

Current management of functional dyspepsia: impact of Rome III subdivision

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Abstract

Functional dyspepsia (FD) is a highly prevalent disease characterized by symptoms originating from the gastroduodenal region in the absence of underlying organic disease. The Rome III consensus made a distinction between meal-induced and meal-unrelated symptoms and proposed subdivision of FD into postprandial distress syndrome and epigastric pain syndrome. The applicability of this subdivision and the impact on management are areas of active research. So far, empirical approaches are still employed for the treatment of FD, although various therapeutic modalities for FD have been explored; acid-suppressive, prokinetic, and fundic relaxant drugs, antidepressants and psychological therapies. FD remains a challenge and presents unmet clinical needs.

Keywords functional dyspepsia, Rome III, treatment

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Introduction

Functional dyspepsia (FD) is a relevant condition for public health due to its high prevalence and associated morbidity and socio-economic cost [1]. Over the last years the definition of FD has undergone major changes. On the basis of the most recent Rome III definition, FD is defined as the presence of dyspeptic symptoms (early satiation, postprandial fullness, epigastric pain or burning) thought to originate from the gastroduodenal region, in the absence of any organic disease that is likely to explain the symptoms [2]. The Rome consensus has also proposed a distinction between meal-induced symptoms and meal-unrelated symptoms. Thus, FD now consists of two main diagnostic categories: i) meal-induced dyspeptic symptoms [postprandial distress syndrome (PDS)], characterized by postprandial fullness and early satiation, and ii) epigastric pain syndrome (EPS), characterized by epigastric pain and burning [2].

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The Rome III subdivision was proposed under the assumption that different pathophysiological mechanisms would be present in each of the subgroups. Thus, careful evaluation of patients' symptom pattern before applying an empirical treatment would offer the most suitable therapy for each subgroup.

Treatment of FD

Reassurance is traditionally proposed as the first step in management of FD. Dietary recommendations (eating more frequent, smaller meals and avoiding food that aggravates symptoms) are logical and are usually prescribed to FD patients, but they have not been systematically studied. For many patients drug therapy is considered, but to date the pharmacological options for treating FD are limited. There is a lack of drugs with established efficacy and drug development is hampered by the large placebo effect and the lack of well-validated endpoints for the Rome III definition of FD [3].

Helicobacter pylori eradication

Eradication of *Helicobacter pylori* (*H. pylori*) infection plays only a limited role in the treatment of FD. A recent Cochrane meta-analysis showed that the yield of eradication in *H. pylori*-positive FD patients in terms of symptom relief was only 10%, with an estimated number to treat of 14 [4].

Moreover, the subgroup of infected FD patients is expected to become progressively smaller as the prevalence of *H. pylori* infection is steadily declining in Western populations.

Acid-suppressive drugs

Acid suppression is a frequently used first-line treatment. It is well known that patients with concomitant symptom of heartburn are best candidates for acid suppression therapy. A meta-analysis of placebo-controlled, randomized trials with proton pump inhibitors (PPIs) in FD patients showed a significant benefit of 13% for this class of drugs over placebo [5]. There was no significant difference in efficacy among various PPI doses. FD patients with epigastric pain (EPS group according to Rome III) rather than patients with meal-induced symptoms seem to respond to PPIs [2,5].

Prokinetic drugs

Prokinetics, drugs that stimulate gastric smooth muscle contractions are widely used in patients with FD. They are a heterogeneous class of agents showing their most convincing efficacy in patients with meal-related symptoms (PDS group according to Rome III). A significant benefit was found for prokinetics (mainly cisapride and domperidone) over placebo with a relative risk reduction by 33% and a number to treat of 6, but concerns were raised about publication bias [6].

Cisapride, the first prokinetic used in FD and gastroparesis, accelerates gastric emptying by stimulating 5-hydroxytryptamine-4 (5-HT₄) receptors and releasing acetylcholine in the myenteric plexus [7]. The drug has been withdrawn due to cardiac safety concerns.

