47]	Randomized controlled trial	FD patients (n = 315)	STW 5 (n = 158) or placebo (n = 157)	STW 5 significantly improved gastrointestinal symptom scores compared to placebo.
Melzer et al[46]	Meta-analysis of 3 randomized controlled trials	FD patients (n = 273)	4 weeks of 1 mL STW 5 three times/day (n = 138) or placebo (n = 135)	STW 5 was superior to placebo in improving epigastric pain, acid regurgitation, retrosternal troubles, nausea, vomiting, and abdominal cramps as well as patients' most bothersome symptom.
Rösch et al[55]	Randomized controlled trial	Dysmotility type FD patients (n = 186)	STW 5 (n = 61), STW 5-II (n = 62), or cisapride (n = 63)	STW 5 and the research preparation STW 5-II showed equivalent efficacy to cisapride for the treatment of FD patients.
Braden et al[48]	Randomized controlled trial	FD patients (n = 103)	4 weeks of 1 mL STW 5 three times/day (n = 41) or placebo (n = 41)	Gastric half-emptying time was comparable between groups. STW 5 improved gastrointestinal symptom score and had a greater treatment response rate compared to placebo.
Xiao et al[56]	Randomized controlled trial	Children with FD (n = 120)	Sea buckhorn (n = 40), sea buckhorn plus domperidone (n = 40), or domperidone only (n = 40)	Sea buckthorn improved gastric emptying, gastric mobility, gastrointestinal digestive function compared to those receiving domperidone alone.
Ohtsu et al[52]	Randomized controlled trial	*H. pylori* (-) FD patients (n = 106)	12 weeks of 10^9 CFU/day *L. gasseri*-containing yogurt (n = 54) or placebo (n = 52)	The elimination rate for postprandial-distress symptoms was 17.8% and 37.5% in the placebo and *L. gasseri* groups, respectively ($P = 0.040$). The elimination rate for epigastric pain symptoms was not statistically significant.
Nakae et al[53]	Open-label trial	FD patients (n = 44) or healthy controls (n = 44)	12 weeks of 10^9 CFU/day *L. gasseri*-containing yogurt (n = 88)	*L. gasseri*-containing yogurt improved FD symptoms as well as helped normalize enteric microbial composition to compositions found in healthy controls. *Prevotella* abundance was inversely correlated with FD symptom severity.

FD, functional dyspepsia; PO, peppermint oil; CO, caraway oil; PDS, postprandial distress syndrome; EPS, epigastric pain syndrome; STW 5, garden angelic root, milk thistle fruits, greater celandine, bitter candy tuft, caraway fruits, liquorice root, chamomile flowers, balm leaves, and peppermint leaves; STW 5-II, bitter candy tuft, caraway fruits, liquorice root, chamomile flowers, balm leaves, and peppermint leaves; *H. pylori*, *Helicobacter pylori*; CFU, colony-forming units; *L. gasseri*, *Lactobacillus gasseri*.

Acupuncture

Acupuncture has been increasingly used as a non-pharmacological treatment of FD. Traditionally, acupuncture involves the stimulation of acupuncture points by penetration of the skin with solid metallic needles, followed by manual manipulation of the needle (ie, twisting, lifting, and thrusting). Acupuncture points can also be stimulated through electro-acupuncture, passing electrical currents through an inserted needle to stimulate a specific acupuncture point at a certain frequency and intensity. Unlike traditional acupuncture, electro-acupuncture provides a more objective, quantifiable method of acupuncture.[57] Two meta-analyses have evaluated the efficacy and safety of acupuncture to treat FD patients. The analysis by Kim et al[58] included 20 RCTs and a total of 1423 FD patients who received either acupuncture or another therapy (meta-analysis 1). The second analysis by Zhou and colleagues[59] included 24 RCTs and a total of 3097 FD patients receiving either acupuncture or electroacupuncture therapy (meta-analysis 2). Both meta-analyses showed that acupuncture was more beneficial than

sham (meta-analysis 1: RR, 2.66; 95% CI, 1.85-3.22; meta-analysis 2: RR, 2.03; 95% CI, 1.55-2.67) and with usual pharmacological medications (meta-analysis 1: RR, 1.18; 95% CI, 1.09-1.27; meta-analysis 2: RR, 1.10; 95% CI, 1.04-1.17). Both meta-analyses also demonstrated that acupuncture enhanced the therapeutic benefit of FD medications (meta-analysis 1: RR, 1.23; 95% CI, 1.02-1.48; meta-analysis 2: RR, 1.24; 95% CI, 1.16-1.33).

In order to better understand acupuncture's therapeutic mechanism, a recent study used functional brain imaging (positron emission scan) in FD patients to evaluate the response in brain activity to acupuncture treatment. Acupuncture treatment resulted in a decrease in FD symptom scores that correlated with an extensive deactivation of cerebral activity in the brainstem, anterior cingulate cortex, insula, thalamus, and hypothalamus.[60] This finding suggests that acupuncture's therapeutic mechanism may involve modulation of the homeostatic afferent processing network.

