

The Efficacy of Mosapride for the Treatment of Functional Dyspepsia

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Abstract: Functional Dyspepsia (FD) is a common affliction in western countries effecting approximately 25% of the population. Due to its heterogeneous pathogenesis, effective therapeutics are limited. Mosapride, a serotonin receptor agonist with enterokinetic properties, has been evaluated for treating dyspeptic symptoms in a limited number of clinical trials. Most trials found mosapride to be as effective as other commonly used treatments for FD including histamine receptor blockers (H₂RAs), and the results of the only randomized double-blind placebo-controlled trial to date found mosapride to be no more effective than placebo. These studies were limited by suboptimal study design and performed prior to sub-classification of FD sub-types as defined by Rome III. Therefore, there is currently inadequate data to comment on the efficacy of mosapride for treating FD. Larger placebo controlled trials differentiating dyspeptic patients by primary symptom associations are necessary.

Keywords: mosapride, dyspepsia, serotonin agonists, prokinetics

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Introduction

Dyspepsia is a common gastrointestinal disorder with a prevalence of 20%–30% in the general populations of western nations.¹ Nearly two-thirds of these patients ultimately receive a diagnosis of functional dyspepsia (FD) with symptoms persisting in nearly 80% five to ten years after the initial diagnosis.² The etiology and pathogenic factors involved in the development of FD remain unclear but are believed to arise from a heterogeneous array of precipitants including genetic predisposition, psychosocial disturbances, altered gastrointestinal secretion and motility, visceral hypersensitivity, or perturbations in gut flora-immune interactions (Fig. 1).³ Patients with dyspepsia usually experience a chronic relapsing course.⁴

Historically, overlapping symptoms have been used to define FD and heterogeneity in the dyspepsia symptom spectrum has resulted in diagnostic uncertainty and difficulty designing appropriate therapeutic trials. Subsequently, the Rome committee has established criteria to assist both clinicians and researchers in overcoming these limitations. The most recent revision, the Rome III criteria, broadly define FD as the presence of symptoms originating in

the gastro-duodenal region occurring in the absence of an organic or metabolic diseases (Table 1).⁵ This comprehensive definition was established for clinical use. Functional dyspepsia is further sub-divided into two pathophysiological-based categories: Post-prandial distress syndrome (PDS) delineating a meal-induced association between symptoms and impaired fundic relaxation and/or delayed gastric emptying, and epigastric pain syndrome (EPS) corresponding to visceral hypersensitivity (Table 2). These classifications were designed for experimental purposes, as it has been purported that certain therapeutics may prove more efficacious if targeted at specific symptom subsets.⁶

Less than half of patients with dyspeptic symptoms seek medical care and, for those who do, efficacious therapies are needed. Many are currently available: dietary and lifestyle modifications, H. pylori eradication, antacids, gastric mucosal protectants, anti-secretory medications, prokinetics, antidepressants, cognitive therapies and complimentary/alternative treatments. However, strong evidence-based efficacy data for the majority are lacking.

Mosapride's Effects on Functional Dyspepsia

Mosapride, a pro-kinetic agent, exerts its effects via selective activation of serotonin subtype-4 (5-HT₄) receptors in the gastrointestinal (GI) enteric plexus. It also elevates plasma levels of motilin, with peak levels of motilin correlating with peak plasma concentrations of mosapride.⁷ These agonistic properties are presumed responsible for multiple physiologic changes including increased amplitude and duration of esophageal peristaltic contractions,⁸ increased esophageal bolus transit,⁹ and augmentation of lower gastrointestinal

