### **Systematic Review**

# CNS or Classic Drugs for the Treatment of Pain in Functional Dyspepsia? A Systematic Review and Meta-Analysis of the Literature

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Disclaimer: This work was supported by a grant from from National Pancreas Foundation and the Harvard-Thorndike General Clinical Research Center at BIDMC (NCRR) MO1 RR01032 - CREFF/BIDMC) to F.F.; Maria Passos was supported by a grant from National Council for Scientific and Technological Development (CNPq) from Braziloo. Conflict of interest: None.

Manuscript received: 04/09/2008 Revised manuscript received: 05/15/2008 Accepted for publication: 06/16/2008

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**Background:** Recent evidence has suggested that pain in functional dyspepsia (FD) is associated with nervous system dysfunction; indicating that therapies aimed at nervous system modulation might be associated with pain relief in FD

**Objective:** To conduct a systematic review and meta-analysis to quantify the efficacy of drugs targeting the central nervous system (antidepressants and antianxiety agents — referred as "CNS drugs") and drugs targeting gastric modulation (antisecretory and prokinetic — referred as "classic drugs") for the treatment of pain in FD and, in an exploratory way, compare these 2 modalities of treatment.

**Methods:** MEDLINE and reference lists were examined for relevant articles. We included prospective studies that evaluated the effects of either CNS drugs or classic drugs (subdivided in prokinetic and antisecretory drugs) on the symptoms of FD.

**Results:** Seven studies for CNS drugs and 11 studies for gastric drugs met our inclusion criteria. The analyses of these drugs showed that the 2 groups of drugs are associated with a significant reduction in dyspeptic symptoms. The pooled effect size (standardized mean difference between pre-treatment versus post-treatment means) from the random effects model was 1.25 (95% C.I., 0.83, 1.67) for CNS; 1.63 (95% C.I., 1.28, 1.97) for prokinetic, and 0.93 (95% C.I., 0.57, 1.29) for antisecretory drugs. The exploratory comparison between classes of drugs revealed no significant difference in dyspeptic symptoms reduction between CNS and prokinetic drugs; however CNS drugs were associated with a larger reduction in symptoms as compared with antisecretory drugs.

**Conclusions:** The results show that both CNS and classic drugs are associated with a significant pain reduction in functional dyspepsia.

**Key words:** antidepressants, antianxiety, prokinetics, antisecretory agents, brain activity, functional dyspepsia, epigastric pain

Pain Physician 2008; 11:5:597-609

yspepsia, defined as pain or discomfort centered in the upper abdomen (1-3) is extremely common. Epidemiological studies suggest that approximately 15% of the general population in western countries suffers from functional dyspepsia (FD) (4). Although the term dyspepsia is non-specific and is often used to describe different symptoms by different individuals, the common thread among dyspepsia sufferers is that they experience a significant decrease in quality of life. Approximately 50% of all individuals with dyspepsia report some limitations of daily activity, and 33% report having moderate to severe limitations in their ability to function (5). Dyspepsia is one of the most common clinical problems in medical outpatients, and is associated with considerable health and economic burden (6).

The most common cause of dyspepsia is functional dyspepsia (also labeled nonulcer or idiopathic dyspepsia). FD is diagnosed when no structural or biochemical explanation for patients' symptoms is identified after appropriate investigations (7). Several symptom-based criteria for FD have recently been developed to facilitate and standardize the diagnosis of FD. These include the Rome (I, II, and III) criteria. The Rome criteria began in Rome, Italy, in 1988; when an international committee began a process of review and analysis of the medical literature to improve the methodology for the study, diagnosis, and treatment of functional gastrointestinal disorders (FGIDs). Rome II published in 1999, resulted from the continued process of analyzing new scientific and clinical evidence in the study of FGIDs. Rome III, the most recent criteria defined by this international working group, was published in 2006 with symptom-based diagnostic criteria for FGIDs (8,9).

The Rome III committee defined FD as the presence of symptoms from the gastroduodenal region, in the absence of any organic, systemic, or metabolic disease that may explain the symptoms (9). The symptoms are complex and include epigastric pain or burning and/or discomfort. Discomfort comprises a large number of non-painful symptoms including upper abdominal fullness, early satiety, bloating, vomiting, belching, or nausea. Any combination of these symptoms may intermittently occur over time. Predominant symptoms of heartburn suggest gastroesophageal reflux disease and exclude the diagnosis of dyspepsia. Based on recent evidence and clinical experience, a subgroup classification in FD (9) is proposed for 1) postprandial distress syndrome (meal-induced dyspeptic symptoms: early satiation or postprandial fullness) and 2) epigastric pain syndrome (pain or burning in the epigastrium).