Tegaserod, a partial 5-HT₄ receptor agonist, accelerates gastric emptying and enhances gastric accommodation in FD [8]. A report of two large phase 3 studies of tegaserod 6 mg b.i.d. in women with mainly PDS-type symptoms showed a small benefit of questionable clinical significance [9]. In a long-term open-label study, tegaserod showed symptom relief and sustained improvement in productivity scores from baseline in FD [10], while another study reported enhancement of gastric accommodation in patients with normal gastric emptying [11]. The drug was generally well tolerated, but was withdrawn for a putative increased risk of cardiovascular ischemic events.

Mosapride is a new 5-HT₄ receptor agonist that also exhibits 5-HT₃ receptor antagonist properties. An open label clinical trial from Japan showed that a two-week treatment with mosapride significantly improved health-related quality of life (QOL) and improved both EPS and PDS-type symptoms [12]. However, a European controlled trial failed to show benefit of mosapride over placebo [13]. The drug is commercially available in several Asian countries.

Other 5-HT₄ receptor agonists. Newer prokinetic agents with 5-HT₄ receptor agonist properties, which were mainly investigated in constipation-predominant IBS (renzapride, prucalopride, ATI-7505, and TD-5108), have been evaluated in healthy volunteers, in patients with gastroparesis and in patients with FD [14].

Domperidone is a butyrophenone derivative that exerts antidopaminergic effects on peripheral dopamine₂ receptors (D₂). For FD, recent reviews suggest that domperidone was more effective than placebo, but the trials were often of poor quality with heterogeneity between studies [15,16]. Moreover, the efficacy of domperidone was largely based on the global assessment of improvement by the investigators [15]. A recent study in a Chinese population with nocturnal dyspeptic symptoms showed that domperidone significantly decreased the severity score of nocturnal dyspeptic symptoms and this improvement was positively correlated with reduced nocturnal bile reflux [17]. However, nocturnal symptoms are not typical of FD, and are more suggestive of gastro-esophageal reflux disease.

Itopride is a mixed dopamine D₂ antagonist and acetylcholinesterase inhibitor. The drug showed significant promise in a phase IIb placebo-controlled trial on the basis of a global efficacy measure [18]. This beneficial effect was not confirmed in phase III studies [19]. The drug is commercially available in several Asian countries and a prospective, multicenter, open-label observational study to assess the effectiveness of itopride was performed in China. After a 4 week treatment period with itopride 50 mg three times daily, 75% of patients who fulfilled Rome III criteria for FD reported improvement in the total symptom score compared to baseline [20].

Motilin receptor agonists. Motilin stimulates motility through its action at gut receptors; there is a gradient of motilin receptors from stomach to terminal ileum, with the highest density in the upper gut. Agonists of motilin receptors, such as erythromycin and structurally related synthetic analogues devoid of antibacterial properties (motilides) are potent prokinetics with clinical efficacy in motility disorders [6,7]. So far, none of these drugs showed beneficial effects over placebo in FD [6,21]. On the contrary, when one of these drugs, ABT-229, was administered at high doses, FD symptoms were worse than with placebo treatment. The inhibitory effect of motilin agonists on gastric accommodation, inducing early satiation, has been implicated in these negative outcomes [22,23]. A number of compounds are currently still under evaluation as it is conceivable that lower doses could enhance gastric emptying without affecting gastric accommodation.

Fundic relaxant drugs

Impaired fundic accommodation is one of the major pathophysiological mechanisms linked to FD. Thus, fundic relaxants including a heterogeneous class of drugs have been under evaluation. Among various drugs, nitrates, sildenafil

(phosphodiesterase-5 inhibitor) and sumatriptan (5-HT₁ receptor agonist) which are able to relax the proximal stomach, seem less suitable for treatment of FD patients for reasons of cost, mode of administration or lack of selectivity [7,14,24].