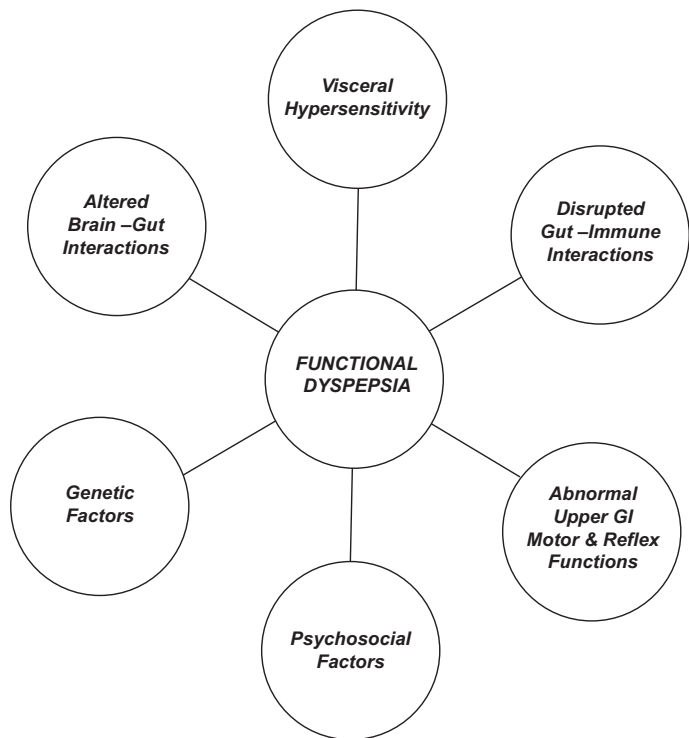


Figure 1. Proposed pathophysiological mechanisms of FD. Adapted from Saad et al.³

Table I. Rome III criteria for functional dyspepsia.

Functional dyspepsia must include one or more of the following:*

1. Epigastric pain
2. Epigastric burning
3. Bothersome postprandial fullness
4. Early satiation

AND

No evidence of structural disease (including at upper endoscopy) more likely to explain patient symptoms

*Criteria fulfilled for the past 3 months with symptom onset \geq 6 months prior to diagnosis. Adapted from Tack et al.⁵

**Table 2.** Sub-classification of functional dyspepsia.**Post-prandial distress syndrome must include one or both of the following:***

- 1) Bothersome postprandial fullness, occurring after ordinary-sized meals, at least a few times each week
- 2) Early satiation that prevents finishing an ordinary-sized meal, at least a few times each week

Supportive criteria:

- a) Upper abdominal bloating, postprandial nausea, or excessive belching
- b) May coexist with EPS

Epigastric pain syndrome must include all of the following:*

- 1) Epigastric pain/burning of at least moderate severity occurring at least once weekly
- 2) Pain is intermittent
- 3) Pain is not relieved by defecation or flatus
- 4) Pain not generalized/localized to other abdominal regions or chest
- 5) Pain symptoms do not meet diagnostic criteria for gallbladder or sphincter of oddi dysfunction

Supportive criteria:

- a) No retrosternal burning component
- b) Pain induced or relieved by meals
- c) May coexist with PDS

*Criteria fulfilled for the past three months with symptom onset ≥ 6 months prior to diagnosis. Adapted from Tack et al.⁵

motility.¹⁰ Mosapride has also been shown to shorten gastric emptying time in healthy volunteers,¹¹ diabetics¹² and patients with chronic gastrointestinal disorders.¹³ These latter findings led researchers to hypothesize that mosapride might be efficacious for treating functional dyspepsia.

The number of studies evaluating mosapride as a treatment for FD is limited. Three electronic databases (Medline, PubMed, OVID) were searched from 1966 to October 2009 to identify potentially relevant articles. The literature search was performed independently by the two primary investigators (E.L.T. and D.M.B.). Only fully-published English manuscripts were included in this review (Table 3).

Mosapride vs. Other Therapeutic Agents

Three studies comparing mosapride to other agents commonly used to treat FD were identified. The first, published by Seno et al¹⁴ in 2005, compared the efficacy 15 mg of mosapride to 40 mg of the H₂RA famotidine and 30 mg of the anxiolytic tando-spironone. Sixty-four patients meeting Rome II criteria for FD were randomly assigned to receive one of the three therapies daily for eight weeks. Symptomatic improvements were assessed at weeks two, four, and eight via a 4-point visual analog scale (VAS). Significant improvements were identified in the mosapride and famotidine groups at weeks two, four, and eight compared to baseline for both interventions ($P < 0.01$). No symptom improvements were

witnessed in the tando-spironone group at any time-point. At two weeks, famotidine proved significantly more effective than mosapride and/or tando-spironone in head-to-head comparisons (change in VAS scores: 1.26 \pm 0.17, 0.86 \pm 0.17, 0.40 \pm 0.16 respectively; $P < 0.05$). Adverse events and tolerability were not reported.

In a subsequent study, Otaka et al¹⁵ randomly enrolled 81 FD patients meeting modified Rome II criteria to receive 20 mg of famotidine or 15 mg of mosapride for four weeks. Treatment efficacy was defined as an improvement from baseline of three or more points on a 10-point VAS. At four-weeks similar symptom improvements were recognized between groups (65.0% famotidine vs. 58.5% mosapride, not significant (NS)). No severe adverse reactions were observed; however, overall adverse events and tolerability were not reported.

