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New Developments in the Treatment of Functional Dyspepsia

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Abstract

Functional dyspepsia is a clinical syndrome defined by chronic or recurrent pain or discomfort in the upper abdomen of unknown origin. Although generally accepted, investigators differently interpret this definition and clinical trials are often biased by inhomogeneous inclusion criteria.

The poorly defined multifactorial pathogenesis of dyspeptic symptoms has hampered efforts to develop effective treatments. A general agreement exists on the irrelevant role played by *Helicobacter pylori* in the pathophysiology of functional dyspepsia. Gastric acid secretion is within normal limits in patients

with functional dyspepsia but acid related symptoms may arise in a subgroup of them. Proton pump inhibitors appear to be effective in this subset of patients with dyspepsia. Non-painful dyspeptic symptoms are suggestive of underlying gastrointestinal motor disorders and such abnormalities can be demonstrated in a substantial proportion of patients. Postprandial fullness and vomiting have been associated with delayed gastric emptying of solids, and early satiety and weight loss to postcibal impaired accommodation of the gastric fundus. Prokinetics have been shown to exert beneficial effects, at least in some patients with dyspepsia. In contrast, drugs enhancing gastric fundus relaxation have been reported to improve symptoms, although conflicting results have also been published. An overdistended antrum may also generate symptoms, but its potential pathogenetic role and the effects of drugs on this abnormality have never been investigated formally. Visceral hypersensitivity plays a role in some dyspeptic patients and this abnormality is also a potential target for treatment. Both chemo- and mechanoreceptors can trigger hyperalgesic responses. Psychosocial abnormalities have been consistently found in functional digestive syndromes, including dyspepsia. Although useful in patients with irritable bowel syndromes (IBS), antidepressants have been only marginally explored in functional dyspepsia.

Among the new potentially useful agents for the treatment of functional dyspepsia, serotonin 5-HT_4 receptor agonists have been shown to exert a prokinetic effect. Unlike motilides, 5-HT_4 receptor agonists do not appear to increase the gastric fundus tone and this may contribute to improve symptoms. 5-HT_3 receptor antagonists have been investigated mainly in the IBS and the few studies performed in functional dyspepsia have provided conflicting results. Also, κ-opioid receptor agonists might be useful for functional digestive syndromes because of their antinociceptive effects, but available results in functional dyspepsia are scanty and inconclusive. Other receptors that represent potential clinical targets for antagonists include purinoceptors (i. e., P2X2/3 receptors), NMDA receptors (NR2B subtype), protease-activated receptor-2, the vanilloid receptor-1, tachykinin receptors (NK_1/NK_2) and cholecystokinin $(CCK)_1$ receptors.

1. Functional Dyspepsia: a Digestive Syndrome with Blurred Edges

Dyspepsia is generally defined as pain or discomfort centred in the upper abdomen.[1] Its prevalence in the general population is reported to range between 25–50%.[1,2] Although only a minority of individuals with dyspepsia are bothered or worried enough by their symptoms to seek medical help, dyspepsia accounts for about 5% of all medical consultations.[3] However, the available epidemiological data might be influenced by different definitions of dyspepsia and inclusion of patients with gastro-oesophageal reflux (GORD) or irritable bowel syndrome (IBS). The prevalence of epigastric painful (localised or diffuse epigastric pain or burning) and non-painful symptoms (early satiety, postprandial fullness, nausea, vomiting) individually evaluated in a recent international survey range between 4–10% and 2–18%, respectively, in different countries.[4]

Dyspepsia represents a major clinical problem for several reasons. First, it may be the presenting manifestation of severe and even life-threatening diseases, although in the majority of patients it is a benign, chronically recurrent condition. Physicians are therefore confronted with the difficult problem of overlooking organic disease on one side and exceeding what is required in expensive and gener-

ally unhelpful diagnostic procedures on the other. Second, even if a secondary form of dyspepsia is reasonably excluded, the syndrome remains a challenging clinical problem, since the quality of life of affected individuals is markedly reduced[5] and patients strongly demand an appropriate response. Unfortunately, since the underlying pathogenic mechanisms are only partially understood, therapeutic strategies remain poorly defined and patient management is still often disappointing. Last but not least, the lack of pathophysiological markers obliges physicians and investigators to rely exclusively on the patients' words describing symptoms. Digestive symptoms represent an imperfect guide to the underlying cause and even if recorded accurately provide a weak basis to build a management strategy. Cultural factors play a major role in the process that brings a personal experience, such as a digestive symptom, to be translated into an internationally accepted definition. Indeed, the published literature is often difficult to interpret and to be translated into clinical practice.

The Rome criteria were proposed[6] and developed[1] to overcome these problems. The proposed Rome II definition of functional dyspepsia (persistent or recurrent pain or discomfort centred in the upper abdomen that is not relieved by defecation nor determined by organic diseases)[1] is substantially accepted by the majority of investigators working in this area but its interpretation varies extensively. There are two main sources of confusion: overlap with other digestive syndromes and interpretation of the term 'discomfort'. Many doctors and investigators do not believe that dyspepsia can be reasonably distinguished from GORD because of the frequent overlaps between the two syndromes, and practical difficulties that are encountered by many doctors and patients in distinguishing between epigastric and retrosternal pain/burning,[7,8] despite the fact that the latter has clinical presentations, natural history, pathophysiology and therapy that are well characterised. Similarly, pain and abdominal distension in the upper abdomen are often interpreted as gastroduodenal symptoms even if related to bowel movements, so that patients with IBS end up being erroneously classified as having functional dyspepsia.[9]

It is obvious that these apparently subtle differences markedly influence inclusion criteria and results of many studies in this area. The term 'discomfort' is difficult to translate in many languages and marked differences in its interpretation exist even among English speaking authors. Some authors, including members of Rome working teams other than that on dyspepsia, interpret it as 'a mild form of pain'.[10,11] Therefore, studies from these groups would not include patients with dyspepsia unless they report some sort of painful sensations arising from the upper abdomen. Other investigators use the term discomfort to describe non-painful unpleasant sensations such as early satiety, fullness, bloating, nausea and retching.[12]

The Rome criteria for functional dyspepsia proposed to include both painful and non-painful symptoms in the definition of functional dyspepsia and identified three main subgroups in the syndrome: (i) 'ulcer-like' characterised by predominant pain; (ii) 'dysmotility-like' characterised by predominant non-painful symptoms; and (iii) 'unspecified' without predominant symptom. Although dyspepsia subgroups are only partially related to underlying pathogenic mechanisms, as will be discussed below in section 2, they are commonly used by general practitioners.[13]

Even the terms 'functional dyspepsia' and 'non-ulcer dyspepsia' are often interchangeably used and may conceal profound cultural differences. The Rome working team discouraged the use of 'non-ulcer dyspepsia' because patients with dyspepsia do not necessarily present with symptoms suggestive of a peptic ulcer and gastroduodenal ulcers are not the only organic disease to be excluded to diagnose functional dyspepsia.[1] Nevertheless 'non-ulcer dyspepsia' is still frequently encountered in the literature, reflecting underlying cultural biases. Other terms such as 'upper dyspepsia', 'essential dyspepsia' and 'chronic idiopathic dyspepsia' were only sporadically used. The use of 'functional dyspepsia' has progressively risen after the publication of the Rome I criteria,[6] becoming as common as 'non-

ulcer dyspepsia'. The semantics of non-organic dyspepsia show an interesting geographical distribution with 'non-ulcer dyspepsia' being virtually the only term used in the published literature from UK and Ireland, and also being still more common in other countries, such as the Netherlands, Australia, France and Italy; whereas 'functional dyspepsia' is more frequently encountered in the literature from North America, Northern European countries and Eastern countries. Looking at the use of different dyspepsia definitions adopted in papers investigating different pathophysiological mechanisms that were published in the year 2000, the term 'non-ulcer dyspepsia' was almost invariably used by investigators interested in traditional ulcer-related issues, such as gastric acid secretion and *Helicobacter pylori* infection, whereas 'functional dyspepsia' is more popular among those investigating gastrointestinal motility, hypersensitivity, psychological aspects and food allergy (figure 1).