While these studies show a beneficial effect on FD symptoms, there are several limitations. The two meta-analyses included studies mostly from Eastern countries, namely China. Secondly, there has not yet been a multicenter, large-scale RCT for acupuncture in the treatment of FD. Furthermore, in many studies included in the meta-analysis, the definition of FD varied widely. FD can be based on Rome I, II, or III criteria or just vague dyspeptic symptoms not defined by Rome, and the outcomes after acupuncture were evaluated either dichotomously or continuously. Thus, the final results may be biased. Thirdly, most studies have had a short (if any) duration of follow-up. Fourthly, studies to date have lacked a standardized method of symptom evaluation, such as the Nepean Dyspepsia Index. Finally, most studies used fixed acupuncture points, such as Stomach-36 (ST36) and Pericardium-6 (PC6) as opposed to the traditional approach of selecting acupuncture points based off of each individual's symptoms. Given these limitations, a recent Cochrane review stated that "It remains unknown whether manual acupuncture or electro-acupuncture is more effective or safer than other treatments" in FD patients.[61] Future large-scaled, multinational, and methodologically rigorous clinical trials are needed to confirm the effectiveness of acupuncture in treating FD patients.

Electrical Stimulation/Modulation

Transcutaneous electrical stimulation of acupuncture points, also known as transcutaneous electrical acu-stimulation (TEA), is a recent variant of electro-acupuncture that has been used in the treatment of FD (Table 4).[62] TEA uses electrodes placed on the skin's surface for electrical stimulation. Having electrodes on the skin's surface reduces the depth of penetration of the electrical current. Compared to electro-acupuncture and conventional acupuncture, TEA is less invasive, can be self-administered by the patient, and can be conducted more frequently. Two trials have evaluated the ef-

Table 4. Summary of Studies on Electrical Acupuncture and Electrical Modulation for the Treatment of Functional Dyspepsia

References	Trial design	Patient	Treatment groups	Main finding
Köklü et al[65]	Randomized controlled trial	FD patients (n = 44)	12 × 15 min sessions over 4 wk of vacuum interferential current therapy at Bladder 18-21 (n = 23) or sham (n = 21)	During treatment, therapy was superior to placebo with respect to epigastric discomfort, pyrosis, bloating, early satiation, and postprandial fullness. One month after treatment, therapy was superior to placebo with regard to early satiation and heartburn.
Ji et al[63]	Randomized crossover trial	FD patients (n = 28)	2 wk of TEA self-administered 3 × 2 hr/day at ST 36 and PC6 followed by 2 wk of sham-TEA, or vice versa (n = 28)	TEA but no sham-TEA significantly improved gastric emptying accommodation as well as dyspeptic symptoms.
Xu et al[64]	Placebo-controlled pilot trial	FD patients (n = 8) and healthy controls (n = 8)	TEA at ST36 and PC6 (n = 8) or sham (n = 8) with 1 × 30 min session before and 1 × 30 min session after a liquid meal	In FD patients, TEA improved gastric accommodation abnormalities in postprandial gastric slow waves, and increased vagal activity.
Kovacik K[66]	Placebo controlled trial	Adolescents with chronic functional abdominal pain (n = 104)	PENFS (n = 57) or placebo (n = 57)	Patients in the PENFS group had lower "worst pain score" than with sham group after 3 wk of treatment. Such analgesic effects were sustained for 9.2 wk.

FD, functional dyspepsia; TEA, transcutaneous electrical acu-stimulation; ST36, Stomach-36; PC6, Pericardium-6; PENFS, percutaneous electric nerve field stimulation.

ficacy of TEA in the treatment of FD. In a crossover study of FD patients, Ji et al[63] conducted TEA at acupuncture points ST36 and PC6 for 2 weeks followed by 2 weeks of transcutaneous electrical stimulation at sham acupuncture points, or vice versa (Figure). They found TEA was superior to sham in decreasing dyspeptic symptom scores, gastric emptying, and gastric accommodation.[63] A pilot study investigated the fasting and postprandial effects of TEA at ST36 and PC6 vs sham on gastric motility and accommodation in FD patients and healthy controls. They found that verum TEA significantly increased gastric accommodation in FD patients only, and increased the percentage and power of postprandial gastric slow waves as well as vagal activity in FD patients.[64] These results suggest that self-administrated TEA can improve gastric motility and symptom relief for FD patients.