In the final published head-to-head comparison,¹⁶ 79 subjects were randomly assigned to receive 5 mg of mosapride three times daily (TID), 20 mg of famotidine twice a day (BID), or 10 mg of tando-spironone TID for four weeks. Prior to trial onset, patients meeting Rome II criteria for FD underwent stratified randomization based on three FD sub-classifications: dysmotility-like FD, ulcer-like FD, and non-specific FD. The primary endpoint, symptom severity, was measured via a 100 mm VAS with a severity score of less than 5 mm at any point during the trial representing symptom resolution. Famotidine was found to resolve dyspeptic symptoms more effectively

**Table 3.** Comparison of trials assessing the utility of mosapride in the treatment of functional dyspepsia.

Study	Year	N	F:M	Mean age (years)	Intervention	Inclusion criteria
Seno et al ¹⁴	2005	64	12:9 13:10 9:9	63 61 62	– Mosapride 15 mg/day – Famotidine 40 mg/day – Tansospirone 30 mg/day	– Patients meet Rome II criteria for FD
Otaka et al ¹⁵	2005	81	22:18 26:15	72 71	– Famotidine 20 mg/day – Mosapride 15 mg/day	– Complaints of upper abd symptoms persisting for more than 4 weeks; modified Rome II criteria
Kinoshita et al ¹⁶	2005	79	17:8 20:7 13:14	56 52 51	– Mosapride 15 mg/day – Famotidine 40 mg/day – Tansospirone 30 mg/day	– Meet Rome II criteria for FD
Hallerbäck et al ¹⁷	2002	566	97:44 84:56 94:49 87:55	<25 (8%) 25–50 (51%) >50 (41%)	– Placebo – Mosapride 10 mg/day – Mosapride 20 mg/day – Mosapride 22.5 mg/day	– Primary care patients – 18–75 years old – History of 3+ months of persistent or recurrent symptoms of upper abdominal pain &/or discomfort centered in the upper abdomen

(15/27 patients) than mosapride (9/25 patients) and tansospirone (4/27 patients) (*P* values not reported). Dyspeptic subtypes did not influence therapeutic effect. No significant side effects were reported and tolerability was not measured.

In aggregate, the data from these three studies suggest that the anxiolytic, tansospirone, is unlikely to improve symptoms of functional dyspepsia. Some benefit might be accrued from mosapride or famotidine, with two studies reporting increased efficacy for famotidine in head-to-head comparisons. However, all three trials suffered from multiple design flaws including short trial duration, a lack of power calculations and placebo groups, and inadequate blinding. Furthermore, given differences in trial

design, outcome assessments and statistical analyses, it is difficult to make comparisons across studies. Further trials are necessary before true comparative evaluations can be made.

Randomized Placebo-Controlled Trials

Only one double-blinded placebo-controlled trial has been published.¹⁷ In this well-designed 2002 multinational study, 566 FD patients, defined by the presence of pain or discomfort centered in the upper abdomen for the previous three months, were randomly assigned to consume placebo, 10 mg (5 mg BID), 20 mg (10 mg BID), or 22.5 mg (7.5 mg TID) of mosapride for six weeks. The primary endpoint was a change, from baseline, in overall dyspeptic symptoms



Exclusion criteria	Primary outcome Measure	Summarized results	Adverse events/ tolerability
<ul style="list-style-type: none"> – High likelihood of alternative diagnoses – Prior upper abdominal surgery – Tx with a PPI &/or antibiotic within 1 month of screening – Treatment within the previous week with another drug that might interfere with study outcome – Risks for poor study compliance – Any organic disorder – Depression 	Improvement in symptoms via 4 cm VAS	– “Some” symptom improvement in 66.6%, and 87.0% of patients receiving mosapride and famotidine respectively @ 2, 4, 8 weeks ($P < 0.01$ compared to baseline).	No SAEs AEs and tolerability NR
<ul style="list-style-type: none"> – Evidence of organic disease 	Improvement in symptom score (≥ 3 points) on 10 point VAS @ 4 weeks	– 65.0% efficacy in famotidine group vs. 58.5% in mosapride group (NS)	No SAEs AEs and tolerability NR
<ul style="list-style-type: none"> – High likelihood of alternative diagnosis – Previous abdominal surgery (other than appendectomy or gynecologic surgery) – Drug/alcohol abuse – Pregnancy/lactation – Need for interpreter 	Symptom resolution (< 5 mm on a 100 mm VAS) @ any time-point during 4 week trial	– 36% mosapride, 56% famotidine, 15% tansospirone symptomatic resolution at any time within the 4 week study (no P values reported)	No SAEs or AEs Tolerability NR
<ul style="list-style-type: none"> – High likelihood of alternative diagnosis – Previous abdominal surgery (other than appendectomy or gynecologic surgery) – Drug/alcohol abuse – Pregnancy/lactation – Need for interpreter 	Improvement in overall dyspeptic symptom score using a 7-point Likert scale @ 6 weeks	– No significant differences between mosapride and placebo for any comparisons	Most common AEs: diarrhea, abdominal pain, headache, nausea; these events were experienced similarly in all 4 study groups. Tolerability NR