The aims of the current review are:

- to summarise the current knowledge of potential pathophysiological mechanisms underlying functional dyspepsia in order to elucidate the main targets for therapeutic intervention;
- to describe potential limitations of published therapeutic studies and provide indications for improvement in this area;

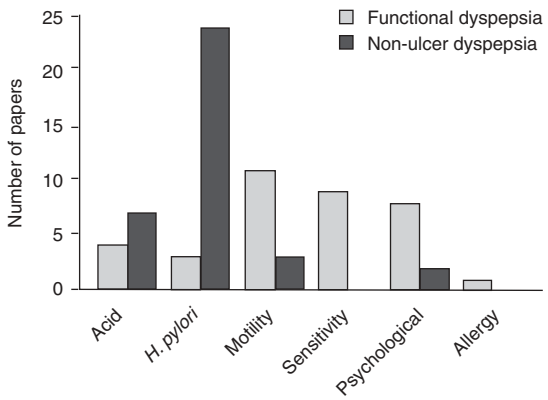

Fig. 1. Number of papers published in English (published in the year 2000 and listed in PubMed) on non-organic dyspepsia defined as 'non-ulcer dyspepsia' or 'functional dyspepsia' addressing different pathophysiological aspects of the syndrome.

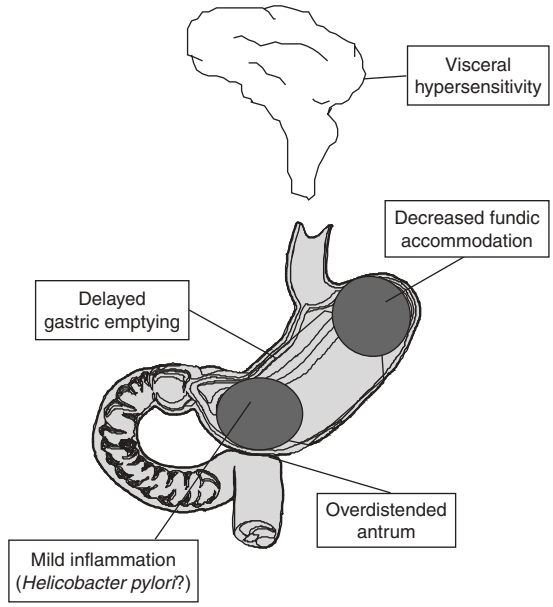

Fig. 2. Proposed pathophysiological mechanisms in functional dyspepsia. Each of them is a possible target of drug therapy. The role of *Helicobacter pylori* is debated. Mild inflammation may be the initial trigger of visceral hypersensitivity.

- to review the main results of the available literature on treatment options with particular emphasis on the treatment of dysmotility and hypersensitivity; and
- to highlight potential targets for future therapies.

2. Pathophysiology

The poor understanding of the pathogenesis of functional dyspepsia has hampered efforts to develop effective treatment strategies. Functional dyspepsia may actually represent a group of disorders with different pathogenic mechanisms, including gastric hypersecretion, gastrointestinal motility disorders, visceral hypersensitivity and psychological disturbances (figure 2). Since each of these mechanisms may concur to determine symptoms alone or in different combinations, no single treatment can be reasonably expected to treat all patients with functional dyspepsia. Before addressing therapeutic options, we briefly summarise the current view on the pathogenetic mechanisms of the syndrome. We will not formally address the issue of *H. pylori* infection,

since it has been clearly demonstrated that it plays a minimal (if any) role in the pathophysiology of functional dyspepsia and that the problem cannot be expected to be solved in the vast majority of patients by eradicating the infection.[14]

2.1 Gastric Acid Secretion

An intragastric infusion of acid induced perception of symptoms in a selected group of patients with ulcer-like dyspepsia[15] but interestingly failed to reliably elicit dyspeptic symptoms in patients with functional dyspepsia,[16] suggesting that a different selection of patients may justify apparently opposite results. Patients with functional dyspepsia have, on average, normal basal and pentagastrin-stimulated gastric acid secretion regardless of their *H. pylori* status,[17] but patients who are *H. pylori* positive have been found to present higher gastrin-releasing peptide-stimulated acid secretion responses than those of healthy controls who are *H. pylori* negative.[18] One may conclude that a subset of patients with functional dyspepsia have a dysregulation of gastric acid secretion, which may be involved in the determinism of their symptoms. In this respect, it is important to remember that epigastric pain is a well known 'extraoesophageal symptom' of GORD and that patients often mistake heartburn for 'pain in the stomach', so that it is possible that the therapeutic efficacy of antisecretory drugs in ulcer-like dyspepsia demonstrated in some studies[19] is actually a result of either coexisting GORD[20] or clear cut mistakes in the diagnosis of the two digestive syndromes.[7]

Few studies have investigated whether instilling gastric acid contents onto the mucosa will induce symptoms in functional dyspepsia. Oesophageal acid perfusion results in mechanical hyperalgesia[21] and this may also occur in the stomach.[22]

Describing in detail the relatively large, contradictory and often outdated literature on the effects of antacids and antisecretory drugs in functional dyspepsia goes beyond the scope of this review. More recently, research has been focussed on the potential therapeutic effect of a more sustained acid inhibition such as that exerted by proton pump inhibitors (PPIs).[23-30] Three main trials have been carried out to elucidate the role of PPIs in functional dyspepsia but, again, results are contradictory.[19,29,30] The pooled results of the Based on Omeprazole in Nonulcer Dyspepsia (BOND)/and Omeprazole and Placebo – Effect on Relieving Abdominal pain/discomfort (OPERA) trials showed that omeprazole 20 or 10mg once daily was significantly superior to placebo in terms of the stringent primary end-point of achieving complete symptom relief at 4 weeks, although differences were small.[19] More marked differences were observed when patients were divided into subgroups according to their symptoms: omeprazole was superior to placebo in patients with predominant pain but it was ineffective in those with predominant non-painful symptoms. Surprisingly, although the presence of GORD was among the exclusion criteria of the study, a consistent subset of patients reported heartburn as their main symptom and the antisecretory therapy was particularly effective in this subgroup.

In a German multicentre study with a slightly different endpoint (i.e. disappearance of dyspeptic symptoms requiring further treatment), these results were not confirmed, although omeprazole 20mg once daily was superior to placebo in achieving complete disappearance of symptoms, a secondary response variable in this study.[29]

More recently, a large study carried out in Hong Kong failed to demonstrate any difference between lansoprazole 30 or 15mg once daily versus placebo on symptoms or quality of life scores.[30]

These different studies adopted very similar inclusion/exclusion criteria, methods and outcome measures, and it is difficult to reconcile the apparently opposite results at first glance. A possible explanation might be represented by different degrees of contamination by GORD patients. Splitting the BOND/OPERA study into its components, it emerges that the OPERA study and the BOND study were the only to find a superiority of PPIs over placebo. Interestingly, while inclusion of patients in both the Hong Kong and the OPERA study was performed by specialists, general practitioners recruited 'dyspeptic patients' for the BOND study. As

a result of the previously discussed difficulties in differentiating non-erosive GORD from idiopathic dyspepsia, it is possible that general practitioners managed to include a more selected group of dyspeptic patients in their study. In this respect, it is mandatory that future trials on functional dyspepsia combine appropriate methods with more precise definitions of patients' clinical features. For instance, if the Rome II criteria[1] were accurately followed through *ad hoc* questionnaires developed for the different cultures of centres involved, overlap between GORD and dyspepsia should be reduced to a minimum.

