Management of functional dyspepsia: Unsolved problems and new perspectives

Ahmed Madisch, Stephan Miehlke, Joachim Labenz

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[4]. 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[5,6]. 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 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, 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. 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. 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.

Management of dyspepsia

Due to geographical, cultural, educational, social, and psychological aspects, universally applicable guidelines on diagnostic and therapeutic measures are difficult to implement. 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. 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.

Nevertheless, useful recommendations regarding the management of dyspepsia are concluded in a recent systematic review of the literature. 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. 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. 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. 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. Currently, the existence of subgroups among dyspeptic patients is neither endorsed nor categorically disproved.

Another approach to a subdivision of patients with FD is the suspected 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. 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. Thus, a benefit of anti-H pylori therapy in FD is not established.

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., antiserotony agents or prokinetics) has been proven in placebo-controlled trials, these treatments yield sufficient relief of symptoms only in a proportion of patients. In ulcer-like (pain predominating) functional dyspepsia, H2-receptor antagonists have produced inconsistent response rates. Patients with dysmotility-like symptoms...
(upper abdominal discomfort predominating) may benefit from prokinetic drug treatment. 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. 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. Particularly, patients with dysmotility-like dyspeptic symptoms, such as postprandial sensations of fullness, premature feelings of repletion, non-acid eructation, or epigastric pain, experience a notable amelioration of their complaints.

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%[34], 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. 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.[38]

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, cytoprotective, and other drugs 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. 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. 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[39] 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[36,37] 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.[26,29] 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.[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.[36,46] 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[39]. 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[5]. At the time of enrollment 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 malignant 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 crossover 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 available. 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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**REFERENCES**

1. Malfertheiner P. Current concepts in dyspepsia: a world perspective. *Eur J Gastroenterol Hepatol* 1999; 11 Suppl 1: S25-S29
2. Knill-Jones RP. Geographical differences in the prevalence of dyspepsia. *Scand J Gastroenterol* Suppl 1991; 182: 17-24
3. Johannesssen T, Petersen H, Kristensen P, Kleveland PM, Dybdahl J, Sandvik AK, Brena E, Waldum H. The intensity and variability of symptoms in dyspepsia. *Scand J Prim Health Care* 1993; 11: 50-55
4. Jones R, Lyeard S. Dyspepsia in the community: a follow-up study. *Br J Clin Pract* 1992; 46: 95-97
5. Talley NJ. Helicobacter pylori and dyspepsia. *Yale J Biol Med* 1999; 72: 145-151
6. Talley NJ, Stanghellini V, Heading RC, Koch KL, Malagelada JR, Tytgat GN. Functional gastroduodenal disorders. *Gut* 1999; 45 Suppl 2: II37-II42
7. Talley NJ, Stanghellini V, Heading RC, Koch KL, Malagelada JR, Tytgat GN. Functional gastroduodenal disorders. *Gut* 1999; 45 Suppl 2: II37-II42
8. Thompson WG, Longstreth GF, Drossman DA, Heaton KW, Irvine EJ, Müller-Lissner SA. Functional bowel disorders and functional abdominal pain. *Gut* 1999; 45 Suppl 2: II43-II47
9. Spiller R. Rome II: the functional gastrointestinal disorders. Diagnosis, pathophysiology and treatment: a multinational consensus. *Gut* 2000; 46: 741B
10. Mullins PD, Colin-Jones DG. Guidelines for the management of dyspepsia. *Eur J Gastroenterol Hepatol* 1999; 11: 215-217
11. Talley NJ, Silverstein MD, Agreus L, Nyrén O, Sonnenberg A, Holtmann G. AGA technical review: evaluation of dyspepsia. *American Gastroenterological Association.* *Gastroenterology* 1998; 114: 582-595
12. Moayyedi P, Zilles A, Clough M, Hemingbrough E, Chalmers DM, Axon AT. The effectiveness of screening and treating Helicobacter pylori in the management of dyspepsia. *Eur J Gastroenterol Hepatol* 1999; 11: 1245-1250
13. Holtmann G, Stanghellini V, Talley NJ. Nomenclature of dyspepsia, dyspepsia subgroups and functional dyspepsia: clarifying the concepts. *Baillieres Clin Gastroenterol* 1998; 12: 417-433
14. Mansi C, Mela FS, Pasini D, Grosso M, Corti L, Moretti M, Celle G. Patterns of dyspepsia in patients with no clinical evidence of organic diseases. *Dig Dis Sci* 1990; 35: 1452-1458
15. Gotthard R, Bodenmaier G, Brodin U, Jönsson KA. Treatment with cimetidine, antacid, or placebo in patients with dyspepsia of unknown origin. *Scand J Gastroenterol* 1988; 23: 7-18
16. Talley NJ, Weaver AL, Tesmer DL, Zinsmeister AR. Lack of
discriminant value of dyspepsia subgroups in patients referred for upper endoscopy. *Gastroenterology* 1993; 105: 1378-1386

