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Article:

Cheong, PK, Ford, AC orcid.org/0000-0001-6371-4359, Cheung, CKY et al. (5 more authors) (2018) Low-dose imipramine for refractory functional dyspepsia: a randomised, double-blind, placebo-controlled trial. *The Lancet Gastroenterology and Hepatology*, 3 (12). pp. 837-844. ISSN 2468-1253

[https://doi.org/10.1016/S2468-1253\(18\)30303-0](https://doi.org/10.1016/S2468-1253(18)30303-0)

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Accepted for publication 4th September 2018

Title: A Randomised, Double-blind, Placebo-controlled Trial of Low-dose Imipramine for the Treatment of Refractory Functional Dyspepsia.

Short running head: Imipramine for Refractory Functional Dyspepsia.

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Abbreviations: FD functional dyspepsia
GI gastrointestinal
HADS hospital anxiety and depression scale

H. pylori Helicobacter pylori

IBS	irritable bowel syndrome
ITT	intention-to-treat
PP	per-protocol
PPI	proton pump inhibitor
RCT	randomised controlled trial
SSRI	selective serotonin re-uptake inhibitor
TCA	tricyclic antidepressant

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Keywords: functional dyspepsia
refractory
functional gastrointestinal disorder
antidepressant

Word count: 4379

SUMMARY

Background: Guidelines recommend the use of neuromodulators in patients with functional dyspepsia (FD) not responding to proton pump inhibitors (PPIs) and prokinetics. However, there are a lack of data from randomised controlled trials (RCTs) supporting their use.

Methods: In this single centre RCT, we enrolled consecutive *Helicobacter pylori*-negative patients with FD (Rome II) aged 18-80 years, with a normal upper gastrointestinal endoscopy and abdominal ultrasound. All patients remained symptomatic after open-label treatment with 8 weeks of esomeprazole and 4 weeks of domperidone. Eligible patients completed questionnaires assessing dyspepsia symptoms, mood, and sleep, and were then randomised 1:1 to receive 12 weeks treatment with imipramine, or placebo, commencing at a dose of 25mg nocte for the first 2 weeks, and then 50mg nocte thereafter. Randomisation was via a computer-generated list of random numbers, and an independent staff member assigned treatments according to consecutive numbers, kept in sealed envelopes. Double-blinding was achieved by repackaging imipramine and placebo as identical-appearing 25mg tablets in sealed bottles. Follow-up visits were arranged at weeks 6 and 12 for evaluation of symptoms, mood, adverse events, and compliance. The primary endpoint at 12 weeks was overall satisfactory relief of global dyspepsia symptoms, via patient-reported assessment. Analysis was performed on an intention-to-treat basis, consisting of all randomised patients. This trial is registered with clinicaltrials.gov, number NCT00164775, and is completed.

Findings: Between 11th September 2005 and 20th August 2010, we recruited 107 patients with refractory FD (85 (79.4%) females, mean age 46 years), 55 to imipramine and 52 to placebo. There

was a higher rate of overall satisfactory relief of global dyspepsia symptoms at 12 weeks with imipramine (35 (63.6%) of 55), compared with placebo (19 (36.5%) of 52) ($P = 0.0051$). In total, 10 (18.2%) patients who received imipramine discontinued the study due to adverse events (three dry mouth, two constipation, two drowsiness, and one each insomnia, palpitations, and blurred vision), compared with four (7.7%) who received placebo (one dry mouth and constipation, and one each palpitations, worsening of gastro-oesophageal reflux, and limb paraesthesia) ($P = 0.19$). There were no serious adverse events.

Interpretation: Low dose imipramine is an effective treatment for patients with FD who do not respond to PPI and prokinetics.

Funding: None.

RESEARCH IN CONTEXT

Evidence before this study

Treatment options for functional dyspepsia (FD) are limited, but include eradication of *Helicobacter pylori*, proton pump inhibitors (PPIs), and prokinetics. However, many patients do not experience symptom-relief with these therapies. As a result, the management of FD remains challenging.

Although most management guidelines recommend tricyclic antidepressants (TCAs) as second-line therapy for refractory FD, evidence for their efficacy is limited.