Abbreviations: PPI, Proton-pump inhibitor; VAS, visual analog scale; FD, functional dyspepsia; IBS, irritable bowel syndrome; (S)AE, severe adverse events; NR, not reported; NS, not significant.

measured on a seven point Likert scale. Secondary endpoints included upper abdominal pain, bloating, post-prandial fullness, early satiety, belching, nausea, vomiting and a subjective global assessment of symptom improvement assessed by a dichotomous yes/no response. At six weeks, no significant differences were identified between the placebo and mosapride groups (mean change in symptom severity score: -0.90 in the placebo group, -0.94 in the 10 mg/day group, -0.88 in the 20 mg/day group, and -0.89 in the 22.5 mg/day group) for the primary endpoint. Furthermore, no differences were detected for any of the secondary endpoints, and approximately 60% of the subjects in each study arm reported global improvement. Sixty percent of patients in the placebo

group, 59% in the 10 mg/day, 59% in the 20 mg/day, and 61% in the 22.5 mg/day mosapride groups felt subjectively better at the end of treatment. The most common adverse events—diarrhea, abdominal pain, headache, and nausea were experienced equally by all four study populations.

Ongoing Investigation

A trial comparing 15 mg/day of mosapride to 60 mg/day of lansoprazole was recently completed in Taiwan.¹⁸ Subjects meeting Rome III criteria were randomized for two weeks of treatment. Improvement in dyspeptic symptom as assessed by a validated questionnaire was the principle outcome measure. The results of this study are currently pending analysis and peer review.



Discussion

Functional Dyspepsia is a common disorder, yet effective treatments are limited. Methodological flaws in individual study designs and significant heterogeneity between trials has hindered the extrapolation of trial outcomes to the clinical setting. Much of the criticism surrounding previous dyspepsia studies rests on variability in enrollment criteria, lack of standardized definitions of dyspepsia, and the inclusion of participants with overlapping upper gastrointestinal disorders (e.g. gastro-esophageal reflux).

Despite these limitations, recent Cochrane systematic reviews have identified small but significant benefits for H₂RAs, proton pump inhibitors and *Helicobacter pylori* (*H. pylori*) eradication.^{19,20} The benefits of pro-kinetic agents have also been evaluated in recent meta-analyses. Moayyedi et al identified fourteen studies comparing pro-kinetics to placebo in 1,053 subjects with non-ulcer dyspepsia. Compared to placebo, significant symptom reductions were identified; however, there was notable heterogeneity between studies and funnel plotting asymmetry yielded evidence of publication bias. Larger studies revealed no benefits for pro-kinetics—suggesting that the findings were likely attributable to small study effects.²¹ A subsequent investigation from Japan analyzed twenty-seven studies with 1,844 and 1,591 patients receiving pro-kinetics or placebo respectively. Pooled analysis yielded a 30% increased probability of symptomatic response in the cohort receiving pro-kinetic agents.²² The difference in outcomes in the latter study was attributed to broader inclusion of non-English studies and a wider range of pro-kinetic agents. Both authors concluded that longer randomized controlled trials are necessary.

Of the pro-kinetic agents, 5-HT agonists have been the most widely studied. In aggregate, these therapeutics directly augment gastrointestinal peristalsis via interactions with various 5-HT receptors and indirectly effect motilin secretion. Cisapride, the most commonly utilized of the agents, has been analyzed in the majority of placebo-controlled trials including 13/14 and 20/27 of the trials in the aforementioned meta-analyses respectively. Additional studies have also compared its efficacy to anti-secretory agents with conflicting results. Quarero and colleagues randomized 563 primary care patients to cisapride or ranitidine in a double-blinded trial. Response rates at

four weeks were equivalent, but relapse rates 3 months after trial completion were lower in initial responders to cisapride.²³ In the CADET-HN study, the efficacy of cisapride was compared to ranitidine, omeprazole and placebo in 512 *H. pylori* negative patients with FD. At 4 weeks, lower symptomatic responses were identified in the cisapride group compared to omeprazole, and no significant differences between cisapride and ranitidine were identified.²⁴ A recent meta-analysis comparing serotonin agonists to other pro-motility agents yielded no differences in response rates between groups.²⁵