17 Verdú EF, Armstrong D, Idstrom JP, Labenj J, Stolte M, Borsch G, Blum AL. Intragastric pH during treatment with omeprazole: role of Helicobacter pylori and H pylori- associated gastritis. *Scand J Gastroenterol* 1996; 31: 1151-1156

18 Talley NJ, Hunt RH. What role does Helicobacter pylori play in dyspepsia and nonulcer dyspepsia? Arguments for and against H. pylori being associated with dyspeptic symptoms. *Gastroenterology* 1997; 113: 567-577

19 Talley NJ. A critique of therapeutic trials in Helicobacter pylori-positive functional dyspepsia. *Gastroenterology* 1994; 106: 1174-1183

20 El-Omar EM, Oken K, El-Nujumi A, Gillen D, Wirz A, Dahil S, Williams C, Ardill JE, McColl KE. Helicobacter pylori infection and chronic gastric acid hypersecretion. *Gastroenterology* 1997; 113: 15-24

21 Farup PG, Wetterhus S, Osnes M, Ulshagen K. Ranitidine effectively relieves symptoms in a subset of patients with functional dyspepsia. *Scand J Gastroenterol* 1997; 32: 755-759

22 Holtmann G, Gschossmann J, Karaus M, Fischer T, Becker B, Mayr P, Gerken G. Randomised double-blind comparison of simethicone with cisapride in functional dyspepsia. *Aliment Pharmacol Ther* 1999; 13: 1459-1465

23 Halter F, Staub P, Hammar B, Guyot J, Miazza BM. Study with two prokinetics in functional dyspepsia and GORD: domperidone vs. cisapride. *J Physiol Pharmacol* 1997; 48: 185-192

24 Carvalhinos A, Fidalg P, Freire A, Matos L. Cisapride compared with ranitidine in the treatment of functional dyspepsia. *Eur J Gastroenterol Hepatol* 1995; 7: 411-417

25 Hansen JM, Bytzer P, Schaffaltzky de Muckadell OB. Placebo-controlled trial of cisapride and nizatidine in unslected patients with functional dyspepsia. *Am J Gastroenterol* 1998; 93: 368-374

26 Talley NJ, Meineche-Schmidt V, Pare P, Dukworth M, Raisanen P, Pap A, Kordecki H, Schmid V. Efficacy of omeprazole in functional dyspepsia: double-blind, randomized, placebo-controlled trials (the Bond and Opera studies). *Aliment Pharmacol Ther* 1998; 12: 1055-1065

27 Pu RT, Osmani SA. Mitotic destruction of the cell cycle regulated NIMA protein kinase of Aspergillus nidulans is required for mitotic exit. *EMBO J* 1995; 14: 995-1003

28 May B, Köhler S, Schneider B. Efficacy and tolerability of a fixed combination of peppermint oil and caraway oil in patients suffering from functional dyspepsia. *Aliment Pharmacol Ther* 2000; 14: 1671-1677

29 Madisch A, Heydenreich CJ, Wieland V, Hufnagel R, Hotz J. Treatment of functional dyspepsia with a fixed peppermint oil and caraway oil combination preparation as compared to cisapride. A multicenter, reference-controlled double-blind equivalence study. *Arzneimittelforschung* 1999; 49: 925-932

30 Talley NJ, Phillips SF. Non-ulcer dyspepsia: potential causes and pathophysiology. *Ann Intern Med* 1988; 108: 865-879

31 Veldhuyzen van Zanten SJ, Talley NJ, Bytzer P, Klein KB, Whorwell PJ, Zinsmeister AR. Design of treatment trials for functional gastrointestinal disorders. *Gut* 1999; 45 Suppl 2: II69-II77

32 Hausken T, Berstad A. Wide gastric antrum in patients with non-ulcer dyspepsia. Effect of cisapride. *Scand J Gastroenterol* 1992; 27: 427-432

33 Hausken T, Berstad A. Cisapride treatment of patients with non-ulcer dyspepsia and erosive prepyloric changes. A double-blind, placebo-controlled trial. *Scand J Gastroenterol* 1992; 27: 213-217

34 Sarin SK, Sharma P, Chawla YK, Gopinath P, Nundy S. Clinical trial on the effect of domperidone on non-ulcer dyspepsia. *Indian J Med Res* 1986; 83: 623-628

