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Functional dyspepsia – A multicausal disease and its therapy

H.D. Allescher

Center for Internal Medicine, Gastroenterology, Hepatology and Metabolism, Klinikum Garmisch-Partenkirchen, Academic Teaching Hospital of the Ludwig-Maximilians-University Munich, Auenstr. 6, 82467 Garmisch-Partenkirchen, Germany

Abstract

Functional dyspepsia is a common chronic disorder with non-specific upper abdominal symptoms which can not be explained by organic or biochemical abnormalities. The dyspeptic symptoms are very compromising and bothersome and result in a substantial reduction of quality of life. The substantial direct and indirect medical and economical costs induce a high socioeconomic interest in the pathogenesis and the treatment options of this disease. Over the past 30 years several theories about the etiology of the symptoms in functional dyspepsia patients have been put forward. These include disorders of gastrointestinal motility, acid secretion, visceral hypersensitivity, adaptation and accommodation, Hp-infection, mucosal inflammation and finally genetic predisposition. There is increasing evidence that functional dyspepsia is a multi-causal disorder, which leads to altered processing of afferent information from the gastrointestinal tract to the CNS. Autonomic hypersensitivity and altered central processing could be a common phenomenon whereas motility changes, inflammation or altered secretion could increase neural afferent inputs. Treatment of this complex disorder could and should involve these different levels of symptom generation. Thus different approaches with anti-secretory, spasmolytic, prokinetic and anti-inflammatory effects and most preferably reduction of visceral hypersensitivity seem logical. This could explain the variety of drugs which show a positive symptomatic response. This could also offer the conclusion, whether a combination of these drugs could be clinically superior which remains to be proven. And this could offer a logical approach for the use of substances with a multi-target action, e.g. STW 5.

Keywords: Dyspepsia; Autonomic hypersensitivity; Motility disorder; Prokinetics; Antiacids; H2 receptor antagonists; PPI; Phytotherapy; STW 5; Iberogast; Iberis amara

Introduction

Functional dyspepsia is a very common cause of upper gastrointestinal symptoms and discomfort. These „dyspeptic" symptoms include postprandial fullness, early satiety, epigastric or localized pain, nausea, belching, bloating (Talley et al. 1987). Uninvestigated dyspeptic symptoms can be caused by organic disorders such as peptic ulcer, cholelithiasis, reflux disease or malignant disease. In a population with un-investigated dyspepsia about one third to half of the patients has an organic disease. However, in the majority of the patients with dyspeptic symptoms the routine clinical diagnostic procedures reveal no reasonable explanation for their "dyspeptic" symptoms. If these symptoms persist for a longer time period (more than 3 month) these patients are categorized as having functional dyspepsia. There are some frequent findings in the upper endoscopy (chronic gastritis, duodenitis) or in functional gastrointestinal tests (e.g. lactose deficiency), which are often

E-mail address: hans.allescher@klinikum.gap.de.

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Table 1. Definition of functional dyspepsia according to Rome II criteria (Talley et al. 1999c)

At least 12 weeks, which need not be consecutive, within the preceding 12 months of:
(1) Persistent or recurrent dyspepsia (pain or discomfort centered in the upper abdomen); and
(2) No evidence of organic disease (including upper endoscopy) that is likely to explain the symptoms; and
(3) No evidence that dyspepsia is exclusively relieved by defecation or associated with the onset of a change in stool frequency or stool form (i.e., not irritable bowel).

taken as a possible explanations for the etiology of the symptoms (Allescher et al. 1999). It has been emphasized in guidelines that only those lesions or biochemical abnormalities will rule out functional dyspepsia which (a) reproducibly explain the generation of the symptoms an (b) lead to disappearance of the symptoms upon treatment (Malfertheiner et al. 2001).

Most importantly, patients with the leading or sole symptom of heart burn or acid regurgitation are no longer regarded as having functional dyspepsia. These patients are believed to have non erosive reflux disease (NERD) and are diagnosed and treated similar to reflux patients (Klauser et al. 1990; Talley and Vakil 2005).