More recently, tegaserod, a selective 5-HT₄-receptor partial agonist has been evaluated for the treatment of dysmotility-like functional dyspepsia. In two identical multicenter double-blind, randomized, placebo-controlled trials, Vakil and colleagues enrolled 2,667 women to 6 mg of tegaserod or placebo BID for six weeks. Interestingly, the first yielded significant improvements in multiple patient reported outcomes (PROs), which were not replicated in the second trial. In meta-analysis, significant overall improvements in PROs were identified and post-hoc analyses revealed that the positive effects of this therapy might be relegated to patients with severe baseline symptoms.²⁶ Chey et al subsequently assessed the long-term safety and efficacy (the secondary endpoint) of tegaserod for 1 year. Subjects from the previous studies were invited to participate in two open-labeled continuation trials. Seven-hundred eighty of the patients who completed the initial trials enrolled. All received 6 mg BID of Tegaserod. At one year, only 279 respondents remained. Despite this limitation, the remaining participants experienced multiple PRO symptom-based improvements.²⁷

Some of the heterogeneity in these study outcomes is likely attributable to the functional variability of individual serotonin agonists. Cisapride not only stimulates 5-HT₁₋₄ receptors, but also acts as a potent antagonist of both 5-HT₃ and human ether-a-go-go-related gene (HERG) K⁺ channels. The latter effects are presumed responsible for its arrhythmogenic potential and subsequent withdrawal from many markets, including the United States. Tegaserod also has affinity for 5-HT receptors, but with higher selectivity. It functions primarily as a potent stimulator of 5-HT₄ receptors of the enteric nervous system in the gastrointestinal tract, but it also interacts with 5-HT₁



and 5-HT_{2b} receptors.²⁸ Tegaserod, like cisapride, has been linked to increased cardiovascular (CV) toxicity. In March, 2007, the sale of tegaserod was suspended in the United States and many other countries when retrospective analyses of clinical trials revealed a small but significantly increased risk of CV ischemic events. Consequently, the continued search for safe and effective serotonergic agents has been ongoing.

Mosapride, while biologically related to cisapride and tegaserod, has little effect on HERG K⁺ channels, and its effect on 5-HT receptors is predominantly limited to the 5-HT₄ receptor subtype. It has no affinity for the 5-HT₁ or 5-HT₂ receptors.²⁹ Thus, mosapride has been purported to have similar prokinetic properties with limited CV effects. No CV events were identified in the trials included in this review, but reporting of adverse events was limited. On the basis of these studies, mosapride has been approved for the treatment of FD in Southeast Asia and South America, but it is not available in the United States. Furthermore, close inspection of current data yields inconclusive results, and the findings of previously reported studies must be interpreted with caution due to methodological limitations in study design. On the basis of the currently published data, we would argue that at best, mosapride is no more efficacious than H₂RAs. Our conclusions are similar to previously reported analyses.²⁹ Furthermore, the most methodologically rigorous study to date revealed no benefits compared to placebo. Further trials are necessary.

It has been argued that the effectiveness of therapeutics for FD may also be limited to specific subclasses of FD patients, and alternative outcomes might be identified if pharmacological investigations are limited to pre-specified symptom subgroups.³⁰ Dyspeptic patients present with a plethora of complaints including epigastric pain or burning, nausea, vomiting, bloating, belching, and early satiety. Therefore, the term FD may represent a conglomerate of distinct subgroups of varying pathophysiologies requiring alternative management strategies. A recent study validates this concept. Choung et al performed a population-based study attempting to determine whether three distinct subclasses of FD—frequent upper abdominal pain, early satiety, and nausea/vomiting exist. Their cross-sectional survey revealed that these three subgroups could be differentiated, and overlap between the groups was significantly less

than expected by chance.⁶ Furthermore, the tegaserod trials^{26,27} suggested potential benefits for treating dysmotility-like FD using agonists of 5-HT₄ receptors and further illustrate the concept that separate treatments might be necessary for individual symptoms or symptom combinations. The recent alterations to the Rome criteria may help elucidate these findings.

Summary

Functional dyspepsia is a complex, heterogeneous disorder, and effective treatments are lacking. Prokinetics have shown some benefit for alleviating symptoms, but the data are inconclusive. Studies assessing the efficacy of the prokinetic mosapride are limited by methodological shortcomings and at best demonstrate that mosapride is no more so effective than H₂RAs. Given its underlying mechanism of action, it may be beneficial for treating patients with FD—PDS, but no previous trials have evaluated this hypothesis. Future randomized double-blind placebo-controlled trials could target this subset of patients.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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