35 De Loore I, Van Ravensteyn H, Amerycx L. Domperidone drops in the symptomatic treatment of chronic paediatric vomiting and regurgitation. A comparison with metoclopramide. *Postgrad Med J* 1979; 55 Suppl 1: 40-2

36 Hausken T, Stene-Larsen G, Lange O, Aronsen O, Nerdrum T, Hegbom F, Schulz T, Berstad A. Misoprostol treatment exacerbates abdominal discomfort in patients with non-ulcer dyspepsia and erosive prepyloric changes. A double-blind, placebo-controlled, multicentre study. *Scand J Gastroenterol* 1990; 25: 1028-1033

37 Skoubo-Kristensen E, Funch-Jensen P, Kruse A, Hanberg-Sørensen F, Amdrup E. Controlled clinical trial with sucralfate in the treatment of macroscopic gastritis. *Scand J Gastroenterol* 1989; 24: 716-720

38 Johannessen T, Kristensen P, Petersen H, Fosstvedt D, Løge I, Kleveland PM, Dybdahl J. The symptomatic effect of 1-day treatment periods with cimetidine in dyspepsia. Combined results from randomized, controlled, single-subject trials. *Scand J Gastroenterol* 1991; 26: 974-980

39 Farup PG, Larsen S, Ulshagen K, Osnes M. Ranitidine for non-ulcer dyspepsia. A clinical study of the symptomatic effect of ranitidine and a classification and characterization of the respondents to treatment. *Scand J Gastroenterol* 1991; 26: 1209-1216

40 Smith PM, Troughton AH, Gleeson F, Walters J, McCarthy CF. Pirenzepine in non-ulcer dyspepsia: a double-blind multicentre trial. *J Int Med Res* 1990; 18: 16-20

41 Veldhuyzen van Zanten SJ, Cleary C, Talley NJ, Peterson TC, Nyren O, Bradley LA, Verlinden M, Tytgat GN. Drug treatment of functional dyspepsia: a systematic analysis of trial methodology with recommendations for design of future trials. *Am J Gastroenterol* 1996; 91: 660-673

42 Leidy NK, Farup C, Rentz AM, Ganozcy D, Koch KL. Patient-based assessment in dyspepsia: development and validation of Dyspepsia Symptom Severity Index (DSSI). *Dig Dis Sci* 2000; 45: 1172-1179

43 Madisch A, Melderis H, Mayr G, Sassin I, Hotz J. A plant extract and its modified preparation in functional dyspepsia. Results of a double-blind placebo controlled comparative study. *Z Gastroenterol* 2001; 39: 511-517

44 May B, Kunz HD, Kieser M, Köhler S. Efficacy of a fixed peppermint oil/caraway oil combination in non-ulcer dyspepsia. *Arzneimittelforschung* 1996; 46: 1149-1153

45 Corazza GR, Biagi F, Albano O, Bianchi Porro G, Cheli R, Mazzacca G, Miglio F, Naccarato R, Quaglino D, Surrenti C, Verme G, Gasbarrini G. Levosulpiride in functional dyspepsia: a multicentric, double-blind, controlled trial. *Ital J Gastroenterol Hepatol* 1996; 28: 317-322

46 Talley NJ, Haque M, Wyeth JW, Stace NH, Tytgat GN, Stanghellini V, Holtmann G, Verlinden M, Jones M. Development of a new dyspepsia impact scale: the Nepean Dyspepsia Index. *Aliment Pharmacol Ther* 1999; 13: 225-235

47 Talley NJ, Verlinden M, Jones M. Validity of a new quality of life scale for functional dyspepsia: a United States multicenter trial of the Nepean Dyspepsia Index. *Am J Gastroenterol* 1999; 94: 2590-2597

48 Wiklund IK, Junghard O, Grace E, Talley NJ, Kamm M, Veldhuyzen van Zanten S, Paré P, Chiba N, Leddin DS, Bigard MA, Colín R, Schoenfeld P. Quality of Life in Reflux and Dyspepsia patients. Psychometric documentation of a new disease-specific questionnaire (QOLRAD). *Eur J Surg Suppl* 1998; 583: 41-49

49 El-Serag HB, Talley NJ. Health-related quality of life in functional gastrointestinal disease. *Aliment Pharmacol Ther* 2003; 18: 387-393

50 Holtmann G, Haag S, Adam B, Funk P, Wieland V, Heydenreich CJ. Effects of a fixed combination of peppermint oil and caraway oil on symptoms and quality of life in patients suffering from functional dyspepsia. *Phytomedicine* 2003; 10 Suppl 4: 56-57