Functional dyspepsia leads to a substantial reduction of quality of life in the range of or higher than peptic ulcer disease, severe reflux disease or gastrointestinal cancer (Table 1).

Un-investigated dyspepsia is one of the most common reasons for medical consultation in western countries. Up to 25% of the population have occasional upper gastrointestinal symptoms, however only a subgroup of these patients will actually consult a doctor (Malfertheiner et al. 2001; Mearin et al. 1991). These patients usually have more severe or more frequent abdominal symptoms and additional extra-intestinal symptoms (Holtmann et al. 1994).

The diagnosis and initial management of patients with un-investigated dyspepsia und with functional dyspepsia have been summarized and outlined in several national and international guidelines and the reader is referred to these recent publications (Malfertheiner et al. 2001; Talley et al. 1998, 1999b; Vakil 2005).

Etiology

The etiology of functional dyspepsia is still unclear. Several factors and mechanisms have been postulated as underlying cause of this disorder and most of these factors seem to play a role in the development of the symptomatology (Table 2).

Table 2. Postulated disorders and mechanisms for the development of dyspeptic symptoms in functional dyspepsia

- Visceral hypersensitivity
  - Increased perception of distention
  - Impaired or altered perception of acid
  - Visceral hypersensitivity as a consequence of chronic inflammation
- Motility disorders
  - Postprandial antral hypomotility
  - Reduced relaxation of the gastric fundus
  - Decreased or impaired gastric emptying
  - Changes of the gastric electric rhythm
  - Gastro-ösophagealer reflux
  - Duodeno-gastric reflux
- Changes in acid secretion
  - Hyperacidity
- *Helicobacter pylori* infection
- Stress
- Psychological disorders and abnormalities
- Genetic predisposition

Visceral hypersensitivity is currently the most likely candidate as a possible underlying cause leading to increased perception and processing of gastrointestinal neural inputs (Mearin et al. 1991). A majority of patients with functional dyspepsia responds to a lower threshold of distention as matched healthy volunteers. If this phenomenon also applies to other modalities, it could also explain why changes in motility, acid secretion and distention show similar symptomatic responses. It is still unclear whether this hypersensitivity only affects a circum-script region of the GI-tract or whether the hypersensitivity affects the whole gastrointestinal tract. Despite changes of the sensibility of the GI-tract there is no change of distention induced pressure (e.g. compliance). This implies that even physiological conditions and normal activities of the stomach and small bowl could lead to symptoms in patients with functional dyspepsia.

The cause of the hypersensitivity is still a matter of debate. There is some evidence that there is up-regulation of afferent mechanisms in the peripheral (intestinal) level, the pre-vertebral and spinal level. This up-regulation could be due to chronic irritation or inflammation or to an initiating process which caused the up-regulation still in a physiological process and now cannot be reversed. In the large bowel recent evidence draws some attention to a possible role of specific Ig G antibodies to certain food allergens. An elimination diet in these patients with irritable bowl syndrome leads to some symptomatic improvement

(Atkinson et al. 2004). In patients with functional dyspepsia (Holtmann et al. 2004b) as well as in patients with other functional disorders there is also some recent evidence for a genetic predisposition. In functional dyspepsia patients there were small but distinct genetic polymorphisms (C825 T) of the G-protein beta 3 (GNB3) subunit. Homozygote GNB3 825C status was slightly correlated with functional dyspepsia (Holtmann et al. 2004b), however, this mechanism, though novel and attractive, needs further confirmation in prospective trials.

In addition to hypersensitivity and genetic predisposition there have been a variety of distinct abnormalities in gastrointestinal motility and psychological characteristics which could be found in subgroups of patients with functional dyspepsia. Whether these disorders are an epiphenomenon or are related to symptom development or altered central processing remains unclear. In 30–82% of functional dyspepsia patients postprandial antral hypomotility, a reduced relaxation of the fundus, changes of the electric gastric rhythm or a reduced rate of gastric emptying can be observed.

Symptom development and aggravation in functional dyspepsia is often linked and attributed to stressful life events. In many cases acute stress or life time events (e.g. death of closely related family member or friend) can lead to an increased reflection about the symptoms, thus motivating the patient to seek medical help and consultation. Additionally, stress could lead to altered intestinal function (e.g. motility, acid secretion) which in connection with the visceral hypersensitivity could lead to increased symptom perception.