2.2 Gastrointestinal Motility Disorders

Gastrointestinal motor abnormalities can be demonstrated in 20–70% of patients with functional dyspepsia.[31] The wide range of these findings are probably the result of the different inclusion criteria and recording techniques adopted. Postprandial antral contractility can be almost invariably recorded in patients with both organic and functional dyspepsia, regardless of the severity of the symptoms.[31] Small bowel manometric abnormalities are rare in patients with functional dyspepsia and can be recorded only in those with the most severe clinical manifestations or with overlapping IBS.[31,32] Delayed gastric emptying of solids affects less than 20% of patients with epigastric pain as their main symptom but up to 40% of those reporting non-painful discomfort.[12]

Although many studies have failed to find a relationship between gastrointestinal motor disorders and symptoms in functional dyspepsia, recent investigations provide evidence that such a relationship exists. Indeed, female patients reporting postprandial fullness severe enough to influence usual activities and vomiting have a 13-fold increased risk of having delayed emptying of digestible solids.[12] Gastric emptying is the gross result of a complex series of motor events. An abnormal distribution of intragastric contents characterised by an impaired relaxation of the proximal stomach with a sudden and prolonged distension of the antrum has also been demonstrated in functional dyspepsia.[33,34] Postcibal impaired fundic accommodation is found in 40% of patients, and is associated with early satiety and weight loss.[34] This could be due to vagal neuropathy as similar findings occur in vagotomised patients.[33] The increased wall tension could conceivably increase visceral afferent traffic.

On the other hand, an overdistended antrum can be detected in patients with functional dyspepsia undergoing a water load test, antral size correlating with nausea.[35] The abnormal intragastric distribution may be secondary either to a neuromuscular disorder affecting compliance and tone of the proximal and distal stomach walls, or to abnormal viscero-visceral reflexes. The latter hypothesis is supported by some studies indicating that the profound gastric fundic relaxations that are physiologically induced by antral or duodenal distensions are absent or markedly blunted in patients with functional dyspepsia.[36,37] Hypothetically, in-series mechanoreceptors should be mainly located in the proximal stomach and in-parallel receptors in the antrum, so that postprandial active gastric accommodation and antral contractions would occur unperceived in health, while increased wall tension of a tight fundus as well as elongation of an overdistended antrum might activate afferent signalling.

2.3 Visceral Hypersensitivity

Because of the difficulties encountered in establishing a relationship between dyspepsia symptoms and abnormal secretory or motor events, the hypothesis these symptoms may derive from hypersensitivity of the afferent neural connections between the upper gut and the brain has gained momentum. The respective roles of 'pure' hypersensitivity of the visceral afferent neural pathways and of increased gastroduodenal wall tension or mucosal inflammation remain to be fully clarified. The main available evidence of selective lowered sensory thresholds in functional dyspepsia is represented by perception of intragastric balloons at distending pressures lower than in controls during fasting, when gastric compliance is normal. Furthermore, pharmacological studies on the effects of clonidine on gastric sensitivity provide indirect evidence that approximately

80% of sensation variance might be attributable to neural hypersensitivity rather than to increased gastric wall tension.[38] Similarly, alosetron a serotonin 5-HT_3 receptor antagonist, has been reported to decrease postprandial nausea and bloating without affecting gastric volumes in healthy volunteers after ingestion of the maximum tolerable volume of a liquid test meal.[39] A correlation between *H. pylori* infection and increased postprandial gastric sensation has been identified in functional dyspepsia,[40] although conflicting results exist.[41] Despite the mechanisms underlying visceral hypersensitivity in patients with dyspepsia and *H. pylori* infection are not as yet clarified, basic evidence suggests that the mucosal inflammatory response associated with the infection may trigger sensitisation of afferent nerve endings.

As a group, patients with functional dyspepsia present with hypersensitivity to distension of the proximal stomach,[42] unlike those with organic dyspepsia.[43] Specifically, 30–50% of patients with functional dyspepsia present with lower thresholds for perception and pain or discomfort induced by gastric distension than controls. Patients with ulcer-like dyspepsia are more likely to report pain when undergoing fasting gastric distensions,[44] whereas those with dysmotility-like dyspepsia tend to report more frequently pressure-discomfort sensations under experimental conditions.[45,46]

Subsets of patients with dyspepsia also have duodenal,[47] oesophageal and rectal hypersensitivity to balloon distension,[48] but higher somatic pain thresholds than healthy volunteers,[42] suggesting an underlying diffuse, selective disorder of visceral afferents.

Specific chemoreceptors also seem to present a lowered activation threshold in functional dyspepsia. Intraduodenal infusion of small amounts of acid, but not of identical volumes of isosmolar saline or lipid infusions, have been reported to induce nausea in patients but not in controls; the former also showing a decreased duodenal clearance capacity.[44]

2.4 Psychological Abnormalities

The role of psychological abnormalities in determining dyspeptic symptoms has long been investigated by researchers and intuitively perceived by practising physicians and patients alike; however, it remains ill defined. Experimental studies in this area are potentially influenced by selection bias, as psychosocially disturbed patients may be more likely to present to those centres where research is being conducted and to accept to participate in this type of study. Nevertheless, in the recent past, our understanding in this area has markedly improved together with our knowledge of the complex relationships between the central nervous system (CNS) and the gut.

Acute stress has long been known to markedly influence gastrointestinal functions via neuroendocrine mechanisms;[49] however, the role of chronic stress in determining functional digestive syndromes is poorly understood. Development of instruments capable of quantifying the influence of stressful events have allowed the demonstration of an association between dyspepsia and events that were highly threatening or led to frustration in achieving goals.[50]

Patients with both idiopathic and secondary dyspepsia have higher scores for anxiety, depression, neuroticism, hostility and tension than controls.[51] Interestingly, patients with abnormal psychological features have a lower incidence of gastrointestinal motility disorders[32] and visceral hypersensitivity[52] than those with normal psychological scores.

Individuals affected by functional dyspepsia or by other functional digestive syndromes often also report non-abdominal complaints, suggesting a tendency to somatisise and have an average of three times as many sick days compared with patients with peptic ulcer disease.[50] Patients with dyspepsia illness behaviours can also be influenced by negative life experiences such as unhappy childhood or sexual abuse.[53]

The practising doctor should take psychological disturbances into account when managing patients with functional dyspepsia since these factors might be either directly involved in determining symptoms

or secondary to the frustration induced in the affected individual by unsatisfactory clinical experiences.

3. Designing Clinical Trials for Functional Dyspepsia

Designing clinical trials for functional dyspepsia, as well as for any other functional digestive syndrome, is a difficult task and published trials often have severe weaknesses. A discussion on all the potential pitfalls of therapeutic trials in this field goes beyond the scope of the present paper and has been the object of a detailed review.[11] We briefly focus on some specific aspects that still receive little attention among investigators and may represent the source of major misunderstanding.

3.1 Definitions or Descriptions

Different authors interpret the definition itself of dyspepsia or even the word used to describe a single symptom differently. A uniform semantic interpretation by individuals with various cultural backgrounds is unrealistic. For this reason, we suggest that a detailed description of the actual meaning of patients' complaints is included in all studies. Torso pictures can help to identify anatomical regions of symptom perception if correctly presented.[9] It is important that results obtained in a pre-selected subgroup of patients with dyspepsia or on a limited number of dyspeptic symptoms are not extrapolated to the whole syndrome.

3.2 Outcome Measures

Outcome measurement is the weakest aspect of any trial on functional syndromes and many aspects need to be considered for selecting an appropriate instrument.

First, a trial's main result should be based on a primary outcome measure providing a global evaluation of patients' clinical conditions.[11] Measurement of 'adequate relief' over a certain period of time has been successfully proposed in trials of IBS[54] and might be appropriate also for dyspepsia, since it represents a parameter commonly used by doctors in everyday practice. Alternatively, indirect measurements such as sick leave days can be used. Generic or disease specific measurements of quality of life are also gaining popularity.[55] The specific measure of an important dyspeptic symptom such as pain has been reported to closely reflect global measures,[11] but these data were obtained in patients affected by 'non ulcer' dyspepsia with the sole symptom of pain. To what extent changes in a predominant symptom correspond to those of a global parameter in patients with a less uniform dyspeptic syndrome is unknown.