The etiology and pathophysiology of FD remains unclear. However, several factors have been proposed, including altered visceral sensitivity and perception, gastrointestinal motor and secretion dysfunction, Helicobacter pylori infection and psychosocial factors (9-13). Delayed gastric emptying and disturbed intestinal motility have also been proposed to be of importance in many cases (7,14). In addition, recent studies have shown altered brain responses in FD, particularly to visceral stimuli, involving activation of several brain regions that are associated with different functions, including sensory, cognitive, and emotional domains (15-17).

The uncertainty in the etiology of FD has actually contributed to the difficulties for the treatment of this disease. Indeed, the results of therapeutic trials in FD are contradictory. Empirical treatment with antisecretory or prokinetics agents for 2 – 4 weeks has frequently been proposed as first line management of these patients (9,18,19); however trials testing these drugs have shown mixed results. Several studies have reported the possible efficacy of antidepressants or antianxiety for FD patients (20-22). Therefore the main question of our study is whether treatments targeting the CNS have the same efficacy as compared to drugs targeting the GI tract. We therefore perform a systematic review of studies that examined the effects of CNS and gastric drugs on symptoms of FD.

#### Methods

## Literature Search

We searched MEDLINE database, limiting our search to (i) English-language articles on humans; (ii) randomized controlled trials from January 1997 to June 2007, and (iii) using the following key words: functional dyspepsia, FD, nonulcer dyspepsia, NUD, antidepressant agent(s), selective serotonin reuptake inhibitor(s), serotonin norepinephrine reuptake inhibitor(s), imipramine, amitriptyline, nortriptyline, fluoxetine, paroxetine, trazodone, venlafaxine, mirtazapine, bupropion, citalopram, desipramine, doxepin, escitalopram, nefazodone, phenelzine, protriptyline, sertraline, antianxiety agent(s), flurazepam, lorazepam, triazolam, clonazepam, chlordiazepoxide, estazolam, diazepam, alprazolam, buspirone, prazepam, cloxazolam, oxazolam, medazepam, bromazepam, fludiazepam, mexazolam, flutazolam, flutoprazepam, loflazepate, clotiazepam, etizolam, tandospirone, hydroxyzine, levosulpiride, prokinetic agents, metoclopramide, domperidone, trimebutine, cisapride, itopride, mosapride, acid suppressive therapy, antisecretory drugs, proton pump inhibitor, PPI, antacids, histamine-2 receptor antagonists, H2RAs, bismuth, sucralfate, cimetidine, famotidine, nizatidine, ranitidine, omeprazole, lansoprazole, pantoprazole, esomeprazole, rabeprazole.

We also examined reference lists of published papers and the Cochrane library (1997 – June 2007), searching the clinical trials registry for randomized trials, and the Cochrane Database of Systematic Reviews for systematic reviews.

#### **Selection Criteria**

We included prospective studies that evaluated the effects of antidepressant or antianxiety agents (CNS drugs); prokinetics and antisecretory agents on pain and abdominal discomfort in FD (in some circumstances, it was not possible to disentangle pain from the general discomfort in dyspepsia; however, we believe that both symptoms - pain and discomfort — are correlated). We adopted the following inclusion criteria: 1) manuscript written in English; 2) Patients with FD (according to the Rome diagnostic criteria); 3) use of CNS or classic drugs (23); 4) randomized, double-blind trials; however, we also analyzed separately open-label studies using antidepressant and antianxiety agents as the number of studies were low in this category (however, open-label studies were analyzed separately); 5) dyspeptic symptoms measured on a continuous clinical scale; 6) the report had to be published in a book, journal, proceeding, or indexed abstraction; and 7) the studies had to report the mean and standard deviation of dyspeptic symptoms before and after the treatment or provide other statistical parameters that could be used to deduce these values. For studies that met our criteria but did not report these scores, the authors were contacted to provide these data if available. However, the contacted authors did not have these data (studies were too old) or they did not reply to our messages. For cases where 2 or more published studies reported overlapping data sets, we chose the study with the largest population. Case reports or series of case reports were excluded. Using these criteria, we identified 9 studies for CNS drugs and 27 studies for classic drugs.