Many patients with functional dyspepsia report an association of gastrointestinal symptoms during or after eating food, however, it is usually not possible to identify certain food components which cause symptoms. There is also no evidence that coffee, alcohol or smoking is associated with the generation of the symptoms, even though these components are usually avoided by patients with functional dyspepsia.

Differentiation and distinction from other gastrointestinal disorders

Helicobacter pylori (Hp) and Hp-induced gastritis is also regarded as a possible cause of dyspeptic symptoms and was also suggested as a possible cause of visceral hypersenstivity. However, most interventional studies were rather disappointing, as only a small subgroup of patients were relieved of dyspeptic symptoms after Hp eradication, especially when compared to placebo. A microscopic chronic active gastritis or duodenitis can often be found in asymptomatic Hp-positive persons and there is little or no correlation between Hp-status and functional dyspepsia. Thus the pure finding of Hp-positive gastritis has no causal link to the development of dyspeptic symptoms.

A similar association can be found for asymptomatic gallbladder stones which can be often found in asymptomatic patients and have no direct link to the development of symptoms (Malfertheiner et al. 2001). Treatment of either gastritis or gallbladder stones by cholecystectomy does not lead to a permanent improvement or disappearance of functional dyspepsia (Talley et al. 1999a).

Dyspeptic symptoms can also originate as typical side effects from certain drugs or drugs components such as non steroidal anti rheumatics (NSAR), oral iron supplementation or makrolide antibiotics (e.g. erythromycin) or prostaglandin analogues.

Patients with predominant heart burn or acid regurgitation, but no endoscopic sign of reflux esophagitis, constitute a certain subgroup of acid predominant functional dyspepsia. Today, these patients are identified as having non erosive reflux disease (NERD) and are no longer regarded as having functional dyspepsia. These patients usually respond to acid suppression therapy with proton pump inhibitors.

A clear distinction to patients with irritable bowel syndrome is not always possible as there is a wide symptomatic overlap. As already mentioned, there might also be a common pathogenetic mechanism of these two functional bowel disorders.

Clinical presentation

Patients with functional dyspepsia are characterized by chronic and long lasting symptoms, which lead to a substantial impairment of quality of life. Common clinical procedures (endoscopy, laboratory or ultrasound) show no evidence of significant clinical disease. Sub-classification according to the main symptoms proved not of clinical use (Talley et al., 1992). However, patients with predominant reflux symptoms are not any

Table 3. Gastrointestinal symptoms, which can be observed in patients with functional dyspepsia (Malfertheiner et al. 2001)

Fullness, especially postprandially
Early satiety
Epigastric pain or pressure
Bloating[a]
Retching
Retro sternal burning (heart burn)[a]
Nausea
Vomiting[a]

[a] In combination with other symptoms, not as leading primary symptom.

Table 4. The spectrum of dyspepsia symptoms and recommended definitions of symptoms (Talley et al. 1999c)

–Pain centered in the upper abdomen	Pain refers to a subjective, unpleasant sensation; some patients may feel that tissue damage is occurring. Other symptoms may be extremely bothersome without being interpreted by the patient as pain. By questioning the patient, pain should be distinguished from discomfort.
–Discomfort centered in the upper abdomen	A subjective, unpleasant sensation or feeling that is not interpreted as pain according to the patient and which, if fully assessed, can include any of the symptoms below.
–Early satiety	A feeling that the stomach is overfilled soon after starting to eat, out of proportion to the size of the meal being eaten, so that the meal cannot be finished.
–Fullness	An unpleasant sensation, like the persistence of food in the stomach; this may or may not occur post-prandially (slow digestion).
–Bloating in the upper abdomen	A tightness located in the upper abdomen; it should be distinguished from visible abdominal distension
–Nausea	Queasiness or sick sensation; a feeling of the need to vomit

Table 5. Alarm symptoms, which require immediate diagnostic work up

–Fever $>38.5\,^{\circ}C$
–Night sweat
–Weakness, reduced physical fitness
–Weight loss $>3\,kg$
–Recurrent vomiting
–Haematochezzie or haematemesis
–Severe localized pain
–Dysphagia
–Findings in the clinical status

longer regarded as having functional dyspepsia and are treated for non erosive reflux disease with PPI (Tables 3 and 4).