Regardless of the type of global assessment adopted, it is mandatory that individual symptom variations are also carefully recorded as secondary endpoints. In fact, global assessment might easily miss a positive effect exerted on a specific symptom, since this may be overlooked by the persistence of other negative sensations. Positive effects on secondary endpoints might represent a strong rationale for *ad hoc* trials.

Second, it is uncertain whether physician assessment is more reliable than patient self-assessment. In order to avoid inter-and intra-individual physician variability in interpreting patients' words, it is considered preferable that the main outcome assessment is done by the patient.[11] Patients are scarcely reliable in communicating the nature and severity of pain.[56] and in understanding words that are commonly used by doctors such as dyspepsia or heartburn.[7] Whether they are reliable in understanding self-administered questionnaires has never been appropriately investigated. Reliabilities of simple, self-administered questionnaires and questionnaires delivered by well trained and dedicated doctors should be formally compared.

Third, a general agreement exists that adjectival and visual analogue scales (VAS) are both reproducible and sensitive to change.[11] To optimise responsiveness to change adjectival scales should include 5–7 points,[11] although there is no evidence to recommend an optimal number of categories. Studies carried out in patients with chronic obstructive pulmonary disease and heart failure with a 7 point adjectival scales have shown that a 0.5 change per question corresponds to the minimal difference of

Table I. Problems encountered in the search for an effective drug for functional dyspepsia

Lack of gold standard for therapy
Subjectivity of symptom relief
High placebo response rate
No validated primary outcome measures; lack of hard endpoints to prove efficacy to regulatory agencies (modification of disease progression/prognosis)
Efficacy vs effectiveness (acceptance of Rome II criteria by primary care physicians)

clinical value.[57] On the other hand, five represents the maximal number of adjectives that can be linked to different effects of symptom severity on daily activities,[58] and can be easily understood and reliably translated into different languages.

3.3 Patient Setting

The results of trials carried out in referral centres can not be generalised, since patients seen in these centres may be representative only of the most severe part of the wide spectrum of clinical manifestations of functional dyspepsia. Furthermore, statistical considerations impose the requirement for large numbers of patients in pharmacological trials. International, multicentre, multi-language studies have therefore become popular in the recent past. Unfortunately, many of these studies adopt outcome measurement instruments that were developed and validated in one single centre, without appropriate translation procedures and which might not be suitable for large, multicultural patient populations.

4. Targets for Pharmacological Interventions

Because of the existence of multiple aetiological factors and patient subpopulations with different pathophysiological features, probably no magic bullet exists for the treatment of all patients with dyspepsia. So far, investigators have targeted pharmacological interventions for functional dyspepsia mainly to motility and visceral hypersensitivity. Therapeutic targets in functional dyspepsia are illustrated in figure 2.

Some of the problems encountered in the search for an effective drug for functional dyspepsia are listed in table I. In patients with functional dyspepsia, a major problem remains the placebo response, which may be as high as 70%,[59] and this of course limits the ability to demonstrate the benefit of the active medication.

From a pharmacological point of view, the search for a selective ligand for a given receptor subtype may be disappointing because this receptor may not be the only one involved in the pathophysiology of dyspeptic symptoms. Indeed, symptoms do not necessarily relate to single physiological abnormalities and the existence of multiple pathways diminishes the effect of strategies focused on a single receptor, which can be easily by-passed. On the other hand, our tendency to label a drug as a 'selective' ligand for a given receptor often leads us to overlook the fact that any single molecule may be endowed with multiple pharmacological actions at therapeutic doses, some of which may contribute to the desired effects, whereas others may be the source of adverse effects. Table II illustrates the complex pharmacological profile of some agents used in functional gut disorders. In any case, even if we theoretically assume that a ligand has affinity for only one receptor subtype, the multiple locations of this receptor will be the source of unwanted adverse effects (e.g. constipation with 5-HT_3 receptor antagonists). Ta-

Table II. Composite nature of drug effects for agents used in functional dyspepsia

Drug	Pharmacological actions
Cisapride	5-HT_4-receptor agonist
	5-HT_3-receptor antagonist
	HERG K^+ channel blocker
Levosulpiride	D_2-receptor antagonist
	5-HT_4-receptor agonist
Antidepressants	Action on neurotransmitter uptake
	Action on ion channels (Na^+, K^+, Ca^{2+})
	Anticholinergic effect
Erythromycin	Antibacterial activity
	Motilin receptor agonist
	CYP3A4 inhibitor
	K^+ channel blocker (high concentrations)

5-HT = serotonin (5-hydroxytryptamine); **CYP** = cytochrome P450; **HERG** = human ether-a-go-go-related gene.

Table III. Multiple locations of 5-HT_3 receptors and effects of 5-HT_3-receptor antagonists

Location of receptors	Effect of 5-HT_3-receptor antagonists
Enteric sensory neurons (extrinsic and intrinsic)	Extrinsic neurons: reduced visceral nociception and inhibition of reflex behaviours (e.g. variations in blood pressure) induced by intestinal distension
	Intrinsic neurons: peristalsis triggered at higher threshold
Enteric motor neurons	Reduced motility, constipation (a well known adverse effect)
Enteric secretomotor neurons and enterochromaffin cells	Increased absorption/reduced secretion of fluids (useful in patients with diarrhoea)
Enteric and CNS neurons activated by chemotherapy-induced release of serotonin	Antiemetic effect (use in chemotherapy-induced emesis)

5-HT = serotonin (5-hydroxytryptamine).

ble III represents the consequences of the multiple locations of 5-HT_3 receptors.

Currently available agents for the treatment of functional dyspepsia (antidopaminergic agents and prokinetics) were developed in the past three decades when research was focussing mainly on delayed gastric emptying, which indeed affects a significant proportion of patients. More recently, visceral hypersensitivity (altered peripheral sensation or central processing of peripheral sensory signals) and decreased fundic accommodation have become the main targets for drug development. Table IV provides a synopsis of the possible effects of different drug classes on the main therapeutic targets in functional dyspepsia.

5. Available Agents for Functional Dyspepsia

The therapeutic armamentarium for functional dyspepsia is limited by the issues outlined in sections 1 to 3. In this section, we review the available agents, although it should be noted that not all drugs discussed here are formally approved for functional dyspepsia. For instance, 5-HT_4 receptor agonists and erythromycin derivatives are available in several countries, although their use in functional dyspepsia has not received regulatory approval.

The use of prokinetics is based on the assumption that upper gut hypomotility is a common pathogenetic factor in dyspepsia. Available prokinetics have several actions that might help normalise disturbed motility. Most importantly, they appear to increase gastroduodenal wave co-ordination, which, in turn, facilitates passage of content from the stomach into the duodenum. These properties have been well documented in isolated organ preparations and experimental animals.[81] Delayed transit may be due, at least theoretically, not only to decreased propulsion of intraluminal contents, but also to enhanced sphincteric resistance (e.g. at the pyloric level). There are indeed data suggesting that both cisapride and motilides favour propulsion of intraluminal contents not only by enhancing propulsive motility but also by reducing gastric outlet resistance (reviewed by De Ponti and Malagelada[81]).

From a clinical standpoint, most support for the use of prokinetics in functional upper gut syndromes comes from clinical trials showing a beneficial effect on symptoms; however, the benefit can be rather small in magnitude, albeit statistically significant.[59,82] Prokinetic therapy with cisapride or domperidone for 12 months also corresponded to improved quality of life in patients with severe dyspepsia.[83]

Unfortunately, most of the studies on the effects of prokinetics in functional dyspepsia have methodological limitations (definition of the patient population, inadequate sample size, physiological motor parameters instead of global symptom scores used as endpoints), which make it impossible to draw firm conclusions on their efficacy. Indeed, very few studies have examined correction of altered physiology and relief of symptoms simultaneously.

