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• *REVIEW* •

Management of functional dyspepsia: Unsolved problems and new perspectives

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Abstract

The common characteristic criteria of all functional gastrointestinal (GI) disorders are the persistence and recurrence of variable gastrointestinal symptoms that cannot be explained by any structural or biochemical abnormalities. Functional dyspepsia (FD) represents one of the important GI disorders in Western countries because of its remarkably high prevalence in general population and its impact on quality of life. Due to its dependence on both subjective determinants and diverse country-specific circumstances, the definition and management strategies of FD are still variably stated. Clinical trials with several drug classes (e.g., proton pump inhibitors, H2-blockers, prokinetic drugs) have been performed frequently without validated disease-specific test instruments for the outcome measurements. Therefore, the interpretation of such trials remains difficult and controversial with respect to comparability and evaluation of drug efficacy, and definite conclusions can be drawn neither for diagnostic management nor for efficacious drug therapy so far. In view of these unsolved problems, guidelines both on the clinical management of FD and on the performance of clinical trials are needed. In recent years, increasing research work has been done in this area. Clinical trials conducted in adequately diagnosed patients that provided validated outcome measurements may result in better insights leading to more effective treatment strategies. Encouraging perspectives have been recently performed by methodologically well-designed treatment studies with herbal drug preparations. Herbal drugs, given their proven efficacy in clinical trials, offer a safe therapeutic alternative in the treatment of FD which is often favored by both patients and physicians. A fixed combination of peppermint oil and caraway oil in patients suffering from FD could be proven effective by well-designed clinical trials.

INTRODUCTION

Symptoms of upper gastrointestinal distress are of world-wide interest and very common in the general population. In developing countries the important form of dyspepsia is organic dyspepsia, whereas the problem of functional dyspepsia (FD) seems to be mainly confined to industrialized Western countries though convincing data for underdeveloped countries are still lacking[1]. It is estimated that the annual prevalence of recurrent upper abdominal discomfort in the United States and other Western countries is approximately 25%, about 2% to 5% of all primary care consultations are related to dyspeptic symptoms[2]. For many patients the symptoms are of short duration or mild severity[3] and are therefore self-manageable. Less than half of these patients consult their general practitioner[2]. Moreover, patients with upper gastrointestinal problems frequently suffer from recurrent affections. However, several long-term studies showed that high percentages of patients with dyspeptic symptoms at entry report similar symptoms of dyspepsia after some years[3,4]. Repetitive diagnostic measures and medical treatments with low success rates lead to high costs and frustrating results. Thus, FD represents not only a clinical challenge but also a major socio-economical problem. In recent years, a lot of efforts have been made by national and international consensus meetings to work out precise definitions as well as adequate management strategies for dyspepsia. Still unsolved problems and new perspectives for both research work and disease management in clinical practice are summarized and discussed in more detail in this review.

Definition of functional dyspepsia

Several definitions of dyspepsia have been proposed in the past decades[5] demonstrating the difficulties in categorizing

dyspepsia as a clearly pathologically defined entity based on the variability of symptoms. According to the proposition of an international committee meeting in Rome in 1991, the term "dyspepsia" refers to pain or discomfort centered in the upper abdomen[6] while discomfort refers to a subjective negative (or aversive) feeling that is distinct from pain. Discomfort may include several specific bothersome but non-painful symptoms, such as early satiety, fullness, bloating and nausea (the so-called Rome criteria). In Rome I and more recent Rome II reports[1,7-9], the symptoms of heartburn, acid regurgitation, and belching are excluded from the definition of dyspepsia because they are more likely related to gastroesophageal reflux disease (GERD) and aerophagia[1,9]. It is important to distinguish subjects with uninvestigated dyspepsia from patients with dyspepsia after adequate diagnostic procedure. Patients who have neither definite structural or biochemical explanation for their symptoms are considered to have FD. Thus, FD is defined as a persistent or recurrent dyspepsia for at least 12 wk in the preceding 12 mo if there is no evidence for organic disease (including upper endoscopy) that could cause the symptoms. The Rome II definitions of FD also exclude patients who report a relief of symptoms by defecation or symptoms associated with the onset of a change in stool frequency or stool form[9]. In the latter case, irritable bowel syndrome (IBS) is the diagnosis by definition. Coexistence of FD and IBS can be considered if there is pain or discomfort in the upper abdomen that is unrelated to bowel pattern and if there is other pain or discomfort that is related to bowel pattern[7].