The management strategies differ in different countries and health care systems, as well as in different levels of care. In most management strategies an immediate clinical diagnostic workup is recommended when alarming symptoms are present (Table 5).

Diagnosis

Management and diagnostic workup has to be separated in un-investigated dyspepsia and functional dyspepsia. Un-investigated dyspepsia with acute onset but without alarm symptoms often requires no imminent diagnosis. However, if symptoms persist or worsen there are different management strategies. In several countries after initial empiric treatment for a limited time period an upper GI endoscopy is recommended as the next step. In several Anglo-American and Scandinavian countries other strategies such as ,,Test(Hp) and treat'' or ,,Test(Hp)-and Scope'' have been developed in order to increase the diagnostic yield of the endoscopy procedure and to avoid unnecessary or negative endoscopies (Delaney et al. 2005; Ofman and Rabeneck 1999). Interestingly, patients seemed to prefer an initial thorough diagnosis before treatment is initiated (Bytzer et al. 1994) leading to less consultations and to lower costs (Delaney et al. 2005).

In patients younger than 50 with normal physical exam an empiric medical treatment for 4–6 weeks is usually started. When symptoms persist, a basic work up with laboratory tests and an upper GI-endoscopy is performed. Abdominal ultrasound is often normal and adds little new information. In many countries abdominal ultrasound is easy accessible and widely used and is becoming part of the ''basic physical status'' of a patient.

In patients with atypical symptoms or abnormalities of the clinical presentation or laboratory, further diagnostic procedures should be initiated. These can include exocrine pancreatic function tests (e.g. pancreatic elastase), glucose breath test for bacterial overgrowth, lactose breath test for lactose mal-absorption, gastric emptying testing (scintigraphy, ^{13}C-octanoate-breath test), biopsies of the duodenum, and stool tests for parasites.

Therapy

As mentioned above, the concepts and definitions of dyspepsia have changed over time. Therefore it is essential to consider the definitions and the target population of certain studies when evaluating them as evidence for treatment success of functional dyspepsia using the current definitions. Additionally, there has to be a clear distinction between dyspeptic symptoms in ''un-investigated dyspepsia'' and in patients with ''proven'' functional dyspepsia. The latter comprise approximately 50–60% of the patients presenting with dyspeptic symptoms.

In contrast to most other gastrointestinal disorders (peptic ulcer, reflux, CED) there is no standard therapy of functional dyspepsia and no generally accepted therapeutic gold standard. The national and international recommendations vary and even textbooks give different management and treatment alternatives. There

are several reasons for these discrepancies. The definitions of functional dyspepsia and inclusion and exclusion criteria for studies on functional dyspepsia have changed substantially over time. In older studies, but also some newer studies, there was no clear distinction between functional dyspepsia („unexplained dyspepsia") and dyspeptic symptoms („un-investigated dyspepsia"). Additionally some studies were not performed as placebo-controlled studies, but were compared to the current therapy gold standard, which make a further evaluation difficult or impossible. Additionally, treatment alternatives differ in many countries and many substances which are preferred in some European countries (e.g. STW 5, domperidone) have not been available in USA or Japan and vice versa (e.g. tegaserode). There are multiple reviews and meta-analyses on different aspects of functional dyspepsia therapy, which have to be seen on the basis of this background (Allescher et al. 2001; Delaney et al. 2005; Dobrilla et al. 1989; Holtmann and Talley 1993; Moayyedi et al. 2005; Talley and Vakil 2005).