Both cisapride and domperidone seem to be efficacious in functional dyspepsia, although this conclusion is largely based on global assessment by the investigator, which may not be an optimal outcome measure.[84]

The effect of prokinetics on visceral sensitivity is unclear (table IV). On one hand, if increased gut wall tension is a mechanism of symptom production in dyspepsia, then the possible increase in tone

Table IV. Possible effects of different drug classes on the pathophysiological targets in functional dyspepsia

Drug class	Examples	Gastric emptying	Fundic accommodation	Visceral hypersensitivity	Comments and references
Antidopaminergic agents	Domperidone, metoclopramide, levosulpiride	Accelerated	?	Reduced sensation; increased discomfort threshold (levosulpiride)[60]	Levosulpiride reported to decrease both gastric compliance and perception,[60] but in a small number of patients
5-HT_4 receptor agonists	Cisapride, tegaserod, prucalopride	Accelerated	Unaffected[61] or possibly increased[62]	Enhanced perception of gastric distension (cisapride)[62]	Cisapride has been reported to enhance gastric accommodation to a meal, but also perception of gastric distension (by barostat) in healthy volunteers[62]
5-HT_3 receptor antagonists	Alosetron, cilansetron	Unaffected (in humans)	Unaffected	Enhanced pain threshold; reduced sensation	39[a]
5-$HT_{1B/D}$ receptor agonists	Sumatriptan	Delayed	Facilitated	Enhanced pain threshold; reduced sensation	63,64[a]
Motilin receptor agonists	Erythromycin, EM-523, mitemcinal (GM-611), alemcinal (ABT-229)	Accelerated	Reduced	Increase in perceived contractions; enhanced sensation	65
Tachykinin receptor antagonists (NK_1, NK_2)	NK_1: nolpitantium (SR-140333), TAK-637; NK_2: saredutant (SR-48968), nepadutant (MEN-11420)			Enhanced pain threshold; reduced sensation	66,67
κ-Opioid receptor agonists	Fedotozine			Enhanced pain threshold; reduced sensation	68,69[b]
α_2-Adrenoceptor agonists	Clonidine	Delayed		Enhanced pain threshold; reduced sensation	70
NMDA-receptor (NR2B subtype) antagonists	Ifenprodil			Reduced sensation; antagonism of central sensitisation	NR2B-selective antagonists seem to have better therapeutic index than non-selective NMDA receptor antagonists[71]
CCK_1 receptor antagonists	Loxiglumide, dexloxiglumide	Antagonise CCK-induced delay		Reduced visceral sensitivity?	CCK_1 receptors are claimed to be involved in the generation of dyspeptic symptoms by duodenal lipids during gastric distension[72]
Antidepressants	Amitriptyline, paroxetine			Enhanced pain threshold; reduced sensation	Used in neuropathic pain[73]
Na^+ channel blockers	Crobenetine		-	Enhanced pain threshold; reduced sensation	These agents are being developed especially for neuropathic and inflammatory pain[74]

Continued next page

Table IV. Contd

Drug class	Examples	Gastric emptying	Fundic accommodation	Visceral hypersensitivity	Comments and references
					Mild gastritis increases the tetrodotoxin-resistant sodium currents in spinal sensory neurons[75,76]
Purinoceptor ($P2X_{2/3}$) antagonists	No selective compounds available			Enhanced pain threshold; reduced sensation	$P2X_3$ immunoreactive neurons are increased in colonic myenteric plexus in human IBD;[77] for the role of purinoceptors, see refs.[78,79]
Vanilloid receptor 1 antagonists	(Capsazepine) no selective compounds available for clinical use			Enhanced pain threshold	No clinical data available[80]

a Data obtained in healthy volunteers.[39,63]

b Only marginally superior to placebo.[69]

5-HT = serotonin (5-hydroxytryptamine); **CCK** = cholecystokinin; **IBD** = inflammatory bowel disease; **NMDA** = N-methyl-D-aspartate.

produced by prokinetics might seem deleterious. However, if transit of luminal contents is promoted simultaneously, stretch will diminish and reduce afferent perceivable input.

5.1 Antidopaminergic Agents

Blockade of dopaminergic inhibitory transmission in the gut has been regarded as the main mechanism of the prokinetic effect of first generation prokinetics such as metoclopramide and domperidone. These drugs have been used for a long time[85] and were developed following the observation that dopamine (which is found in the gut wall of several mammals) can decrease lower oesophageal sphincter tone and intragastric pressure, and impair antroduodenal co-ordination. The question whether the effects of dopamine are due to activation of dopamine receptors or to an interaction with α- and β-adrenoceptors has generated much debate.[86] The issue is further complicated *in vivo* by the fact that dopamine may affect gastrointestinal motility via receptors outside the gut (i.e. by acting in the CNS). Thus, it is not surprising that dopamine may both inhibit and stimulate motility *in vivo* depending on the experimental model and the gut level considered.[87-92] The inhibitory effects of dopamine on upper gut motility and their blockade by dopamine receptor antagonists such as metoclopramide and domperidone have been interpreted as evidence for the existence of dopamine receptors in the gut, although, from a pharmacological standpoint, the functional significance of dopamine receptors in relation to motility is still controversial. Nevertheless, several dopamine antagonists have been used as prokinetic agents for their ability to improve gastric emptying and gastroduodenal co-ordination. In addition, antidopaminergic compounds remain a therapeutic option for their antiemetic properties.[93]

Recently, there has been renewed interest in some antidopaminergic compounds such as levosulpiride.[93-96] This compound, at the dose of 25mg three times daily, is marketed in some countries in the treatment of functional dyspepsia. However, it should be remembered that the same compound, at higher doses (50–100mg), is used as an anti-

psychotic and the question arises whether at least some antidopaminergic agents may affect visceral sensitivity acting at some level along the brain-gut axis. Distrutti et al.[60] investigated whether levosulpiride modulates gastric sensitivity and compliance in eight healthy volunteers and 16 patients with functional dyspepsia defined according to the Rome II criteria, who underwent graded gastric distensions using a tensostat. Although healthy volunteers and patients with dyspepsia had similar gastric compliance, the latter tolerated lower tension levels. At the same distending tension levels, levosulpiride significantly decreased perception score (38% change) only in the patients. A 4-week treatment with levosulpiride significantly reduced dyspeptic symptoms and increased discomfort threshold.

5.2 5-HT_4 Receptor Agonists

5-HT_4 receptors mediate a number of responses in the gut.[81] Prokinesia may result from increased release of acetylcholine (and tachykinins) from excitatory neurones and may operate in human stomach and small bowel.[97,98]

Well known prokinetics such as cisapride are classified among 5-HT_4 receptor agonists since there is evidence that the prokinetic effect[85] and at least some of the adverse effects (e.g. urinary urge[99,100]) are mediated by this receptor subtype. However, the potential of cisapride to induce ventricular arrhythmias and prolongation of the QT interval through blockade of HERG K+ channels[101] led to withdrawal of the compound, which is now available on a limited access basis.

Interestingly, the facilitatory effect of cisapride on gastric emptying correlates with the number of temporally associated antro-duodenal pressure waves or with antral pressure waves of ≥6cm, but not with the total number of antral contractions.[102,103] Indeed, stimulation of antro-pyloro-duodenal motility by cisapride can both impede and facilitate gastric emptying depending on the concurrent changes in antro-duodenal resistance.[104] The net prokinetic effect exerted by cisapride may derive by an increase in the volume of chyme emptied in each flow pulse (stroke volume) rather than by an increased number of flow pulses.

