Functional Dyspepsia : still a serious challenge for medical practitioners and new drug investigators ?
A Belgian, French, German and Hungarian opinion

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Abstract

The diagnosis of Functional Dyspepsia is based on the identification of long term specific symptoms and the absence of organic lesions. Many pathophysiological mechanisms are intricate and, at least, partially responsible for the syndrome. Widely accepted technical procedures for the identification of these mechanisms are missing. The final etiopathology is not yet established. The relationship between symptoms and putative mechanisms is unclear. At the moment of the prescription, the physician faces a real therapeutic gap. Moreover, Functional Dyspepsia is an evolving area of study and knowledge has to be updated regularly. As a result, consultations for Functional Dyspepsia are usually very challenging and patients look desperately for medical support. It is likely that this disease is both under-diagnosed and under-treated. Classifying patients into symptomatic subgroups is a promising approach proposed by Rome III. It is assumed that these subgroups are based on different pathophysiological mechanisms, and may allow for more specific therapeutic approaches. However the assessment of the symptomatic profiles of patients is time-consuming. It is also a risky process, because the Rome III subgroups have yet to be validated. There are currently no translations of the definitions in the different European languages. Interviews of the patients are biased by cultural, educational and subjective factors. Identification of suitable subjects for clinical trials is uneasy for the same reasons and can explain several recent Research and Development (R&D) failures. Therefore, there is a need for an updated, step by step approach, a real diagnostic algorithm of the consultation including the use of simple, clear, universal and cross-cultural validated tools, as word-figure questionnaires, designed to establish the symptomatic profiles of the patients. (Acta gastroenterol. belg., **2010**, 73, **360-365.**

Key words : Functional Dyspepsia, Rome III, Diagnosis, Algorithm, Symptomatic Profiles, Word-figure questionnaires

Introduction and Background

Functional digestive disorders affects up to 30% of the Western population (1,2). They are usually not life-threatening conditions but exhibit a serious impact on quality of life and costs, both direct and indirect (3,4).

Brain-gut axis, infections, delayed gastric emptying (DGE), impaired meal accommodation (IMA), hypersensitivity to distension (HSD), acid exposure, duodenal hypersensitivity, environmental factors, and modern lifestyle play a role but a very final underlying mechanism is missing (5). The role of genetics is developing (6).

Patients can be affected successively or concomitantly by gastroesophageal reflux (GERD) and/or functional dyspepsia (FD) and/or irritable bowel syndrome (IBS). Overlaps are common and the participation of each disease varies with time (4, 7).

The pharmaceutical industry has invested substantial efforts for the development of reliable treatments for IBS and for FD. In general these efforts have not been successful and few disease modifying molecules have come to the market. Tegaserod, a 5-HT4 agonist, effective in treating irritable bowel syndrome received access to the market a few years ago. However it has been recently withdrawn because of a higher rate of cardiovascular events over placebo in clinical trials (8). A few months ago, prucalopride, effective in functional constipation, has been registered. It starts to be reimbursed in some European countries (9). Hopefully, at the same time, our knowledge has progressed seriously and research and development challenges are now clearly identified.

Symptomatic profiles were attributed to DGE, IMA and HSD but have not been definitively confirmed (10, 11,12,13). In addition, the diagnosis of IMA, DGE and HSD cannot be routinely performed. The use of barostat, scintigraphy, breath tests, PET scan, MRI and ultrasound have been all applied, but these require specific expertise, and are expensive and/or invasive. The correlation between the data obtained by these different methods is not clear. The Slow Caloric Drinking Test has been developed recently and shows promising results but its precise interpretation and therapeutic impact is yet to be determined (13,14,15,16).

Last Rome classifications attempted to clarify the different clinical entities and their therapeutic approaches. They provided guidelines for drug development. They delivered substantial progresses, but overlap still exist in classifications and therapeutic approaches are not yet definitively defined (1,17).

In this context the conduction of FD consultations and of the recruitment of FD subjects for clinical trials is not a streamline process.

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The functional dyspeptic patient

FD affects all ages. The highest prevalence rate occurs in 40-50 years old females (2). The evolution profile of symptoms between patients and over time is variable. A substantial part of acute episodes are relieved after a few weeks. The mean duration of a flare is not established.