Positive diagnosis with clarification and explanation, disease model

Therapeutic management of patients with functional dyspepsia is primarily based on a positive and reliable clinical diagnosis after exclusion of relevant organic disorders. Thus the clinical evaluation of the patient is also an important step in the therapeutic management confirming to the patients that his concerns and fears of severe organic disease is taken seriously, but has been excluded with the appropriate care. This step should consider and eliminate fears and concerns of the patients. As a next step a clear, easy and understandable disease model should be developed and explained to the patient. This disease model can incorporate the opinions and explanations of the patient and should also integrate the possible individual psychological factors and peculiarities. It is very important to explain to the patient, that even after negative or normal findings in modern diagnostic procedures such as endoscopy, ultrasound or radiology, there is a clear scientifically plausible mechanism for the development of the symptoms based on the visceral hypersensitivity and that this disturbance cannot be positively diagnosed with the current routine clinical diagnostic tools. Based on this "disease model", it is possible to explain the symptom generation and basis for possible therapeutic alternatives to the patient.

Nutrition, diet, smoking and alcohol

In most patients there is a clear link between clinical symptoms and food intake. Anecdotally, dyspeptic symptoms may be reduced by avoiding offending foods, high fat diet, coffee, alcohol, and cigarette smoking. Additionally, if early satiety, postprandial bloating, or nausea is predominant, taking six small low fat meals per day may help decrease the intensity of the symptoms. However, there are so far no real proven dietary or nutritional recommendations, which on a general basis will help to reduce the symptoms (Mullan et al. 1994; Talley et al. 1994). There is a general recommendation to avoid fat meals and bloating food components such as cabbage, nuts and certain drugs known to worsen clinical symptoms such as NSAR or iron supplementation. There is also the general recommendation to avoid large meals especially in the evening hours and to preferable divide the daily food intake in several small meals. Lactase supplementation or avoidance of lactose can be beneficial in a subgroup of patients with a lactose malabsorption. It is generally not recommended to adhere to very strict or one sided diets such as completely avoiding meat or wheat products. Many patients tolerate or even do better with Mediterranean or non spicy Asian food.

Medical therapy

After the development of a disease model for the patient, it has to be clarified whether the patient wants and needs medical treatment. Currently there is no standard medication for the treatment of functional dyspepsia which will eliminate the symptoms with high likelihood and high effectiveness. Most active treatment alternatives show only a small superiority of 10–20% above placebo treatment. On the other side, the rate of placebo effect is high (40%) ranging from 30 to 70%. Thus the estimated "combined" treatment effect is between 40 to almost 90%. Treatment should be explained to the patients in the context of the disease model.

Several drugs and treatment alternatives have been tested in the past for their symptomatic benefit in patients with functional dyspepsia. These substances include prokinetics and spasmolytics, acid suppressing drugs (H2-blockers, PPIs), Hp-eradication, phytopharmaca and alternative drugs.

Prokinetics

Domperidone

Domperidone is a peripheral dopamine D_2-antagonist which does not cross the blood brain barrier. In several older placebo controlled trials, a positive effect in patients with functional dyspepsia has been proven.

However, the inclusion and exclusion criteria of these mostly older studies on domperidone in functional dyspepsia are not consistent with current definitions and standards. Therefore the evidence level for the effect of domperidone has some limitations (Allescher et al. 2001; Dobrilla et al. 1989). Domperidone has an anti-emetic effect, which is due to a direct effect in the area prostrema. Despite the fact, that domperidone does not cross the blood brain barrier, its main side effect are extra-pyramidal movement disorders.

Metoclopramide

Metoclopramide is primarily an anti-emetic drug acting via blockade of the dopamine (D_2) receptor as well as via antagonism of the 5-HT_3 receptor. By its agonistic action on the 5-HT_4 receptor and the increase of acetylcholine release, metoclopramide has prokinetic and motility enhancing effects. There are only few studies on the effect of metoclopramide in functional dyspepsia and only some show positive clinical effects when compared to placebo (Dobrilla et al. 1989). A prolonged application is not advisable, especially due to the substantial extra-pyramidal side effects and motor disorders.