Several studies are available on the effects of cisapride in functional dyspepsia[93,105,106] but these will not be discussed here since they are reviewed elsewhere.[107]

Whether 5-HT_4 receptor agonists can affect visceral sensitivity is controversial. In healthy volunteers, cisapride significantly lowered thresholds for perception and for discomfort during gastric distension, but also significantly enhanced the size of the meal-induced fundus relaxation (i.e. improved gastric accommodation).[62] In another study,[61] eight healthy volunteers were studied on two different days, each after 7 days' treatment either with placebo or cisapride. Intraduodenal infusion of lipids caused relaxation of gastric fundus and this effect was not affected by cisapride. Cisapride did not influence gastric sensitivity to distension or gastric compliance.

Among second-generation 5-HT_4 receptor agonists, tegaserod[108,109] and prucalopride[110,111] have already undergone clinical trials; however, these have been as yet targeted to the treatment of lower gut disorders.[112,113]

5.3 Motilin Receptor Agonists

The reviews by Peeters[114] and Itoh[115] provide a full coverage of the history of erythromycin and its derivatives as prokinetics. It is now well established that erythromycin is a potent motilin receptor agonist and displays prokinetic effects. The ability to interact with motilin receptors is shared, although to a lesser extent, by other antibacterial macrolides with a 14-member ring structure, such as clarithromycin, oleandomycin, roxithromycin and troleandomycin, but not by those derivatives with a 16-member ring structure, such as josamycin, midecamycin, miokamycin (midecamycin acetate), rokitamycin and spiramycin.[116] Recent research into this area has developed erythromycin derivatives with no antibacterial activity, but preserved or even higher motilin-like properties (the so-called motilides such as EM-523, alemcinal [ABT-229] and mitemcinal [GM-611]).[117,118]

The use of erythromycin and its derivatives as upper gut prokinetics finds a rationale from the observation that there is a gradient of motilin receptors from stomach to terminal ileum, with the highest density in the upper gut. Erythromycin can stimulate gut motility both through a direct action on smooth muscle motilin receptors and probably also through neural receptors.[114,119-121]

After intravenous injection, erythromycin dramatically improves gastric emptying in patients with diabetic gastroparesis.[122] The intravenous dose ranges between 1–3 mg/kg when the drug is needed in acute situations. Oral erythromycin appears to be less effective in improving gastric emptying, especially in long-term regimens (because of the occurrence of tachyphylaxis), but no accurate comparative data are available.

Recent studies have assessed the effect of erythromycin on gastric tone. In healthy volunteers, erythromycin enhances fasting and postprandial gastric tone,[123] increases meal-induced satiety,[124] and decreases the pressures and volumes needed to induce threshold perception or discomfort during gastric distension.[125] These observations may have important therapeutic implications, e.g. in those dyspeptic patients with impaired gastric accommodation, since erythromycin would be expected to be contraindicated in these patients.

Indeed, trials with the motilin receptor agonist alemcinal were unequivocally disappointing for symptom improvement regardless of gastric motor function.[65,126] In the study by Talley et al.,[126] with chronic upper abdominal discomfort were assigned to either the delayed or normal gastric emptying strata and were then randomised within each strata, to receive one of four oral doses of alemcinal (1.25, 2. 5, 5 or 10mg twice daily before breakfast and dinner) or placebo for 4 weeks, following a 2-week baseline. The primary outcome was the assessment of change in symptom severity over the 2 weeks from baseline to final visit, based on a self-report questionnaire measuring severity on VAS. No significant differences in the upper abdominal discomfort severity score were observed for any active treatment arm versus placebo. Significantly more patients on placebo reported a good or excellent global response than patients receiving 1.25 or 5mg of active therapy. The results were very similar in those with and without delayed gastric emptying.

In conclusion, motilin receptor agonists are potent gastroprokinetics and improve delayed gastric emptying, but have the potential to worsen dyspeptic symptoms possibly because of their detrimental effect on gastric accommodation.[65] For the ongoing debate on their potential in functional dyspepsia, the reader is referred to recent opinion by experts in the field.[127,128]

6. Emerging Agents for the Treatment of Functional Dyspepsia

In the past, the prevailing pharmacological therapeutic approach to resolve pain and discomfort in patients with functional bowel disorders focussed on the restoration of normal motility patterns (e.g. with prokinetics acting mainly on the final neuronal efferent pathways or on the smooth muscle effector). In recent years, the role of afferent neural pathways arising from the gut has been emphasised and has provided both new insights into gut pathophysiology and an alternative approach to treatment.[129]

Primary afferent nerves express a wide range of membrane receptors that can modulate their sensitivity and be potential therapeutic targets[130] (figure

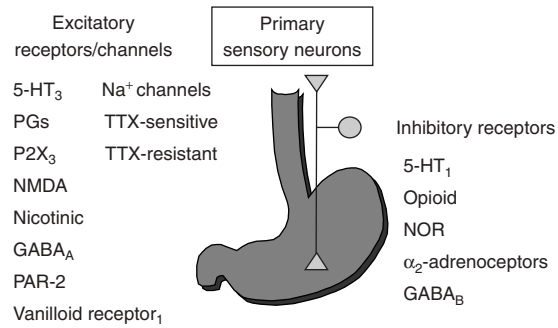

Fig. 3. Receptors on primary afferent nerves as potential therapeutic targets to control visceral hypersensitivity. **5-HT** = serotonin (5-hydroxytryptamine); **GABA**$_{A/B}$ = gamma amino butyric acid receptor A and B; **NMDA** = N-methyl-D-aspartate; **NOR** = nociceptin/orphanin FQ; **P2X**$_3$ = purinoceptors (2X$_3$ subtype); **PAR-2** = protease activated receptor-2; **PGs** = prostaglandins; **TTX** = tetrodotoxin.

3). Some receptors are part of transduction pathways involved in sensory signalling. Others are activated by substances released during ischaemia, injury or inflammation, and act in a synergistic fashion to cause acute or chronic sensitisation of the afferent nerves to mechanical and chemical stimuli. Hypersensitivity to gastric distension is thought to be the hallmark of a least a subset of patients with functional dyspepsia.[131] Table IV provides a synopsis of the possible effects of different classes of drugs on the main therapeutic targets in functional dyspepsia.

The main problem in the preclinical evaluation of drugs with potential beneficial effects on visceral hypersensitivity is the inadequacy of animal models because of several limitations. Indeed, efficacy on pain induced by irritants injected into the peritoneal cavity, or ileus produced by laparotomy or visceral manipulation, does not necessarily mean efficacy on visceral hypersensitivity, since pathways activated by peritoneal irritation are probably different from those mediating gut sensations. As in humans, gut distension is the most widely used stimulus. It induces visceromotor and cardiovascular reflexes, aversive behavioural responses and electrophysiological modifications, all parameters that can be quantified to evaluate nociception in animals. Chemical irritation by intraluminal stimuli (e.g. acetic acid or turpentine) or subcutaneous 5-hydroxytryptophan (oxitriptan) are also used.

6.1 5-HT_3 Receptor Antagonists

The rationale for investigations on serotonin (5-HT) receptor ligands in functional gut disorders rests mainly on the fact that serotonin, which may be released from enterochromaffin-like cells in the gut as well as from other non-neuronal or neuronal sources, has a number of well documented motor effects on the gut and can produce hyperalgesia in several experimental models.[132]

Apart from the well known involvement of 5-HT_3 receptors in mediating (centrally and peripherally) emesis of various origin, several animal models point to their role in modulating visceral sensitivity.[81] Granisetron and tropisetron (but not ondansetron) were found to inhibit the fall in blood pressure and intragastric pressure observed in rats after duodenal distension.[133] Whether the site of 5-HT_3 receptors modulating afferent information is on peripheral afferent nerve fibres or outside the gut, however, is unclear. For instance, alosetron, administered either centrally or peripherally in dogs, seems to modulate the visceral nociceptive effect of rectal distension in dogs.[134] In humans, reduced perception of colonic distension may also depend on an increased compliance of the colon to distension.[135]

In humans, granisetron was found to reduce rectal sensitivity in patients with IBS,[136] whereas ondansetron had no effect.[137] Interestingly, however, ondansetron reduced nausea and gastric sensitivity to distension during intraduodenal lipid infusion in healthy volunteers.[138] An important issue when evaluating different studies with 5-HT_3 receptor antagonists is that, even in the same experimental model, differences among different compounds[139] are not easily explained on the basis of current pharmacological knowledge.