#### **Data Extraction**

The data were collected using a semi-structured form for each study by one of the authors (MP) and checked by another investigator (FF). The discrepancies were resolved by consensus and a third author was consulted if needed (DD). All the following variables were extracted: name of the first author, year of publication, location of the study, study design, pre-treatment characteristics of the population sample (age of participants in the intervention arm and the placebo arm, male-to-female ratio in each arm, number of participants in each arm), treatment dose and duration, side effects, and symptoms that improved after treatment. Data were collected on dyspeptic symptom scores using either individual or global symptom assessments.

For the studies with more than one active group, we considered each group as one study in the quantitative analysis. This approach was used for 7 studies (24-30).

### **Qualitative Analysis**

We did not perform qualitative analysis. There are advantages and disadvantages for performing this analysis. The main advantage is to preclude including studies that would bias the data due to low quality. However there are many disadvantages of such approach as well, such as decreasing the external validity of the results and lack of satisfactory quality information in some studies. When weighing up these factors; we decided not to use qualitative analysis; however, in order to control for bias of including studies of poor quality, we performed a sensitivity analysis. Indeed, sensitivity analysis is critical to assess the robustness of combined estimates using different assumptions and inclusion criteria.

#### **Quantitative Analysis**

All of our analyses were performed using STATA statistical software, version 8.0 (Statacorp, College Station, Texas). For the continuous measures of motor function, we calculated the standardized mean difference (Cohen d) based on the pre- and post-test values of the active treatment within each study — note that the comparison with placebo was not possible as some double-blind studies compared 2 different types of active drugs. We initially conducted a separate analysis to evaluate the CNS and classic drugs; and then, performed an exploratory analysis, comparing the effect sizes of these 2 types of treatment. Finally, we performed an additional analysis evaluating the effects of the open label studies for CNS drugs and the main reason for this additional analysis is that the number of controlled studies for this category is low and therefore more information about this treatment is desirable. We measured the pooled weighted effect size using the random and fixed effects models. The random effect model gives relatively more weight to smaller studies and wider confidence intervals than the fixed effect models and its use has been advocated if there is heterogeneity between studies. Although the test for heterogeneity failed to detect heterogeneity in one analysis, we decided to report both values (from random and fixed effects model). Heterogeneity was evaluated with Q statistic.

As our meta-analysis included small studies and these studies usually have large effect sizes, we performed a sensitivity analysis in which we evaluated the influence of individual studies, computing the meta-analysis estimates and omitting one study at a time. Finally, in order to assess publication bias, we performed Begg modified funnel plot (31), in which the standardized mean difference from each plot was plotted against the standard error.

#### RESULTS

We initially retrieved 92 articles by performing a computer search of the MEDLINE database; but only 18 articles met our inclusion and exclusion criteria. We included information on a total of 2,746 patients (Tables 1 and 2). Fifteen articles were randomized controlled trials and 3 were open-label trials — we only included open trials assessing CNS agents. Seventy-three articles were excluded. The main reasons for exclusion were that the articles were review articles or observational studies, assessed dyspepsia as a side effect only, or included patients with IBS and FD symptoms or patients with organic gastrointestinal diagnosis. Some studies were excluded because they did not show mean and SD before and after the treatment. We asked the authors for these data, but the majority did not have these data or did not reply to our messages.

#### **CNS Drugs**

We identified 4 randomized, double blind controlled trials with antidepressants or antianxiety drugs that involved the use of amitriptyline (32) or levosulpiride (33) or combination therapies were used