Cisapride

Cisapride was the classical prokinetic acting on the 5-HT_4 receptor and was originally developed and marketed for the treatment of functional dyspepsia. Due to drug interactions and possible cardiac side effects with prolonged QT-times and ventricular tachycardia, this drug is not available in most but not all countries. In meta analysis a positive and additional effect over placebo was demonstrated, even though the therapeutic benefit was rather small and there are also some negative studies especially in functional dyspepsia (Allescher et al. 2001; Dobrilla et al. 1989). Due to its current legal status and the known side effects, the use of cisapride cannot be recommended. It should be restricted to severe and otherwise therapy resistant patients.

There are several promising prokinetics under development such as tegaserode, mosapride or renzapride, however, none of them proved to be of significant clinical use in larger placebo controlled trials in functional dyspepsia so far. In a smaller study, mosapride was not superior to an anti-secretory therapy with H2-blockers. Motilides (e.g. Erythromycin) showed not beneficial effect in functional dyspepsia. Another promising target are substances which relax the gastric fundus. However, for most substances (e.g. sumatriptane, busprirone, tegaserode, clonidine, serotonin-reuptake inhibitors SSRIs, NO-donors) there are no larger positive clinical studies available or relevant randomized placebo controlled studies (Galligan and Vanner 2005; Halder and Talley 2005; Talley and Vakil 2005).

Antacids and acid-blocking agents

Antacids

Antacids are often used by patients as OTC drugs mostly prior to visiting a doctor. There is no proof from placebo controlled prospective studies that antacids have a beneficial therapeutic effect in proven functional dyspepsia (Holtmann and Talley, 1993; Soo et al., 2000). This is also the reason why antacids are not recommended as a treatment alternative in acute guidelines. Similar holds true for the use of the mucosa protective agent sucralfate or alginate.

H2-receptor antagonists

In the mid eighties H2-receptos antagonists were one of the standard therapeutics in functional dyspepsia. However, there are only few controlled studies which demonstrate superiority above placebo, whereas others showed no effect. It could be speculated that this could be due to the contribution of patients with other diseases and with acid predominant symptoms in the study population. Most of these studies had a wide and unprecise definition of ‘‘dyspepsia’’ and most importantly they did not exclude endoscopic negative reflux disease (NERD). Most studies, which concentrated on clearly defined patients with functional dyspepsia without acid predominant symptoms, failed to show a clear benefit. Thus, depending on the selection criteria of the individual studies and the evaluation of the individual parameters, meta-analysis did (Dobrilla et al. 1989) or did not (Allescher et al. 2001) show a significant therapeutic effect in functional dyspepsia. H2-receptor blockers are active in acid predominant subtypes which mostly consist of NERD patients, however, in this setting they are less effective than proton pump inhibitors. The substances available (ranitidine, famotidine) are well tolerated and show little side effects.

Proton pump inhibitors (PPI)

Proton pump inhibitors (PPI) are the current standard of treatment for patients with gastro-esophageal reflux disease. Most PPIs have a limitation or even a contraindication for the use in patients with functional gastrointestinal disorders. Despite this limitation in patients with functional disorders, PPIs are nonetheless increasingly used in patients with functional dyspepsia.

In a recent meta-analysis, PPIs were regarded superior to H2-blockers and antacids in patients with ''non-investigated'' dyspepsia (Delaney et al. 2005). H2-receptor blockers and antacids showed positive effects in approximately 40% of patients (which is in the range of the placebo response rate), whereas PPI response rates were significantly higher adding an additional 20%. PPIs improved especially the symptom categories epigastric pain and heart burn. Whether these patients really represent patients which fulfil the current criteria of functional dyspepsia remains unclear. In several prospective studies in patients with acid predominant symptoms, PPIs were shown to be more effective than placebo or other treatment alternatives. However, from the type of symptoms and the selection of patients this could only reflect the known positive treatment effect in patients with NERD reflux symptoms. This could also explain why best responses in comparison to placebo were observed in patients with ,,reflux-type'' and ,,ulcer-type''(van Pinxteren et al. 2000), whereas patients with ,,non-ulcer'' or dysmotility type showed no significant advantage (Soo et al. 2000).

Therefore, a positive effect of PPIs can be expected when reflux symptoms predominate or at least contribute to the dyspeptic symptom spectrum of the patients (Delaney et al. 2005).