Acotiamide (Z-338) is a novel compound with gastroprokinetic properties, based on a mechanism of action that differs from other gastroprokinetic agents. Z-338 exerts its activity via antagonism of the inhibitory muscarinic type 1 and type 2 (M1/M2) auto-receptors. A pilot placebo controlled study showed that the drug provided significantly better overall symptom relief in patients with FD through a mechanism related to enhancement of gastric accommodation [25]. Reports of phase II studies in FD patients in Japan showed that 100 mg t.i.d. of acotiamide improved symptoms of postprandial fullness, early satiety and abdominal bloating, suggesting a beneficial effect in patients with PDS [26]. A recent phase III multicentre, randomized, placebo-controlled trial in Japan confirmed the efficacy of acotiamide in patients with PDS, yielding a significant benefit of 17.4% over placebo, with a number needed to treat of 6 for overall treatment efficacy [27]. Moreover, in a long-term 48-week open-label study of acotiamide 100 mg t.i.d. administration, increasing overall treatment efficacy occurred over time, reaching a level of 61% at week 8, to be maintained subsequently. In addition, in patients who met criteria of drug cessation, re-administration of the drug was successful in again achieving remission of PDS symptoms [28].

5-HT_{1A} receptor agonists. Activation of 5-HT_{1A} receptors can achieve inhibition of excitatory motor neurons and as a result it may enhance gastric accommodation [29]. *Buspirone* is a non-selective 5-HT_{1A} receptor agonist, used in the treatment of panic attacks. In a placebo-controlled study in patients with FD, buspirone was superior to placebo in alleviating dyspeptic symptoms, and this was associated with an enhancement of the accommodation to a meal [30]. Short-term studies in healthy volunteers using the novel 5-HT_{1A} receptor agonist *R-137696*, established that the drug had a dose-dependent relaxatory effect on the proximal stomach [31]. However, a subsequent four-week multi-center placebo-controlled study failed to show any symptomatic benefit possible owing to desensitization [32]. A clinical trial with the anxiolytic 5-HT_{1A} receptor agonist, *tandospirone* showed significant benefit over placebo [33].

Antidepressants

A number of literature data suggesting that tricyclic antidepressants showed a significant benefit over placebo with a relative risk reduction by 45%, but the available trials were small and of poor quality [34]. The mechanism of action of antidepressants is unclear, although there is some evidence that the drugs affect gastric sensitivity [35]. A large, randomized, double-blind, placebo-controlled trial with the serotonin/noradrenalin reuptake inhibitor venlafaxine in 160 patients with FD failed to show any benefit [36]. Paroxetine, a selective serotonin reuptake inhibitor (SSRI), enhanced

gastric accommodation in healthy volunteers, but clinical studies in patients with FD are lacking [37].

Psychological therapies

A recent Cochrane review of psychological therapies including hypnotherapy and cognitive-behavioral therapy for FD showed clinical benefits that persist for almost 1 year [38]. However, the studies included were small, with high dropout rates, and biased patient recruitment. Hypnotherapy was suggested to be effective in specialized centers and this benefit may be achieved by accelerating gastric emptying [39].

Other treatments

A systematic review on *herbal medications* reported almost 44 products that have been used in patients with FD [40]. Among various herbal products, *Rikkunshito*, a traditional Japanese herbal medicine, was administered in 16 patients with FD. Two weeks treatment increased gastric accommodation, and enhanced antral contractility and gastric emptying rate [41].

Visceral analgesics, such as κ -opioid receptor agonists are under evaluation as visceral hypersensitivity plays a key role in the pathogenesis of FD. Fedotozine showed efficacy in FD, but development of the drug was discontinued, whereas asimadoline failed to improve symptoms in a small pilot study [42,43].

Conclusions – Practical management

In FD patients with mild symptoms reassurance and some dietary recommendations may be sufficient. In patients with severe symptoms or in those who do not respond to lifestyle measures, drug therapy is considered. Before drug administration, testing for *H. pylori* and eradication treatment, if positive, should be proposed, but the yield in terms of symptom relief will be low. Both PPIs and prokinetics have been used as first line treatment, but Rome III subdivision of FD may determine the most suitable choice for each subgroup. Thus, in patients with EPS a 4-8 week trial of PPI therapy is the treatment of choice, whereas in patients with PDS a prokinetic drug should probably be proposed as initial therapy. In cases of insufficient therapeutic response combined therapy or a change of drug class is advisable, or combination therapy can be considered. In patients who remain refractory to initial therapy, a trial of a low-dose tricyclic antidepressant may be considered. Serotonin/noradrenaline reuptake inhibitors should probably be avoided. In patients motivated for psychological therapies, hypnotherapy can be an interesting option although data are limited.

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