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|-------------------------------|--|-----------------|----------------------|--|---|
| Keterence<br>(author, year)   | Study Design                               | (F:M)           | Mean<br>Age          | Agent (dose, duration)   | Improvement of symptoms   |
| Mertz et al.<br>1998 (32)     | Blind, RCT<br>crossover                    | 7 (2:5)         | 43.6                 | Amitriptyline 50mg nocte (4 weeks)<br>x Placebo washout (3 weeks)                  | 71% amitriptyline 28% placebo   |
| Song et al.<br>1998 (33)      | Double-blind,<br>RCT, parallel             | 42 (33:9)       | 40                   | Levolsupiride 25mg tid (3<br>weeks) x Placebo                                      | Levosulpiride group response was higher than placebo  |
| Mansi et al.<br>2000 (24)     | Double-blind,<br>RCT, crossover            | 30<br>(17:13)   | 36                   | Levolsupiride 25mg tid<br>x Cisapride 10mg tid (4 weeks)                           | Response was similar in both groups   |
| Mearin et al.<br>2004 (25)    | Multicenter,<br>RCT, double-blind<br>trial | 140<br>(106:34) | 42                   | Levolsupiride 25mg tid<br>x Cisapride tid 10mg (8 weeks)                           | 79.9% levolsupiride 71.3% cisapride   |
| Distrutti et al.<br>2002 (35) | Open trial                                 | 16 (11:5)       | 21-45<br>(range)     | Levolsupiride 25 mg tid (4 weeks)  | Levosulpiride was effective in reducing<br>early satiety, nausea, pain, and fullness<br>( $P < 0.05$ vs. pre-levosulpiride for all<br>symptoms) |
| Wu et al.<br>2003 (34)        | Open trial                                 | 40<br>(24:16)   | 35.5                 | Fluoxetine 20 mg uid<br>(4 weeks)  | Depressive FD patients had higher<br>symptom scores and responded well to<br>fluoxetine treatment than non-depressed<br>patients                |
| Seno et al.<br>2005 (30)      | Open trial                                 | 62<br>(34:28)   | 63.1<br>61.5<br>62.1 | Mosapride 15 mg uid x<br>Famotidine 20 mg uidx<br>Tandospirone 30 mg uid (8 weeks) | Famotidine was significantly more<br>effective than mosapride or<br>tandospirone ( $P < 0.05$ )   |

 Table 1. Characteristics of studies included in the meta-analysis: CNS drugs

RCT - randomized clinical trial; F-female; M=male

| Reference<br>(author, year)   | Study Design                                   | N (F:M)       | Mean<br>Age | Treatment<br>Agent (dose, duration)  | Improvement of symptoms<br>according to the treatment                                   |
|---|--|---------------|-------------|--|---|
| Holtmann et al.<br>2006 (62)  | RCT, placebo<br>controlled trial               | 548 (348:200) | 47.9        | Itopride 50mg tid<br>Itopride 100mg tid<br>Itpride 200 mg tid<br>placebo (8 weeks) | 57% Itopride 50 mg<br>59% Itopride 100 mg<br>64% Itopride 200 mg<br>41% placebo         |
| Champion et al. 1997<br>(36)  | Double-blind,<br>RCT                           | 123 (85:38)   | 41          | Cisapride 10 mg tid<br>Cisapride 20 mg tid<br>placebo (6 weeks)                    | 38% Cisapride 20 mg<br>47% Cisapride 10 mg<br>33% placebo                               |
| Yeoh et al.<br>1997 (63)  | Double-blind,<br>RCT, placebo-<br>controlled   | 76 (42:34)    | 39.5        | Cisapride 10mg tid<br>placebo<br>(4 weeks)   | 55% Cisapride 10 mg<br>49.5% Placebo  |
| Amarapurkar et al, 2004<br>(26)   | Double-blind,<br>RCT                           | 60 (30:30)    | 42.5        | Itopride 50mg tid<br>Mosapride 5 mg tid (2 weeks)                                  | 93.3% Itopride<br>63.3 % Mosapride  |
| Talley et al.<br>2000 (64)  | Double-blind,<br>RCT<br>placebo-<br>controlled | 569(388:174)  | 46          | ABT-229 (1.25mg, 2.5mg, 5mg,<br>10mg) bid<br>placebo (4 weeks)                     | ABT-229 10 mg<br>was inferior to placebo<br>in relief of dyspeptic symptoms             |
| Holtmann et al.<br>2002 (27)  | RCT, placebo-<br>controlled                    | 178 (94:84)   | 49.5        | Cisapride 10 mg tid<br>simethicone 105 mg tid placebo<br>(8 weeks)                 | Simethicone / cisapride (p values < 0.0001) better than placebo                         |
| Gerson et al.<br>2005 (28)  | Double blind,<br>RCT<br>placebo-<br>controlled | 40 (5:35)     | 54          | Omeprazole 20 mg uid<br>x placebo<br>(4 weeks)                                     | There was no significant<br>change in the abdominal pain<br>scores after treatment.     |
| Lee et al.<br>2006 (29)   | Double<br>blind, RCT<br>Prospective            | 272 (178:94)  | 45<br>47.5  | Ecabet sodium 1.5 g bid<br>cimetidine 400 mg bid<br>(4 weeks)                      | Ecabet has similar clinical efficacy to Cimetidine                                      |
| Miwa et al.<br>2006 (65)  | Double-blind,<br>RCT<br>placebo-<br>controlled | 71 (56:15)    | 48.5        | Remapride 100 mg tid<br>placebo (4 weeks)  | Rebamipide did not produce<br>a significant reduction<br>in the overall symptom scores. |
| Kato et al. Double-blind,<br>2005 (66) RCT<br>placebo-<br>controlled<br>crossover |  | 19 (12:7)     | 43          | Famotidine 20 mg bid<br>placebo (4 weeks)  | Significant improvement in famotidine group was observed ( $p = 0.007$ )                |
| Wong et al.<br>2002 (67)  | Double-blind,<br>RCT<br>placebo-<br>controlled | 453 (335:118) | 42          | Lansoprazole (30 mg uid)<br>Lansoprazol (15 mg uid)<br>placebo<br>(4 weeks)        | 23% Lansoprazole 30 mg<br>23% Lansoprazole 15 mg<br>30% placebo                         |