Helicobacter pylori eradication

Hp-infection and consecutive chronic gastritis has been regarded as one plausible patho-mechanism of functional dyspepsia. In several larger interventional trials, the effect of Hp-eradication on patients with functional dyspepsia was evaluated (Moayyedi et al. 2005). In this recent meta-analysis 17 randomized controlled studies were analyzed, showing very small (8%, NNT 18) but positive effect of Hp-eradication in patients with functional dyspepsia. In another meta-analysis, with slightly different inclusion and exclusion criteria, there was no significant benefit (Laine et al. 2001). Thus, at the moment there is no general recommendation for Hp-eradication in patients with functional dyspepsia.

In contrast to the situation in patients with functional dyspepsia, there is a clear role of Hp-diagnosis and treatment in patients with un-investigated dyspepsia. Especially in Anglo-American countries, Hp-diagnosis is part of a suggested management strategy (Talley and Vakil 2005). Whether this management strategy is superior to empiric PPI treatment cannot be answered. A comparison of ,,Hp-test and treat'' with an anti-secretory treatment with PPI over 1 month showed no clear result. Strategies are clearly influenced by the prevalence of Hp-infection, cost of upper GI endoscopy and PPI-medication (Talley and Vakil 2005).

Antidepressants

Low dose antidepressants have been suggested as treatment alternative for patients with functional dyspepsia. It was postulated that the mechanism of action should involve a positive effect of peripheral afferent neural function. There are several smaller studies which presented a positive treatment effect, however, this positive clinical effect was not accompanied by an effect on the changes in visceral perception. Thus the possible mechanism of action remains unclear (Mertz et al. 1998). In addition to traditional tricyclic antidepressants (e.g. amitryptilin) newer antidepressants such as serotonin- and noradrenalin reuptake inhibitors have been suggested as treatment alternatives even though no prospective studies support their use (Talley and Vakil 2005).

Alternative therapeutic options

Beside these well characterized pharmacotherapies, there are several substances, compounds and preparations which have been used in the clinical treatment for functional dyspepsia mostly on an empirical basis. However, some of these compounds proved beneficial and significantly superior to placebo in controlled clinical trials.

Bismut/Wismut

Bismut and wismut have been used in combination with acid suppressants and antibiotics for Hp-eradication. There are limited data on the use of bismut subsalicylate in the treatment of dyspeptic symptoms even as a mono therapy which show positive effects. The mechanism of action does not seem to involve a growth inhibiting effect on *Helicobacter pylori*. The use of bismuth is primarily limited by availability and side effects during long term treatment courses.

Iberis amara, STW 5

An alcoholic extract of *Iberis amara* in combination with 8 other herbal extract (STW 5) showed consistent positive clinical effects in prospective controlled clinical trials. STW 5 treatment was superior to placebo treatment and equivalent or even superior to the former standard treatment cisapride (Roesch et al. 2002). There is recent experimental evidence that the individual constituents of STW 5 contribute different effects to the overall action of the herbal extract combination, which could be mediated by actions on various receptor types such as 5-HT_3-, 5-HT_4- and M_3-receptors. The actions involve a suppressant effect on gastric acid secretion, both stimulatory and inhibitory effects on

motility depending on the underlying basal activity, anti-inflammatory effects and effects on gastrointestinal autonomic afferent function. The experimental data for these actions are described in the articles within this Supplement Issue and demonstrate the multitude of actions of the various plant extracts. These multiple sites of action acting at different targets could result in the positive clinical effect. Moreover, the combination of various herbal extracts (STW 5) is very well tolerated and has, compared with placebo, little or no side effects. (Holtmann et al. 2004a; Melzer et al. 2004; Roesch et al., 2006).

Caraway oil and peppermint oil

Caraway and peppermint oil are basic constituents of carminative and spasmolytics and of extract components of the phytotherapeutic STW 5 (Iberogast®). A fixed combination of caraway and peppermint oil, which is marketed in Germany for treatment of functional gastrointestinal disorders, has been shown in a prospective placebo-controlled clinical trial to have positive effects in patients with functional dyspeptic complaints (May et al. 2000). These promising data need further confirmation (Talley and Vakil 2005), but could offer a treatment alternative in patients with functional dyspepsia.