Management of dyspepsia

Due to geographical, cultural, educational, social, and psychological aspects, universally applicable guidelines on diagnostic and therapeutical measures are difficult to implement[1,10]. Management strategies should be individualized and developed for each major community taking into account the prevalence of risk factors for gut diseases such as prevalence of *H pylori* infection, use of non-steroidal anti-inflammatory drugs, dietary habits, tobacco smoking and alcohol consumption[1,10]. Beyond these patient-related factors, the available financial and technical resources in each particular country may dictate the individual steps in the management of dyspepsia[1].

Nevertheless, useful recommendations regarding the management of dyspepsia are concluded in a recent systematic review of the literature[11]. To date, five management strategies can be offered to the physicians treating dyspeptic patients: (1) wait and see-strategy without diagnostic and therapeutic interventions; (2) empiric medical therapy with any subsequent investigation reserved for treatment failures; (3) immediate diagnostic evaluation in all cases; (4) testing for *H pylori* infection and reserving endoscopy for *H pylori*-positive cases to look for organic diseases (test-and-scope strategy); and (5) testing for *H pylori* infection by serology or urea breath test and treating all positive cases with *H pylori* eradication therapy (test-and-treat strategy).

For adult patients in Western countries with new onset of dyspepsia, endoscopy is the gold standard approach providing a firm diagnosis and facilitating decisions on treating or excluding organic diseases. In elderly patients or in those with alarm symptoms such as weight loss, immediate endoscopy is strongly advised. In respect of cost-effectiveness, a repeated endoscopy in those with an initially negative result should be avoided. An alternative management strategy in young dyspeptic patients under 45 years is non-invasive testing for *H pylori* infection and antibacterial treatment of positive cases[10-12]. Because of many substantial disadvantages such as antibiotic resistance, overtreatment, or undertreatment, there is ongoing discussion about the benefit of this strategy.

Management of functional dyspepsia

Patients with FD typically present an array of painful and non-painful symptoms demonstrating the multifactorial nature of this syndrome[13,14]. In order to identify pathophysiological abnormalities with subsequent targeted treatment and to promote more homogeneity, patients can be subdivided into ulcer-like, dysmotility-like and unspecified dyspepsia subgroups based on the concept of a cluster of symptoms[13,15]. Several studies have shown that this arbitrary classification seems to be unsustainable because of the considerable overlap of the subgroups, the lack of stability over time, and the inconsistent responses to therapy[13,16]. Currently, the existence of subgroups among dyspeptic patients is neither endorsed nor categorically disproved[7,8,13].

Another approach to a subdivision of patients with FD is the sus pected association with *H pylori* infection. Between 30% and 60% of patients suffering from FD have *H pylori*-induced gastritis. However, *H pylori* infection is also common in the asymptomatic background population[17,18]. Even most recent trials with prolonged follow-up, analyzing the association between *H pylori* status and specific symptom profiles in FD have produced inconsistent and conflicting results. To date, there is no convincing evidence for the relief of specific dyspeptic symptoms after an eradication therapy[5,13,19,20]. Thus, a benefit of anti- *H pylori* therapy in FD is not established [5,11,19].

Drug therapy for functional dyspepsia

The wide range of therapies reflects the uncertainty about the pathogenesis and the lack of satisfactory treatment. The pathophysiology of FD remains inadequately understood, even though various mechanisms may play a role in the development of symptoms. As yet, there is no cure for this disorder and available treatments are aimed at the relief of symptoms. Even though the efficacy of some currently established treatments (e.g., antisecretory agents or prokinetics) has been proven in placebo-controlled trials, these treatments yield sufficient relief of symptoms only in a proportion of patients[5].