Added value of this study

To our knowledge, this is the first randomised controlled trial to assess the efficacy of a TCA for patients with FD refractory to both PPIs and prokinetics. We found that low-dose imipramine was more effective than placebo for the treatment of patients with refractory FD. However, withdrawal due to adverse events was significantly more common in the imipramine group.

Implications of all the available evidence

Low dose TCAs should be considered as a possible therapy for patients with FD refractory to both PPIs and prokinetics, although patients should be cautioned about the adverse event profile.

INTRODUCTION

The prevalence of dyspepsia in the general population has been estimated to be 20% to 40%¹, and approximately 65% of individuals in the community with dyspepsia remain symptomatic over a 10-year follow-up period². Most people with dyspepsia have no identifiable cause by standard diagnostic tests such as upper gastrointestinal (GI) endoscopy³, and these individuals are classified as having functional dyspepsia (FD). This is one of the commonest functional GI disorders, and is defined by the recent Rome IV criteria as burning or pain in the epigastrium, early satiety, or post-prandial fullness, in the absence of an organic, systemic, or metabolic explanation for the symptoms⁴. The prevalence of FD using this definition is between 8% and 12% according to a recent survey⁵. FD is a clinical problem of considerable magnitude for the health care system due to its high prevalence, the chronic relapsing nature of symptoms, and the lack of effective treatments⁶.

FD reduces patients' quality of life and imposes a substantial economic burden⁷, partly because efficacy of available treatments is far from satisfactory. Large, rigorous studies have shown that proton pump inhibitors (PPIs) have only a modest therapeutic gain over placebo⁸, with an updated Cochrane review reporting a number needed to treat of 11⁹. Previously, this benefit appeared to be confined to those patients with ulcer-like and reflux-like dyspepsia, with no advantage of PPI treatment over placebo in patients with dysmotility-like dyspepsia¹⁰. However, the updated Cochrane review suggested that there was a trend towards a benefit of PPIs in those with post-prandial distress syndrome, but no benefit in those with epigastric pain syndrome⁹. Although a previous Cochrane review suggested that prokinetic agents were also more effective than placebo¹¹,

the majority of trials were of low quality, and there was significant heterogeneity between studies.

In addition, most trials used drugs such as cisapride or domperidone, which have either been withdrawn, or their use restricted, due to safety concerns. Furthermore, any correlation between symptom improvement and enhanced gastric emptying with prokinetic drugs is lacking¹².

Tricyclic antidepressants (TCA) are another important class of drug that is commonly used as an off-label treatment in various functional GI disorders, such as irritable bowel syndrome (IBS)¹³, as well as chronic pain disorders¹⁴. The effectiveness of TCAs in functional GI disorders has been supported by a recent Rome Foundation working team report, which summarised their efficacy across all of these disorders of gut-brain interaction¹⁵. The mechanism of action of TCAs in the treatment of functional GI disorders remains poorly understood, but the therapeutic effect is evident even at low doses, suggesting that it is independent of their effects on mood. Neither does it seem to be related to alterations in perception of gastric distension, or to measures of arousal from sleep¹⁶. They may exert their beneficial effects via release of neurotransmitters that lead to changes in visceral hypersensitivity, neuroplasticity, and pain modulation^{15,17}. Previous functional magnetic resonance imaging studies suggest that TCAs are likely to work in the central nervous system, rather than peripherally to alleviate pain and other symptoms exacerbated by stress in functional GI disorders¹⁸. Some studies showed superiority of TCAs over placebo in FD^{19,20}. However, the consistency of this effect remains uncertain.

Despite this, TCAs have been recommended as a second-line treatment for patients with FD who do not respond to PPIs or prokinetics in several management guidelines^{6,21,22}. However, there

are a lack of data supporting their efficacy in this particular group of treatment-refractory patients.

To date, adequately powered clinical trials of TCAs in the treatment of refractory FD, using

well-defined clinical endpoints, are lacking. There has been only one large randomised controlled

trial (RCT) of amitriptyline in patients with FD, conducted in North America, which recruited 292

patients, and demonstrated a borderline significant benefit of amitriptyline over both escitalopram

and placebo.²³ However, the results of this trial cannot necessarily be extrapolated to other TCAs,

or other geographical regions. The aim of this RCT was to evaluate whether 12 weeks of therapy

with low dose imipramine, a TCA, was more efficacious than placebo in the treatment of Chinese

patients with FD who were refractory to PPIs and prokinetic agents.