Table 2: Characteristics of studies and data included in the meta-analysis: Classic drugs.

RCT – randomized clinical trial; F-female; M=male

(24,25). There were 3 open trials; in these 3 studies, investigators used fluoxetine (34), levosulpiride (35) or tandospirone (30).

Four CNS studies met our inclusion criteria. All these 4 studies show a significant difference between the pre vs. post treatment dyspeptic symptoms (Fig. 1). Combining data from these 4 studies, the pooled effect size (standardized mean difference between before and after CNS drugs) from the random effects model was 1.48 (95% C.I., 0.75, 2.22) and from the fixed effects model was 1.25 (95% C.I., 0.83, 1.67) (Fig. 1). The test for heterogeneity showed no significant heterogeneity in this analysis (Chi-square [df = 3] = 6.52; p = 0.09).



Fig. 1. Effect sizes (standardized mean difference in dyspeptic symptoms/pain scores from baseline to immediately after treatment) from the random effects model for trials using antianxiety or antidepressant agents (controlled trials). A positive effect indicates an improvement when comparing before vs. after treatment. Effect sizes are Cohen d (standardized mean difference), error bars represent the 95% confidence interval.

#### **Classic Drugs**

Because the number of studies was significantly higher for the classic drugs, we could analyze separately studies using prokinetics and antisecretory agents. For prokinetic drugs, we found 6 studies. Most of the studies showed a significant effect towards reduction of dyspeptic symptoms after treatment; only one study (corresponding to 2 different doses of Cisapride) reported a non-significant effect — the study of Champion et al (36). Combining data from these 6 studies, the pooled effect size (standardized mean difference between before and after prokinetics drugs) from the random effects model was 1.63 (95% C.I., 1.28, 1.97) and from the fixed effects model was 1.48 (95% C.I., 1.39, 1.57) (Fig. 2). The test for heterogeneity confirmed that there was a significant heterogeneity in this analysis (Chi-square [df = 13] = 189.29; p < 0.001).

For the antisecretory agents, although we only found 5 studies, 4 of these studies showed significant effects towards reduction of dyspeptic symptoms. Combining data from these 5 studies, the pooled effect size (standardized mean difference between before and after antisecretory agents) from the random effects model was 0.93 (95% C.I., 0.57, 1.29) and from the fixed effects model was 1.05 (95% C.I., 0.92, 1.19) (Fig. 3). The test for heterogeneity confirmed that there was a significant heterogeneity in this analysis (Chi-square [df = 5] = 31.34; p < 0.001).



#### **Sensitivity Analysis**

In order to evaluate the influence of individual studies, we computed the meta-analysis estimates; omitting one study at a time. The results showed that the effects would not change if we omitted any of the studies in the 3 main analyses. Confidence interval would be the following according to sensitivity analysis: CNS drugs (95% C.I, 0.4, 2.93); antisecretory drugs (95% C.I., 0.38, 1.40), and prokinetics (95% C.I., 1.17, 2.06).