In ulcer-like (pain predominating) functional dyspepsia, H_2-receptor antagonists have produced inconsistent response rates[21]. Patients with dysmotility-like symptoms

(upper abdominal discomfort predominating) may benefit from prokinetic drug treatment[22-24]. Proton pump inhibitors appear to be efficacious especially in patients with ulcer-like pain and accompanying reflux symptoms. The majority of controlled clinical trials have shown only minor advantages of these drugs compared to placebo[25,26].

Thus, efforts should be made to identify and develop new effective treatments. Various herbal medications are used in many countries for the treatment of patients with FD. While some clinicians believe that clinical experience appears to support the use of these remedies, randomized controlled studies supporting the efficacy of these treatments have been lacking in the past decades. Recently, several well-designed placebo-controlled clinical trials have provided evidence for the efficacy of herbal preparations used in the treatment of dyspepsia[27]. Particularly, patients with dysmotility-like dyspeptic symptoms, such as postprandial sensations of fullness, premature feelings of repleteness, non-acid eructation, or epigastric pain, experience a notable amelioration of their complaints[28,29].

Problems with evaluating drug efficacy in functional dyspepsia

Clinical trials in functional GI disorders remain a challenge due to a variable placebo response ranging 20-60%[30], marked spontaneous fluctuations of symptoms and a lack of widely accepted primary response variables. In addition, patients recruited at tertiary referral centers may represent a highly selected population that is less likely to respond to therapy[31]. It is likely that patients with FD present to general practitioners when their symptoms are worse. Therefore, spontaneous improvement may partially explain at least part of the placebo response[18].

Beside these well-known problems, the differences in the design of clinical drug trials in FD call for caution when interpreting their results. A systematic analysis of more than fifty eligible published placebo-controlled clinical trials testing prokinetics[32-35], cytoprotectives[36,37] or anti-ulcer agents[38-40] and other drugs[36,37] used in the treatment of functional dyspepsia revealed that single substantial items for the consistency of clinical studies such as inclusion and exclusion criteria for trial design and outcome measures are common but differ quite definitively in specific determinations[41]. Particularly, it is of importance how investigators deal with symptomatic GERD and other organic diseases. In 50% of the analyzed studies other upper GI disorders such as esophagitis and duodenal or gastric ulcer were not excluded; only 27% of the trials exclude or account for patients with overt irritable bowel syndrome as an overlapping functional disorder. The study design varies from parallel group, cross-over to multiple cross-over design[41]. The majority of analyzed trials fail to fulfill the indispensable requirement for efficacy evaluation and comparability of drug classes, i.e. use of clearly defined patient groups according to the consensual definition of FD and the use of validated outcome measures regarding described symptoms, their severity, and quality of life yielded with validated categorical and visual analog scales (VAS). Thus, the authors concluded that convincing conclusions for efficacious drug therapy in the treatment of FD cannot be drawn.

Promising outcome measures for clinical trials

Although some research work has been done to develop validated outcome measures of symptoms[42] which can be used in FD, no generally accepted scales are available. Categorical scales (often referred to as Likert Scales) and VAS (horizontal line, usually 10 cm with endpoints on which the patient must place a mark) have been extensively applied[29,39,43-45] and qualified as most eligible measurement scales by their reproducibility and ability to detect changes in a wide variety of clinical trials of different diseases. The usefulness of a reasonable combination of a categorical scale and a VAS is demonstrated by the dyspeptic discomfort score (DDS) which records the existence, frequency and severity of the symptoms of functional dyspepsia[28,29]. Integrating the dyspeptic, intestinal and extraintestinal autonomic discomforts assessed by means of numerical scales, the DDS seems to consider the entire complexity of this syndrome. Nevertheless, the DDS has not been validated yet.

A noteworthy measurement instrument to be mentioned is the clinical global impression (CGI) scale consisting of three items, namely severity of illness, global improvement and efficacy index. The first and second items are rated on a point scale while the third is a rating of the interaction of therapeutic effectiveness and adverse reactions. Originally conceived for schizophrenic studies, the CGI scale facilitates prognosis, survey and assessment of drug efficacy during the treatment period[28,29,44].