METHODS

Study design and participants

Consecutive patients aged 18-80 years, and who met the Rome II diagnostic criteria of FD,²⁴ were invited to undergo upper GI endoscopy and abdominal ultrasound in order to rule out organic pathology. During endoscopy, biopsy specimens were obtained from both the antrum and body of the stomach for a rapid urease test, and for histologic examination for *Helicobacter pylori* (*H. pylori*) infection. Patients with prior *H. pylori* infection in whom eradication therapy had been successful, but who had no response in terms of their symptoms of dyspepsia, were also considered eligible for recruitment.

Patients were required to have at least moderate FD symptoms on a rating scale of global dyspepsia symptoms (0-nil; 1-mild; 2-moderate; 3-severe), as reported by the patient, after at least 8 weeks of open-label therapy with esomeprazole 20mg once daily, followed by at least 4 weeks of open-label therapy with domperidone 10mg thrice daily. Exclusion criteria included presence of organic pathology detected at upper GI endoscopy, alarm symptoms such as anaemia or GI bleeding, symptoms suggestive of an eating disorder or gastroparesis, including recurrent vomiting or unexplained weight loss of >10% of body weight in the last 3 months, predominant symptoms of gastro-oesophageal reflux disease or IBS, untreated glaucoma, benign prostatic hypertrophy, concomitant use of non-steroidal anti-inflammatory drugs, neuroleptics, or antidepressants, major GI surgery, pregnancy, or any patient with a known history of hypersensitivity or contraindications

to TCAs. Electrocardiogram was performed in all patients to exclude cardiac arrhythmias. The use of PPIs, histamine-2 receptor antagonists, or prokinetic agents was prohibited during the 12 weeks of the study.

The study protocol received ethical approval on 7th June 2005, from the Joint Chinese University of Hong Kong New Territories East Cluster Clinical Research Ethics Committee, and was conducted from 11th September 2005 to 20th August 2010 at the gastroenterology specialty clinic of Prince of Wales Hospital in Hong Kong. The study was conducted in accordance with the principles of good clinical practice and the declaration of Helsinki. All patients provided written informed consent.

Randomisation and masking

Eligible patients had a 2-week run-in and baseline assessment period prior to randomisation. Patients were then assigned at random, 1:1, to receive either imipramine or placebo. Randomisation was carried out with the use of a computer-generated list of random numbers. An independent staff member assigned the treatments according to consecutive numbers, which were kept in sealed envelopes. Double-blinding was achieved by repackaging imipramine and placebo as identical-appearing 25mg tablets in a sealed bottle, provided by the School of Pharmacy at the Chinese University of Hong Kong, according to international good manufacturing practice guidelines for pharmaceuticals. All investigators were blinded to treatment allocation. An independent statistician performed the data analysis. Patients were provided with an emergency

telephone number for advice regarding adverse events between scheduled visits. In the case of a suspected serious adverse event considered to be treatment-related, patients were advised to attend the emergency department at the Prince of Wales Hospital. The study information, patient study number, and contact number of the principal investigator had been entered into each patients' electronic record. The principal investigator could therefore be contacted, if required, to break the randomisation code. The reasons for any break in the codes had to be documented in the patient's electronic record.

Procedures

Patients were randomised to receive 12 weeks of either imipramine 50mg, or a placebo that was identical in appearance, nocte. To minimise side effects, patients who were randomised to the imipramine arm received imipramine 25mg nocte for the first 2 weeks. All enrolled subjects in both study arms were therefore instructed to take one tablet of study drug for the first 2 weeks of the study, and to take two tablets thereafter.

After randomisation, all patients received baseline assessments including an 8-item dyspepsia symptom score questionnaire assessing epigastric pain, epigastric burning, postprandial fullness, early satiety, belching, bloating, nausea, and vomiting on a scale of 0-3 (0-absent; 1-mild; 2-moderate; and 3-severe, interfering with daily activities)²⁵ over the last 7 days, and co-existent IBS, as defined by the Rome II criteria²⁶. Concomitant insomnia was assessed by asking patients if they had insomnia on ≥ 1 day per week, and mood was assessed via the hospital anxiety and

depression scale (HADS)²⁷. Scores for each subscale (anxiety and depression) range from 0 to 21, with scores categorised as follows: normal 0–7, mild 8–10, moderate 11–14, and severe 15–21.