Among 5-HT_3 receptor antagonists, alosetron was initially approved by the US FDA for the treatment of diarrhoea-predominant IBS in female patients, but safety concerns (occurrence of ischemic colitis) lead to drug withdrawal only a few months after approval (see the US FDA dedicated internet address: http://www.fda.gov/cder/drug/infopage/lotronex/lotronex.htm). Recently, alosetron was reintroduced into the market with restrictions on its use. This compound has an indication only for women with severe diarrhoea-predominant IBS who have failed to respond to conventional therapy.

Other 5-HT_3 receptor antagonists (e.g. cilansetron) are now in the development pipeline. Theoretically, these compounds may act on multiple therapeutic targets in functional gut disorders:[140-142] (i) by modulating visceral sensitivity;[143] (ii) by increasing compliance (i.e. increasing the ability of the gut to adapt to distension);[135] (iii) by blocking excitatory 5-HT_3 receptors located on sensory, ascending and descending neuronal pathways involved in peristalsis; and (iv) by increasing jejunal fluid absorption.[140] For this reason, 5-HT_3-receptor

antagonists may slow transit. However, alosetron did not affect perception of gastric distension in volunteers.[144] A recent study,[145] which failed to observe a significant effect of alosetron on transit parameters, discusses important issues to optimise experimental design of trials initiated to find mechanistic explanations for drug action in functional gut disorders.

Talley et al.[146] performed a pilot, dose-ranging, placebo-controlled, multicentre, randomised trial with 320 patients with functional dyspepsia who received placebo (n = 81), or alosetron 0.5mg twice daily (n = 77), 1.0mg twice daily (79) or 2.0mg twice daily (83) for 12 weeks, followed by 1 week of follow-up. Primary efficacy was the 12-week average rate of adequate relief of upper abdominal pain or discomfort. Average rates of adequate relief of pain or discomfort at 12 weeks were 46, 55, 55 and 47% in the placebo, 0.5, 1.0 and 2.0mg alosetron groups, respectively. Alosetron 0.5 or 1.0mg showed potential benefit over placebo for early satiety and postprandial fullness. Constipation was the most commonly reported adverse event. Thus, the therapeutic gain with alosetron appeared to be relatively modest in this population of patients with dyspepsia.

Another trial carried out in 36 healthy volunteers[39] assessed the effects of placebo, and alosetron 0.5 and 1mg twice daily on fasting and postprandial gastric volumes (using single photon emission computed tomography) and symptoms based on 100mm VAS, 30 minutes after maximum volume ingested. Alosetron reduced postprandial symptoms (1mg alosetron reduced aggregate score by approximately 40% with respect to placebo; $p < 0.05$), nausea ($p < 0.001$) and tended to reduce bloating ($p = 0.08$). Both 0.5 and 1mg alosetron reduced nausea ($p < 0.025$), and 1mg alosetron reduced aggregate symptoms ($p < 0.05$) and bloating ($p < 0.05$). Effects on pain ($p = 0.19$) and fullness ($p = 0.14$) were not statistically significant. There was no significant effect of the 5-HT_3-receptor antagonist on volume of meal tolerated.

The effects of 5-HT_3-receptor antagonists on gastric emptying were debated for some time over the past 2 decades (for a detailed discussion Tonini and De Ponti[147]). Early reports showing accelerated emptying of polystyrene-coated barium sulphate in guinea pigs after administration of tropisetron or ondansetron lead to the hypothesis that 5-HT_3 receptors might be involved in the regulation of gastric emptying.[148,149] Accordingly, most 5-HT_3-receptor antagonists were shown to enhance gastric emptying in rats with potencies comparable with that required to inhibit the Bezold-Jarisch reflex, a well characterised 5-HT_3-receptor-mediated response.[150] However, the gastrokinetic effect of $5HT_3$ receptor antagonists observed in rodents is not predictive for other species, including humans. Apart from a minor facilitatory effect of tropisetron on gastric emptying of a solid meal in healthy volunteers found by Akkermans,[151] subsequent studies[152,153] failed to detect any significant effect of ondansetron or tropisetron on gastric emptying in participants with delayed gastric emptying. However, 5-HT_3 receptor antagonists may reverse lipid-induced slowing of gastric emptying, at least in dogs,[154] an effect that might turn out to have potential clinical significance.

6.2 5-$HT_{1B/D}$ Receptor Agonists (Triptans)

Several studies have documented the effects of the 5-$HT_{1B/D}$ receptor agonist sumatriptan on gastric motility and sensitivity in the same dosage range used in migraine (for a review, see Cipolla et al.[63]). Ten years ago, Houghton et al. first reported that sumatriptan (3mg intravenously) delayed gastric emptying of a liquid meal in healthy volunteers.[155] Subsequently, Coulie et al.[156] showed an important delay in gastric emptying of both solids and liquids by sumatriptan (6mg subcutaneously).

The observed delay in gastric emptying would contraindicate sumatriptan in patients with delayed emptying. However, Tack et al. tested the hypothesis that sumatriptan might actually exert a beneficial effect at least in some patients by improving fundic accommodation. An electronic barostat was used to monitor variations in gastric fundus tone in healthy volunteers before and after placebo or sumatriptan (6mg subcutaneously). Sumatriptan indeed relaxed the proximal stomach and allowed larger intragas-

tric volumes before thresholds for perception of discomfort were reached.[64] Thus, sumatriptan may turn out to be a useful drug to target decreased fundic accommodation observed in some dyspeptic patients. Indeed, in patients with functional dyspepsia, sumatriptan is reported to improve gastric accommodation to a meal and reduce perception of gastric distension, hence relieving epigastric symptoms.[34,64] It should be noted, however, that a recent study[157] failed to demonstrate a relationship between postprandial symptoms and proximal stomach function, or to confirm the effect of sumatriptan on the maximal ingested volume.

Animal models have allowed more insight into the possible mechanism mediating the gastric motor effects of sumatriptan. Coulie et al.,[158] using an *in vivo* cat model, suggested that sumtriptan-induced fundic relaxation occurs through activation of a nitrergic pathway. However, they did not provide evidence on the 5-HT receptor subtype involved in this response. More recently, a selective 5-$HT_{1B/D}$ receptor antagonist (GR-127935) has become available, which, at least in dogs, has enabled demonstration that sumatriptan improves the ability of the proximal stomach to adapt to a distending stimulus (i.e. increases gastric compliance) by acting at 5-$HT_{1B/D}$ receptors.[159] Whether the site is central or peripheral, remains to be determined. The fact that sumatriptan penetrates the blood-brain barrier poorly and can relax the isolated guinea pig stomach[160] would argue against a central site of action, although evidence for the presence of 5-$HT_{1B/D}$ receptors is still lacking. To the best of our knowledge, no published data are available on possible gastrointestinal motor effect of second-generation triptans in humans, but preliminary studies carried out with rizatriptan and naratriptan in conscious dogs confirm their ability to enhance gastric compliance.[161]

In conclusion, in dyspeptic patients with impaired fundic relaxation to a meal and/or altered gastric sensitivity to distension, conventional prokinetics are contraindicated, whereas a gastric relaxing drug could decrease early satiety, a cardinal symptom of dysmotility-like dyspepsia. Another serotonergic agent, buspirone, may have similar effects.[162] Long-term studies with different classes of orally active fundus-relaxing drugs seem warranted to confirm their therapeutic potential.

6.3 Antidepressants

Antidepressants (both tricyclic agents and selective serotonin reuptake inhibitors) are often included in management algorithms for functional gastrointestinal syndromes, but their role is still debated since only a small number of controlled studies are available.[163] Antidepressants are recommended for severe or refractory symptoms of pain and most of the studies on the use of antidepressants in functional syndromes were carried out in patients with IBS.[164] The effects in patients with functional dyspepsia are virtually unexplored, although there is renewed interest in their therapeutic potential. This is the reason to list these drugs among emerging agents.