During the last years, attention has been drawn to the fact that in diseases without obvious biological or clinical markers such as functional dyspepsia, the use of quality of life instruments and psychometric documentation as an outcome measure can reflect treatment efficacy evaluated by its impact on symptoms as well as on patient well-being and functioning[41,46]. The underlying philosophy is that quality of life is affected by the severity of disease-specific symptoms. Hence, the reciprocal conclusion can be drawn by any change of symptom severity. Recently, validation data of the new disease-specific Nepean dyspepsia index (NDI)[46,47] and the quality of life in reflux and dyspepsia patient (QOLRAD) questionnaire[48] measuring frequency, intensity, and bothersomeness of upper gastrointestinal symptoms have been presented. The remarkable feature of the NDI is the consideration not only of a subject's ability to perform or engage in an aspect of life but also the enjoyment of that aspect of life. In a systematic review of full-length publications during 1980-2002 reporting studies in patients with FD and measuring health-related quality of life, none of the studies used dyspepsia-specific health-related quality of life instruments[49]. However, recently a first methodologically well-designed clinical study proving efficacy of the study drug by use of the NDI was reported by Holtmann and colleagues[50], which demonstrates a

statistically significant and clinically relevant superiority of a fixed combination of peppermint oil and caraway oil (PCC) in comparison to placebo. The reported outcome confirms the results formerly obtained with this herbal preparation in placebo-controlled clinical trials[28,44] and in a double-blind equivalence study with the prokinetic drug cisapride[29], measured by VAS, CGI and the DDS.

Recommendations for future trials

In view of the mentioned weaknesses in present trials, the most essential recommendations are summarized as follows.

According to the consensus for a diagnosis of FD, a minimum set of diagnostic measures including upper endoscopy, an abdominal ultrasound and basic laboratory is obligatory[6]. At the time of enrolment for a treatment study, eligible patients must have persistent symptoms that are of a sufficient degree to seek medical attention. Any definite structural abnormalities of the upper GI tract, explaining the symptoms, e.g., peptic ulcer confirmed by endoscopic evidence and biochemical agents such as daily use of NSAID or high dose aspirin must be excluded. To avoid an overlap with gastroesophageal reflux disease, patients in whom heartburn or acid regurgitation are the predominant symptoms or patients suffering from irritable bowel syndrome and other known organic diseases that might explain the dyspepsia symptoms must not be enrolled.

Despite some well recognized problems such as the occurrence of period-by-treatment interactions of cross-over trials resulting in ambiguous interpretation of data, the randomized, double-blind, placebo-controlled parallel group design is strongly advocated as the trial design of choice.

It is not to deny that even among physicians there is great variation in the definitions of common dyspeptic symptoms. In addition, terminology and possibly also the sensations experienced vary between cultures and countries. Therefore, it is advisable that clinical investigators use definitions of symptoms suggested by the Rome Working Party report and accommodated to common parlance in the respective study population.

As validated outcome measures like the NDI and the QOLRAD questionnaire are now available, their use is strongly recommended regarding described symptoms, their severity, and aspects of quality of life. In order to support the results obtained with these validated disease specific questionnaires, categorical scales, VAS and the CGI could be used as secondary outcome measures. Promising outcome measures such as DDS, should be validated soon in order to broaden the range of appropriate devices for evaluating drug efficacy in functional dyspepsia.

Further research using well-validated outcome instruments for measurement of individual symptoms as well as their severity and their impact on quality of life may perhaps result in a valid symptom-related categorization of functional dyspepsia that may be used to improve treatment strategies.

Causally determined by the aforementioned unsolved problems concerning the definition and management of FD as well as the listed weaknesses in trial methodology of present treatment studies, convincing conclusions for efficacious drug therapy cannot be drawn yet. However, it is very likely that effective drug therapies are av-ailable. Further research on well-validated measurement instruments for outcome data permitting comparability of drug classes may perhaps result in better insights with respect to effective treatment strategies. Quite recently, new perspectives have been arising from presented efficacy of a fixed peppermint oil/caraway oil preparation in a methodologically adequate clinical trial.

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