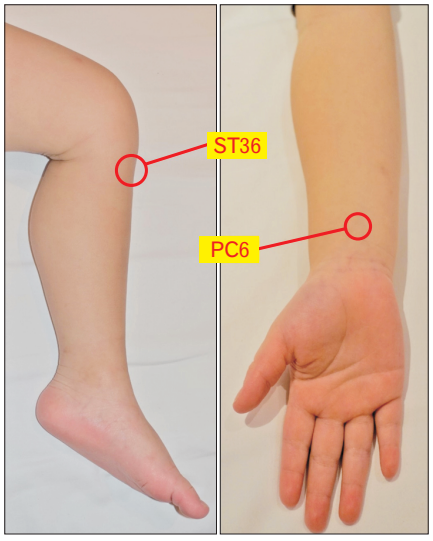

Figure. The location of Stomach-36 (ST36; Zusanli) and Pericardium-6 (PC6; Neiguan) acupoints. ST 36 is located in the tibialis anterior muscle, around 4 fingerbreadths below the kneecap and 1 fingerbreadth lateral from the anterior crest of the tibia. PC6 is located 2 cm above the transverse crease of the wrist, between the tendons of muscularis palmaris longus and flexor radialis.

In a study by Köklü et al,[65] transcutaneous electrical stimulation was conducted via vacuum interferential current therapy. Therapy was superior to placebo in improving epigastric discomfort, pyrosis, bloating, early satiation, and postprandial fullness in FD patients.[65] The location of electrical stimulation in this study corresponded to 4 acupuncture points: Bladder 18-21.[67]

Vagus nerve stimulation has demonstrated anti-nociceptive effects on various types of pain.[68-70] A recent study showed an impressive analgesic effect using percutaneous electric nerve field stimulation (PENFS) in the external ear to treat patients with functional abdominal pain (including FD patients).[66] One hundred and 4 adolescents (aged 11-18 years) with chronic functional abdominal pain were enrolled. Fifty-seven received PENFS with 3.2 volts in rectangular pulse wave and alternating frequencies (1 msec pulses of 1 Hz and 10 Hz) every 2 seconds, while the remaining 47 patients received sham stimulation. Patients in the PENFS group had a lower "worst pain score" than with sham group after 3 weeks of treatment (5 vs 7, $P < 0.03$). Such analgesic effects were sustained

Table 5. Summary of Non-pharmacological Methods in Management of Functional Dyspepsia

Category	Methods	Clinical evidence	Efficacy	References
Reassurance	Reassurance	Placebo effect in randomized controlled studies	6-72%	21,22
Psychotherapy	Cognitive behavioral therapy	Randomized controlled studies	54% and 87%	34,71
	Hypnotherapy	Randomized controlled study	73%	29
	Other psychotherapy	Meta-analysis of randomized controlled studies	63-93%	37
Food	Gluten free diet	Retrospective cohort study and randomized controlled study	86-91%	39,72,73
Medical food	Caraway oil + peppermint oil	Randomized controlled studies	61-94%	43,44,54,74-76
	STW 5	Randomized controlled study	86%	47
Acupuncture	Acupuncture over ST36 and PC6	Meta-analysis of randomized controlled studies	60-97%	58,59
Electrical stimulation	Transcutaneous electrical stimulation over ST36 and PC6	Single blinded cross-over study	40% improvement in dyspeptic score	63
	Percutaneous electric nerve field stimulation in the external ear	Randomized controlled study	60%	66

STW 5, garden angelic root, milk thistle fruits, greater celandine; ST36, Stomach-36; PC6, Pericardium-6.

for a median follow-up of 9.2 weeks. The authors postulated that such effects might be driven via stimulation of brainstem nuclei involved in pain pathways (ie, nucleus of the solitary tract). Such results suggest that noninvasive PENFS can be a safe and effective therapeutic option for the treatment of pain in patients with functional gastrointestinal disorders. But, again, more studies are necessary to confirm the above findings using different modalities in electrical stimulation/modulation and to determine the most efficient stimulation paradigm, stimulation methods, and treatment duration for the FD patients.

Conclusion

Non-pharmacological therapies including reassurance, lifestyle modification, psychotherapy, dietary management, medical food, acupuncture, and electrical stimulation/modulation can be useful options for the treatment of FD (Table 5). Non-pharmacological therapies for FD are increasingly being sought by families and medical providers for treating dyspeptic symptoms. The non-invasive nature and potentially minimal side-effects of these non-addictive, non-pharmacological therapy are likely to benefit FD patients, especially those who have failed conventional therapies. The current evidence to warrant the routine use of non-pharmacological therapies in treating FD patients remains limited, though some FD patients do respond well to non-pharmacological management. The timing to incorporate non-pharmacological therapy into the standard therapy and its position in the current treatment algorithm for FD patients remains to be settled. It is still unclear whether it should be used for refractory FD patients or used as an adjunct to the pharmacological therapy. More well-conducted and large-scaled clinical trials are required to confirm their effectiveness and to identify possible adverse effects in FD treatment.

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