Mertz et al.[165] tried to determine how amitriptyline affects digestive symptoms and perceptual responses to gastric distension. Patients were randomised to 4 weeks of amitriptyline 50mg taken at bedtime versus placebo. Seven of seven patients reported significantly less severe gastrointestinal symptoms after 4 weeks of amitriptyline compared with placebo. Five of seven patients had evidence of altered perception of gastric balloon distension with placebo. However, the subjective symptom improvement on amitriptyline was not associated with a normalisation of the perceptual responses to gastric distension. The authors concluded that the beneficial effect of low-dose amitriptyline was not related to changes in perception of gastric distension and that an increased tolerance to aversive visceral sensations might play a role in the therapeutic effect; however, the results need to be confirmed in sufficiently powered studies.

Because of their complex pharmacological properties (both central and peripheral), antidepressants may exert useful actions at more than one site along the brain-gut axis. Two studies have shown that imipramine can prolong oro-caecal and whole gut transit times in patients with diarrhoea-predomi-

nant IBS and controls, whereas paroxetine reduced oro-caecal transit times with no effect on whole gut transit times.[166,167] Although, as the authors acknowledge, demonstration of altered transit by antidepressants does not imply therapeutic usefulness, the above studies have shown that antidepressants can alter motor function independently of mood effects, since the antidepressants were taken only for 4–5 days. As regards modulation of afferent information from the gut by antidepressants, a report suggests that this is a possible mechanism of action: in healthy volunteers, imipramine can increase pain and perception thresholds to oesophageal balloon distension.[168] Thus, antidepressants seem to have analgesic and neuromodulatory properties independent of their psychotropic effects, and these effects may occur sooner and at lower dosages than is the case when these drugs are used for the treatment of depression.[163,169]

Two pharmacological actions of antidepressants deserve special mention: Na^+ channel blockade[170] and the ability to upregulate brain-derived neurotrophic factor (BDNF) and trkB receptor expression in the CNS.[171] The former effect is shared by some antidepressants and is of potential interest in conditions associated with neuropathic/inflammatory pain (see section 6.6). Notably, two recent studies[75,76] have shown that gastric injury (even mild gastritis) alters the properties of Na^+ currents in sensory neurones (increase in the tetrodotoxin-resistant current). Upregulation of BDNF and trkB in the CNS after administration of antidepressant drugs is of special interest since preliminary data indicate that recombinant BDNF and neurotrophin (NT)-3 can accelerate intestinal transit in humans.[172]

6.4 κ-Opioid Receptor Agonists

Inhibition of somatic and visceral pain is a general feature of opioid agonists, which unfold their antinociceptive effects acting through different opioid receptors located peripherally as well as centrally. Recently, κ-opioid receptor agonists have been proposed as a new pharmacological approach to the treatment of functional gut disorders[69] on the basis that κ-receptors are thought to be located on vagal and non-vagal afferent pathways. Activation of these receptors causes a decrease in calcium currents, resulting in increased nociceptive thresholds and attenuation of neuronal excitability. Peripherally acting κ-receptor agonists would also have the advantage of avoiding the central adverse effects of opioids as well the potent inhibitory effect on gut motility exerted by μ- and δ-receptor agonists. Interestingly, fedotozine is reported to be effective after intravenous but not intracerebroventricular administration.[69]

Fedotozine has been shown to suppress afferent visceral activity in several animal models, such as experimental ileus, acetic-acid induced colonic hypersensitivity and colo-gastric inhibitory reflex.[173]

In healthy humans, fedotozine decreases gastric sensitivity to distension,[174] without modifying gastric compliance or somatic sensitivity. In patients with dyspepsia, oral fedotozine 30mg three times daily was reported to reduce postprandial fullness, bloating, abdominal pain and nausea.[175] However, the therapeutic gain of fedotozine with respect to placebo appears to be modest, at least in functional dyspepsia.[68]

6.5 Herbal Remedies

Several herbal medicinal products (e.g. peppermint oil and caraway oil,[176] and red pepper[177]) have been suggested for the treatment of functional dyspepsia. Although most of these agents have an encouraging safety profile, a recent review concluded that further research is needed to establish their therapeutic value in functional dyspepsia.[178]

6.6 Miscellaneous Agents

Visceral hypersensitivity is an attractive therapeutic target in functional dyspepsia. A large number of basic science studies are investigating receptors and pathways involved in pain transmission along the brain-gut axis.[130,179]

Figure 3 illustrates receptors that may become target of future drugs controlling visceral pain (especially in the case of concomitant 'minimal inflammation' leading to peripheral/central sensitisation phenomena). Special mention should be made of the

following: purinoceptors (especially the P2X2/3 receptors),[77-79] the NMDA receptor (especially the NR2B subtype),[179] the protease-activated receptor (PAR)-2[180] and the vanilloid receptor 1.[80] Na^+ channel blockers are also being studied for their potential in neuropathic and inflammatory pain.[74] Interestingly, several antidepressants are known to affect Na^+ channels.[170]

Cholecystokinin $(CCK)_1$ receptor antagonists such as dexloxiglumide are under scrutiny since CCK_1 receptors are claimed to be involved in the generation of dyspeptic symptoms by duodenal lipids during gastric distension.[72]

Finally, tachykinin receptor antagonists (especially NK_1/NK_2 receptor antagonists) also have a potential because of their effects on two important targets: visceral sensitivity and motility (blockade of smooth muscle NK_2-receptors is expected to facilitate relaxation).[66,67]

Although a large number of compounds targeting the aforementioned receptors are now under development for conditions associated in visceral or neuropathic pain, to the best of our knowledge, none are at present specifically focussed for the treatment of functional dyspepsia.

7. Conclusions

This review has summarised the current thinking on the pathogenesis of symptoms in patients with functional dyspepsia and on the drugs carrying potential benefits for the management of these difficult to treat patients. A subset of patients with dyspepsia may benefit from antisecretory therapies, although it has not been established to what extent unrecognised GORD is responsible for this favourable response. Abnormalities in gastrointestinal motility and sensitivity alone or in combination seem to be involved in the majority of patients. Future therapies should be targeted towards these abnormalities, however, this appears to be a difficult task.

Gastrointestinal dysmotility is a vague term that encompasses different and often opposite neuromuscular events that are at variance with those recorded with current technology in the alimentary canal of individuals who consider themselves healthy and asymptomatic. Drugs capable of simultaneously restoring timely changes in funding tone and appropriate antral tone, as well as powerful and co-ordinated antro-pyloro-duodenal contractions that can be used safely will play an important role in the management of patients with dyspepsia unable to maintain a normal bodyweight and/or to perceive food ingestion as a pleasant life requirement. Afferent neural pathways are modulated by numerous excitatory and inhibitory receptors, and it is likely that drugs interfering with only one of the receptors involved may induce marginal effects on the final message brought by the neural fibres from the gut to the brain. Drugs modulating the final central effect of afferent nerves without blunting their peripheral reflex activity could represent the 'holy grail' of functional dyspepsia therapy for the majority of patients.

Future clinical trials must be carried out in such a way that the formal structure required by good clinical practice can be adapted to detect significant effects in subgroups of patients. Therapy should be targeted to the different pathophysiological abnormalities of these subgroups. Since these abnormalities are not firmly established as yet, research must still be based on thorough analysis of a patient's symptoms. Painful and non-painful sensations arising from the gut are perceived through neural pathways that are at least partially different even from an anatomical point of view and different drugs are likely needed to control these different symptoms.

Research is unpredictable. Sometimes the 'magic bullet' comes out of the blue and precedes the intimate understanding of the disease that it can effectively cure. We hope this can be the case for functional dyspepsia.

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