There was a telephone call at 2 weeks to assess for treatment-related adverse events. The patients returned at weeks 6 and 12, for monitoring of dyspepsia symptoms, insomnia, mood, adverse events, and drug adherence. The latter was assessed via pill counts. There was a final post-treatment visit at week 16. A direct telephone line was provided for patients to use to report adverse events that occurred between the scheduled visits to the study physicians.

Outcomes

The primary endpoint was overall satisfactory relief of dyspepsia at week 12, and was patient-reported (yes/no) via the question “Did you experience overall satisfactory relief of dyspepsia symptoms with the current treatment?” by global symptom assessment. Secondary endpoints included effect on total and individual dyspepsia symptom scores, using the 8-item dyspepsia symptom score questionnaire, sleep, and mood, as well as adherence and adverse events.

Statistical analysis

Our power calculation was based on the assumption that 30% of patients receiving placebo would experience treatment success. Owing to the high prevalence of anxiety and depressive disorders in patients with FD, we anticipated that the treatment success rate at week 12, defined by overall satisfactory relief of global dyspepsia symptoms, in the imipramine group would be 60%,

compared with 30% in the placebo group. A sample size of 49 patients in each of the two treatment groups was required to detect a 30% difference in the efficacy of the two treatments, with a power of 80% and a 5% level of significance. Assuming 10% of patients would not complete follow-up and/or violate the trial protocol, a total sample size of 110 patients would therefore be required. No interim analysis was performed. The data analysis was carried out exclusively by the data review committee.

We used a Chi-square test to compare the endpoint of overall rates of satisfactory relief of global dyspepsia symptoms between the two groups, or a Fisher's exact test where cell numbers were small, and Wilcoxon signed rank testing to compare total and individual dyspepsia symptom scores and HADS scores, due to the skewed distribution of these data. Analysis was by both intention-to-treat (ITT) and per-protocol (PP). The ITT population included all randomised patients. Missing data were imputed with the use of the last-observation-carried-forward method, whereby missing values were replaced with the last non-missing value, baseline values were not carried forward. However, we also performed a sensitivity analysis without imputation. The PP population included all randomised patients who had taken $\geq 80\%$ of the study drug, with those who did not complete follow-up excluded. We performed *post hoc* subgroup analyses examining the effect of imipramine according to presence of concomitant IBS, anxiety, or depression at baseline, improvement in total HADS scores by ≥ 3 at 12 weeks, and independent predictors of overall satisfactory relief of global dyspepsia symptoms were examined in a multivariate logistic regression model, controlling for all baseline characteristics. All statistical analyses were conducted using

SPSS version 25.0 (SPSS Inc., Chicago, IL, USA), with P values <0.05 considered statistically significant. This study is registered with [clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00164775) (NCT00164775).

Role of the funding source

This study was not funded. The senior author had full access to all of the data and the final responsibility to submit for publication.

RESULTS

Patients

In total, 260 consecutive patients with dyspepsia were screened and underwent upper GI endoscopy. There were 72 individuals who were excluded because of erosive oesophagitis (n = 11), peptic ulcer disease (n = 35), current *H. pylori* infection (n = 10), or other reasons (n = 16). A further 81 patients were not recruited for study randomisation because of symptom resolution (n = 17), complete response to open-label treatment with esomeprazole and/or domperidone (n = 52), or unwillingness to continue treatment (n = 12). Therefore, 107 patients who met eligibility criteria were recruited. The ITT analysis included all 107 patients: 55 were assigned to imipramine 50mg nocte, and 52 received placebo of identical appearance (Figure 1). Patient demographics including age, gender, duration of dyspepsia symptoms, dyspepsia subtype, previous *H. pylori* infection, disturbed sleep on ≥ 1 day per week (Table 1), total and individual dyspepsia symptom scores (Table 2), and HADS scores (Table 3) were balanced between the two treatment arms, although IBS was more prevalent in the imipramine group as compared with the placebo group.