#### **Publication Bias Assessment**

In order to test for publication bias, we used the funnel plot for visual assessment. The funnel plot is helpful to identify whether the results are biased due to exclusion of unpublished, negative studies, as the exclusion of these studies results in an asymmetrical funnel plot. The plots for the 3 main analyses (anti-secretory, prokinetic, and CNS drugs) show that the distribution of the funnel plot is fairly symmetrical, thus speaking against publication bias. Finally, the *p* value for the Egger test was not significant for any of these analyses (p = 0.16 for CNS drugs; p = 0.36 for antisecretory drugs; and p = 0.16 for prokinetics).



# Exploratory Analysis: Comparison Between CNS and Classic Drugs

In an exploratory manner, we compared the effect sizes of CNS and classic drugs. This analysis revealed that there were no significant differences between prokinetics and CNS drugs (t = -1.14 [df = 16], p = 0.27); however there was a significant difference between antisecretory and CNS agents (t = 3.18 [df = 8]; p = 0.01).

# Exploratory Analysis of Open Studies of CNS Drugs

In order to increase the information on CNS

drugs, we performed an additional analysis in which we included the open label studies of CNS drugs. We were able to identify 3 additional studies. We combined the data from these 3 studies with the other 4 randomized studies and calculated the pooled effect size. This analysis disclosed a slightly higher effect size (as compared with controlled studies only) of 1.96 (95% CI, 0.82, 3.11) from the random effects model and 1.11 (95% C.I., 0.86, 1.36) from the fixed effects model (Fig. 4). The test for heterogeneity confirmed that there was a significant heterogeneity in this analysis (Chi-square [df = 6] = 99.3; p <0.001).



#### Discussion

In this meta-analysis we compared the efficacy of drugs targeting the central nervous system (antidepressants and antianxiety agents) and drugs targeting gastric modulation (antisecretory and prokinetics) for the treatment of pain in functional dyspepsia. The results show that both CNS and classic drugs are associated with a significant change in dyspeptic symptoms. In addition, all these treatments are associated with large effect sizes when comparing before to after treatment. Finally the direct comparison between CNS and classic drugs showed no differences in the reduction of dyspeptic symptoms for the comparison of CNS vs. prokinetic drugs; however there was significant difference for the comparison between CNS and antisecretory drugs. We therefore discuss the implications of our findings.

First, this meta-analysis has some limitations that need to be discussed. An important limitation is the comparison of different classes of drugs (e.g., CNS vs. classic drugs). As aforementioned, this was an exploratory comparison as study populations were different and therefore the results might be a consequence of different individual characteristics. However, we believe that this comparison is meaningful as it generates a research question to be addressed in a head to head randomized clinical trial. Another important limitation is that we needed to study only the group that received active drug as most of the studies were not placebo-controlled, but rather the comparison with another drug. Because treatment of dyspeptic symptoms is associated with a high rate of placebo response rate — from 20% to 60% (37); this might explain the large effect sizes we encountered. It also gives additional support for the involvement of CNS in the pathophysiology of this disorder. Second, the number of studies was relatively small (as most of the studies were not controlled studies or did not have sufficient information for the qualitative analysis); however, most of the studies show similar results — in fact results from the random and fixed effects model were similar.

Second, our results might provide some insights on the role of central mechanisms on visceral pain and therefore generate hypotheses for further studies. The results showing that drugs targeted to CNS and classic drugs are associated with similar effects (or a small advantage for CNS drugs as showed in the comparison of anti-secretory vs. CNS drugs) suggesting that pain in functional dyspepsia might be associated with an overall dysfunction of the CNS (17,38,39), characterized by central and peripheral sensitization (see review (40)). Therefore one possible mechanism of action of these drugs might be due to the de-activation of limbic structures associated with chronic pain (via the use of antidepressants and antianxiety agents) and change in the peripheral sensitization (via the use of classic drugs) (41,42). Indeed, a large neuronal net modulates gut function and reciprocally affects the experience and the regulation of visceral pain. However, it should also be noted that the comparison between classes of drugs used different patient populations; therefore this conjecture should be viewed with caution.