Most of patients have a vague idea about the nature of their problems, cannot clearly explain their complaints, do not discriminate them and use general expressions specific to their own culture, age, sex, social level and society (18). Based on a 10 year experience of conducting clinical trials in more than 100 hospitals in Europe, we confirm that "Slow digestion and/or Nausea" appear to be used in France/Belgium and in the US. "Bloating", often confused with visible distension, is favoured in the UK and in Hungary. Claims about upper abdominal "Discomfort" are common in the English-speaking and German cultures. Unfortunately, "Discomfort" is merely a virtual "basket" that contains many more specific symptoms. These problems affect seriously the quality of the consultation and of the data collected during clinical trials (the international agencies request now the symptom definitions and translations to be validated). It is difficult to decide which symptom(s) should be identified (most bothersome, most frequent, global assessment), how severity should be defined and assessed (intensity, frequency, duration or a composite score of the three). Symptom evaluation is biased by subjectivity and psychological factors. Hypervigilance is common (19).

Most of patients consult their general practitioner at least a number of times (20). They are quite often referred to a gastroenterologist who will exclude an organic disease. by upper endoscopy, abdominal ultrasonography and *Helicobacter pylori* (HP) test (21). The patients are reassured by their lack of organic lesions. If present, HP is eradicated. Proton Pump Inhibitors (PPIs) are usually prescribed. A minority of the patients respond to this therapeutic approach as verified by Moayyedi using the Cochrane Database System Review (22). It is assumed that response to PPIs usually occurs in patients with heartburn. The eradication of HP is efficient in a small number of cases (23). Other patients receive symptomatic treatments : acid suppressants, prokinetics, antispasmodics, herbal preparations (24), antiemetic drugs, and anxiolytics or antidepressants in the case of psycho-somatic problems. The success of these prescriptions is partial, unpredictable and temporary. It is difficult to identify their real therapeutic impact because of the placebo effect and of frequent spontaneous relieves (25). A lot of patients become accustomed to their problems and reluctant to look for medical support as the response to their complaints is inappropriate : they are told that the results of the investigations are negative but that the "magic bullet" does not exist. They identify some medications inconstantly helpful and return to their general practitioner when flares are exceptionally serious or when they are afraid about cancer. Auto-medication and purchase of over the counter drugs (antacids, bismuth citrate, simethicone and sucralfate and herbal preparations) are common (26).

Rare patients are referred to the tertiary care. It is the case when patients lose weight due to severe early satiety and/or epigastric pain (11). They are then assessed for DGE, HSD and/or IMA. Depending on the results they will receive motilin-agonists, 5-HT1A partial agonists (27) and/or 5HT3/5HT4 antag/agonists (28) in countries where they are still available under severe regulation.

Finally, FD patients, ignore the meaning of their digestive problems and their verbal complaints are not precise. They display many psychological problems (29). Lower economic status and aging appear to be in favour of medical quest (30). As the medical support is very limited, the FD patients often resign and attempt to manage their situation by themselves.

Ambulatory FD consultations

The very first classification for unexplained dyspeptic symptoms used the terms of "Reflux-like", "Ulcer-like", "Motility-like", "Unspecified" and "IBS-like" dyspepsia (31). The Rome II and III classifications introduced a new two step criteria to define and categorise FD patients (1,17,22,26) (see Fig. 1). In some countries, the term "Functional Dyspepsia" has only recently been introduced : The Japanese physicians have used the general term of "gastritis" until a few years ago. Only recently the Universities have started teaching the latest developments. This legacy has resulted in a poorly set knowledge foundation of FD subgroups.

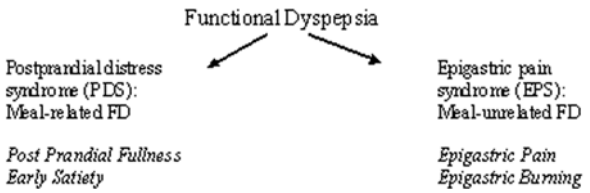

Figure 1. — Subgroups of Functional Dyspepsia as defined by Rome III classification
(Tack *et al.*, *Gastroenterology,* 2006, 130 : 1466-79)

FD diagnosis is now defined as the presence of symptoms thought to originate in the gastroduodenal region over the last 3 months with onset at least 6 months before diagnosis, in the absence of any organic, systemic, or metabolic disease that can be responsible for the symptoms. The presence of heartburn, potentially present in FD, must be cautiously addressed in order to exclude GERD (32). Symptoms associated with stool movements and/or relieved by defecation should be