Artichoke leaves and tumeric (curcuma)

Artichoke leaves and curcuma constitute phytotherapeutic treatment alternatives. A dry extract from artichoke leaves showed a significant clinical benefit compared to placebo in patients with functional dyspepsia (Holtmann et al. 2003). There is also experimental and clinical evidence that curcuma could exert positive clinical effects in upper gastrointestinal functional disorders (Niederau and Gopfert 1999; Saller et al. 2001). Similar to the data on caraway and peppermint oil these interesting findings need further confirmation, but could also offer a treatment alternative in patients with functional dyspepsia

Anti-foaming agents (Simethicon, Dimethicon)

Polisiloxan derivatives are widely used in clinical medicine as defoaming agents prior to diagnostic or therapeutic procedures. These substances are not resorbed from the gastrointestinal tract and act by changing the surface tension and dissolving little air bubbles in the gastrointestinal lumen, which could enhance the clearance of air. In a clinical pilot trial a positive effect of these defoaming agents on clinical symptoms in dyspeptic patients has been demonstrated (Holtmann et al. 2002). This interesting data also need further confirmation.

Psycho-therapeutic treatment

Besides medical and phytotherapeutic interventions, there is a long list of psychological treatment alternatives including hypnotherapy, relaxation therapy (e.g. autogenic training, Jakobson progressive relaxation etc.) and cognitive behavioural therapy, which have been suggested as being beneficial for patients with functional gastrointestinal disorders. There are experimental data which suggests a positive effect in functional gastrointestinal disorders, especially in irritable bowl syndrome. Whether these interventions are effective in functional dyspepsia cannot be answered conclusively and no general recommendation on the use of these interventions can be given.

Summary

Patients with functional dyspepsia are a heterogeneous population of patients with chronic dyspeptic symptoms and no apparent morphological abnormality in routine clinical testing. They constitute more than 50% of all patients presenting at primary care with upper abdominal complaints and symptoms. From the terminology there should be a sharp and clear distinction between patients with dyspeptic symptoms (uninvestigated dyspepsia) and patients who have already undergone diagnostic workup, where functional dyspepsia is suspected. Despite the enormous importance and impact of these patients on health care systems and clinical practice relatively little is known on the etiology and patho-mechanism of this disease. Currently a disorder in the afferent function of the autonomous nervous systems and the central processing of this information is regarded as the underlying mechanism.

The management of patients presenting initially with dyspeptic symptoms depends primarily on patient characteristics (age, presence of alarm symptoms), history, duration and intensity of the complaints. Cost structures within a health care system (e.g. cost of endoscopy compared to medical treatment or Hp-Testing) can have influence on further diagnostic and therapeutic pathways. Empirical therapy for 4–6 weeks, initial endoscopy and specific therapy, Hp-test and treat, or Hp-test and (endo-) scope as well as initial acid suppressant therapy with proton pump inhibitors are current management alternatives in un-investigated dyspepsia. Treatment of functional dyspepsia is built on a positive and reliable clinical diagnosis, as well as considering and eliminating fears and concerns of the patient. After presenting an understandable disease model the necessity for medical treatment should be

evaluated. There are several alternatives for medical treatment. In general, there is a relatively high placebo-response rate of approximately 40% and most positively tested treatments then add an additional 10–20%. Currently there is no gold standard in the treatment of functional dyspepsia patients. While prokinetics and PPIs have relative small clinical effects and are relatively costly, phytotherapeutic alternatives offer a good price-benefit ratio and have little to no side effects. STW 5 is currently the most intensively studied and best documented phytotherapeutic alternative. The interesting multiple individual actions of the various constituents of STW 5 offer a promising concept that treatment of functional dyspepsia should not only be directed to one target site, but more effectively act on different multiple targets to exert the clinical benefit. It is worthwhile to consider this ''multi target'' treatment concept as an interesting and new concept for the treatment of functional disorders. The pharmacological actions of a multiphytopreparation with a therapeutic multi-target profile are described in the following contributions of this supplement.

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