Third, according to our hypothesis, the effects of classic drugs should be discussed. The common classic drugs are proton-pump inhibitors (PPIs), histamine H2-receptor blockers (H2-blockers), mucosal protection agents, prokinetics agents, and Helicobacter pylori eradication therapy (19). Currently, antisecretory or prokinetic agents are recommended as first-line treatment for FD patients with epigastric pain and meal-induced dyspeptic symptom, respectively (18,19). Antisecretory agents are used to reduce gastric acid secretion and prokinetic agents are used to correct disordered gastrointestinal motility. Therefore the effects of these drugs might be associated with a change in the peripherical sensory visceral sensation (normalization of GI transit, fundic relaxation); in other words, prokinetic drugs, for instance, might change the pattern of visceral receptors stimulation and therefore decrease the peripheral sensitization associated with this disorder. Interestingly, we found a small difference between CNS and anti-secretory drugs (favoring the former); indeed, anti-secretory drugs have a smaller effect on visceral pain as compared with prokinetic drugs.

Fourth, antianxiety and antidepressant agents are associated with a significant pain reduction in FD. These drugs are occasionally prescribed for symptoms of FD. The real utility of these drugs in the treatment of FD remains inconclusive, because the number and size of these studies are small. Usually, these agents are indicated in the presence of significant psychiatric symptoms and the objective of this therapy is relief in psychosocial distress as well as dyspeptic symptoms (39,43,44). However, these drugs might be valuable even in the absence of psychiatric symptoms as they can decrease the over-activity in some structures of the limbic system such as insula and cingulate cortex and modulate activity in areas such as prefrontal cortex that can decrease the over vigilance in pain-related neural networks in FD (45). In addition, these drugs have an effect on sleep and psychiatric symptoms that are commonly associated with FD. Moreover, epidemiological studies suggest that symptoms of neurosis, anxiety, and depression are more common in patients with FD (17,19,46-49).

The results of this meta-analysis are in line with previous meta-analyses studying each class of drug separately. For example, Hojo et al (50) conducted a systematic review on the treatment of functional dyspepsia with antianxiety and antidepressant agents and showed that, in 11 of the 13 studies, dyspeptic symptoms were improved significantly by this therapy. However, this meta-analysis performed quantitative analysis for 4 studies only.

Six meta-analyses of prokinetic agents for treatment of FD have been reported (19,51-55). Although initial studies showed a large benefit; more recent large trials did not show such a benefit. Hiyama et al (56) recently published a study of the effects of prokinetic agents in patients with functional dyspepsia. In this meta-analysis, the authors demonstrated a significant treatment benefit in favor of prokinetic agents (metoclopramide, domperidone, trimebutine, cisapride, itopride, and mosapride) in patients with FD. However, the efficacy in terms of symptom relief was assessed over very short periods, ranging from 2 to 6 weeks, whereas FD is a chronic condition often persisting for many years.

Empiric antisecretory agents have been hypothesized to provide symptom relief to the majority of dyspepsia sufferers who present in clinical practice (19,57,58). Previous studies have shown in patients with reflux-like and ulcer-like dyspepsia, the relative risk reduction of dyspepsia was significantly greater in patients receiving antisecretory agents than those treated with placebo. However, no significant difference in the efficacy was observed between protonpump inhibitors and placebo in patients with dismotility-like and unspecified dyspepsia (52,59,60). In a recent meta-analysis, Wang et al (61) showed that proton-pump inhibitors were significantly more effective for controlling dyspeptic symptoms than placebo, especially in patients with ulcer-like and reflux-like dyspepsia. However, the effects of antisecretory agents for the treatment of FD remain to

be determined; indeed, we showed that CNS drugs might be more effective for the treatment of FD symptoms as compared with antisecretory drugs. Additional sudies were included in the meta-anallysis (62-67).

#### CONCLUSION

Although the number of studies included in this meta-analysis is small; the results from our study suggest that CNS drugs might be as effective as classic therapies (prokinetics and antisecretory drugs) for the treatment of FD; therefore sheding light on the pathophysiology of this condition. However, further larger, appropriately designed clinical trials with headto-head comparisons (between CNS and classic drugs) as well as the investigation of new approaches such as combination therapy of antianxiety or antidepressant agents with antisecretory or prokinetic agents are warranted.

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