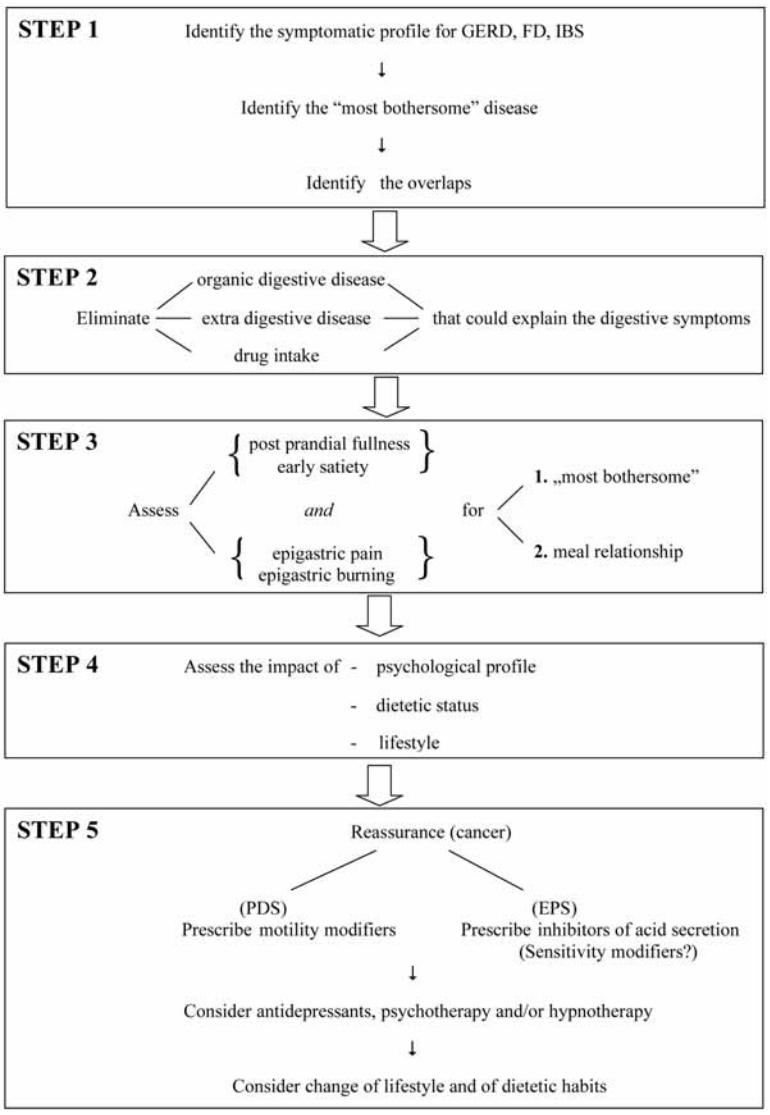

Figure 2. — Diagnostic and therapeutic algorithm :
Step1 : GERD, FD and/or IBS are assessed for presence, "most bothersome" and potential overlap.
Step 2 : Other digestive, extradigestive diseases and medications that could be responsible for dyspeptic symptoms are excluded.
Step 3 : Postprandial fullness (PPF), early satiety (ES), epigastric burning (EB) and pain (EP) are assessed for "most bothersome". It should confirmed that PPF/ES are meal-related and EB/EP meal-unrelated'.
Step 4 : Psychological profile, dietetic habits and lifestyle are addressed
Step 5 : Treatment approach includes : reassurance, appropriate prescription for PDS (targeting delayed gastric emptying and/ or meal accommodation), prescription for EPS (targeting the acid secretion) and, finally, psychological/ psychiatric approach and modification of lifestyle (e.g. : sedentarity) and diet if indicated.

absent (1). For experimental and, in a lesser extension, for clinical purpose, functional dyspeptic patients are divided in two categories : patients who suffer Post Prandial Distress Syndrome (PDS) and patients who suffer from Epigastric Pain Syndrome (EPS). PDS subjects suffer from meal-related symptoms (Post Prandial Fullness and/or Early Satiety). EPS subjects suffer from meal-unrelated symptoms (Epigastric Pain and Epigastric Burning) (1)

We propose to summarize a diagnostic and therapeutic algorithm in five steps (Fig. 2) :

Step 1 : FD, IBS and GERD symptoms have to be identified and evaluated precisely. Frequency and severity are probably less relevant than the identification of the "Most Bothersome Symptoms". Correct and reciprocal understanding of the symptoms by patient and physician is a key issue. Cross-checked interviews are useful. Very often patients do not know the difference between "Mild and Moderate". Post-Prandial Fullness related to meals can be confused with Upper Abdominal Bloating not related to meals and more frequent in IBS ; Epigastric Burning can be confused anatomically with Heartburn, Upper Abdominal Bloating with asymptomatic visible distension, general nauseous status with Nausea exacerbated by meals, Early Satiety with a general loss of appetite. Epigastric pain is confused with any other very

severe symptom and "most bothersome" confused with "very severe". Patients are convinced that excessive belching, aerophagia, nausea and vomiting are generated by their digestive tract. These symptoms are now considered as coming from a central origin. The lack of validated translations of symptom definitions is a serious gap. Standardised word-figure questionnaires can be here of high interest (see Fig. 3).

At the end of the interview, the symptomatic profile is often a mix between FD and/or GERD and/or IBS. "Pure" patients are very rare. The physician must assess the weight of each component.

Step 2 : Any digestive and extra digestive disease and/or medication which can potentially cause dyspeptic symptoms has to be excluded : ulcer and cancer disease, biliary tract problems, celiac disease, lactose intolerance, gastroenteritis, anorexia mentalis, drugs with affinity for digestive receptors, and many others. Medical history, physical examination, endoscopy, ultrasound, HP testing and biology are key.

Step 3 : The final diagnosis is established based on the presence of most bothersome Post Prandial Fullness (PPF), Early Satiety (ES) and/or Epigastric Pain (EP) and Epigastric Burning (EB), during 12 weeks out of the last 6 months. It is useful to confirm definitively the onset or exacerbation by meals. ES and PPF are by nature meal-related and EP and EB are not. There is still a grey zone as EP and EB can sometimes be exacerbated by meals. At this stage it is possible to address the diagnosis of Post Prandial Distress Syndrome (PDS or "Meal related FD") and/or Epigastric Pain Syndrome (EPS or "Meal unrelated FD" (see Fig. 1). Overlaps are not uncommon.

Step 4 : The psychological profile, the dietetic status and the lifestyle of the patient are assessed. Indeed, anxiety, depression, sleep problems, alcohol consumption, smoking and inappropriate lifestyle are common.

Step 5 : The therapeutic approach is complex. The evaluation of the numerous mechanisms responsible for FD is not feasible and its therapeutic impact difficult to manage even in experienced hands (13). Reassurance is critical and includes the withdrawal of cancer fear. Based on Rome III, it is assumed that PDS patients should better respond to "motility modifiers" and EPS patients to PPIs. If PPIs (33) and anti-H2 receptor inhibitors show some efficacy they are often disappointing. Existing prokinetics are not much better than placebo (25). Antidepressants can improve the perception of the symptoms but exhibit serious side-effects (34). Psychological therapies and hypnosis are adjuvant (35, 36). Most recent drugs were withdrawn from the market or discontinued in Phase II/III either for safety concerns or lack of efficacy (37,38). New drugs as acetylcholinesterase inhibitors, indicated in DGE, and/or IMA are in late development (39). Change of lifestyle, physical exercise and the correction of harmful dietetic habits are useful but compliance is poor.

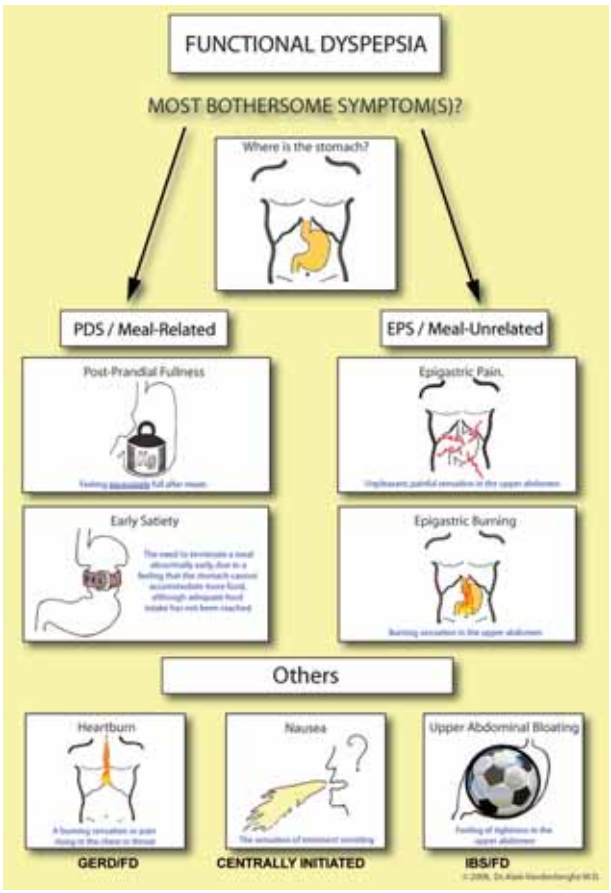

Figure 3. — After simple verbal explanation of the figures, the patient identifies :

a.) The main reason(s) for consulting the physician ("Most bothersome"). b.) Assesses the meal relationship of the symptoms. c.) The duration of the disease during the last 6 months (12 weeks, consecutive or not).
N.B. Vomiting, Excessive Belching and Aerophagia are not represented here : they are more self-explaining and, as nausea, considered as from central origin.
(PDS : Post Prandial Distress Syndrome ; EPS : Epigastric Pain Syndrome)

Ambulatory consultations for functional dyspepsia remain a real challenge both for the patient and for the physician (40).

Identification of subjects for clinical trials

The inclusion of suitable subjects for clinical trials (CT) in FD suffers from the same difficulties besides the inherent problems related to the conduction of trials. These problems generate failures and, if efficacy is evident in small samplings (Phase IIb), the confirmation in large Phase III is exceptional. Poor Research & Development staff expertise, complexity of FD diagnosis and of eligibility for CTs, absence of standardisation for pre-screening of patients and biases in Patient's Reported Outcomes (PROs), translations and recordings.

Common roots for all these concerns are poor training and knowledge. Solutions exist. Rome II and III

Experts when attending Advisory Boards always claim" : "Train, train and train constantly and make responsible : R&D staff, Investigators, Co-Investigators, Study nurses, Patients ; keep ongoing communication with national and international agencies" but also : "Document, Justify and Communicate". This is the central job usually performed by experienced Medical Advisers.

Discussion

The management of FD appears in general unlikely to be effective. There is no physiopathological or therapeutic nirvana (41).

The Rome III classification, based on the interview of approximately 30,000 patients, is close to the standard consultation (1,41). It is evidence-based medicine and is focused on symptomatic profiles. This substantial progress has still to be confirmed in larger samples, daily practice and clinical trials.

In our experience in clinical practice and of recruiting hundredths of FD patients for clinical trials all over Europe, the cornerstone for FD diagnosis and identification of subjects for randomisation is the symptomatic interview. However medical backgrounds, translations of Rome definitions, cultural interpretations and expressions, confusions by patients and the lack of attention for the meal relationship induce a lot of biases besides other influencing factors as sex, age and social level (40).

It is important to develop simple, validated and cross-culturally applicable tools for FD consultations. Figures and videos presented by the practitioners to their patients have potential here.

We propose a very initial set of word-figures. Their validation in different languages is ongoing. They were designed for the collection of an initial symptom profile and to discriminate meal-related from meal-unrelated FD. The patient can rapidly identify the type of sensation, its location, the relationship with meals and the most bothersome symptoms that motivated him to seek medical attention. The written definitions are based on Rome III. Each consulting practitioner should add his own comments and explanations adapted to the specific level of background and culture of his patient. We suggest all figures to be presented at the same time.

When the initial symptom profile is obtained, FD diagnosis can be confirmed as per Rome III criteria (duration and the chronic nature of the complaints, absence of organic disease and absence of predominant IBS and/or GERD).

Patients presenting diffuse bloating and pain should be assessed for the onset of complaints by changes in stool movements and for relief by defecation. A "Most Bothersome" level of heartburn is the proof of, at the very least, a striking GERD component. It has to be noticed here that patients suffering from oesophageal/cardia hypersensitivity (Non Erosive Reflux Disease or NERD) have similar complaints to GERD.

When "Meal-related "or "Meal-unrelated" FD is confirmed, a therapeutic approach may be proposed.

Patients suffering from"Meal-related" FD will be improved by medications that relaxes the fundus, accelerate gastric emptying and/or decrease the visceral hypersensitivity. However, all medications do not have a drug approval for these conditions and have limited evidence of efficacy. Relapse is usual some time after cessation of their administration. The pharmacological treatment has to be constantly adapted in relationship with the variability of the disease. IBS and/or GERD/NERD components should be taken into account and combined therapy can be indicated.

Solutions exist regarding the selection of the right patients for clinical trials and their compliance after inclusion. With Rome II and III experts, it is to be repeated here : "Train, train and train constantly and make responsible : R&D staff, Investigators, Co-Investigators, Study nurses, Patients ; keep ongoing communication with national and international agencies" but also : "Document, Justify and Communicate".

Conclusion

The efficiency of consultations for digestive functional disorders and especially for FD will probably progress dramatically thanks to a step by step approach and algorithm including the accurate assessment by word-figures of the symptomatic profiles of the patients and the distinction between meal-related and pain-predominant complaints (42,43,44). These progresses will support the access to the market of efficient new treatments.

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