In total, 26 patients withdrew from the study or did not adhere to therapy. There were 14 dropouts due to adverse events detailed below. A further three patients receiving placebo withdrew consent. In addition, five patients in the imipramine group were non-adherent to study medication, compared with four patients in the placebo arm. Therefore, of the 107 patients recruited, 81 (75.7%) completed the 12-week treatment trial and 16-week post-treatment follow-up visit, of whom 40

were assigned to imipramine and 41 allocated to placebo.

Symptom relief

In the ITT analysis, overall satisfactory relief of global dyspepsia symptoms at week 12 was experienced by 35 (63.6%; 95% CI 50.4% to 75.1%) of 55 imipramine patients, compared with 19 (36.5%; 95% CI 24.8% to 50.1%) of 52 placebo patients ($P = 0.0051$) (Figure 2). The number needed to treat with imipramine to prevent one treatment failure was 4. In the PP analysis of 81 patients, 28 (70.0%) of 40 patients assigned to imipramine had overall satisfactory relief of global dyspepsia symptoms, compared with 18 (43.9%) of 41 randomised to placebo ($P = 0.018$) (Figure 2).

Those with concomitant IBS were more likely to respond to imipramine than those without, although this did not reach statistical significance (11 (84.6%) of 13 with concomitant IBS, compared with 24 (57.1%) of 42 without, $P = 0.10$). However, after removal of all individuals with concomitant IBS from the analysis a trend towards a benefit with imipramine over placebo remained (24 (57.1%) of 42 responded with imipramine, vs. 18 (37.5%) of 48 with placebo, $P = 0.062$). Presence of anxiety or depression at baseline had no effect on response to imipramine. In total, 17 (58.6%) of 29 patients with anxiety at baseline responded to imipramine, compared with 18 (69.2%) of 26 without ($P = 0.41$), and nine (60.0%) of 15 with depression responded, compared with 26 (65.0%) of 40 without ($P = 0.73$). Among those with available data assigned to imipramine, 14 had an improvement in HADS score of ≥ 3 at 12 weeks, and 26 did not. Overall, 11 (78.6%) of

14 patients with a decrease in HADS score of ≥ 3 reported overall satisfactory relief, compared with 14 (53.8%) of 26 without ($P = 0.12$). The effect of imipramine on overall satisfactory relief of global dyspepsia symptoms remained significant based on multivariate logistic regression, controlling for all baseline characteristics (odds ratio 3.06; 95% CI 1.24 to 7.58, $P = 0.016$), but there were no other predictors of treatment response.

There were significant reductions in total dyspepsia symptom scores, as well as epigastric pain, bloating, postprandial fullness, early satiety, and vomiting scores, compared with baseline, in patients allocated to imipramine (Table 2). At 16 weeks, total dyspepsia symptom scores, bloating, postprandial fullness, and early satiety scores remained significantly lower. Patients assigned to placebo reported significantly lower belching scores at both 12 and 16-week follow-up, but there were no other significant differences. Results were broadly similar when a sensitivity analysis without imputation was performed (Table 4). There was no significant difference in terms of effect on sleep, with 7 (12.7%) patients receiving imipramine, compared with 11 (21.1%) patients receiving placebo, reporting insomnia on ≥ 1 day per week ($P = 0.24$). With respect to mood, total HADS scores were reduced at 12 weeks ($P = 0.049$), and anxiety scores were also lower ($P = 0.035$) (Table 3). No differences were seen with placebo.

Adverse Events and Adherence

There were more withdrawals due to adverse events among patients receiving imipramine as compared with patients receiving placebo. In total, 10 (18.2%) patients who received imipramine

did not complete the study due to adverse events (three dry mouth, two constipation, two drowsiness, one insomnia, one palpitations, and one blurred vision), compared with four (7.7%) patients who received placebo (one dry mouth and constipation, one palpitations, one worsening of gastro-oesophageal reflux, and one limb paraesthesia) ($P = 0.19$). There were no treatment-related deaths. The proportion of patients taking $<80\%$ of study drug in the imipramine group and placebo group were 9.1% and 7.7 % respectively.

DISCUSSION

This randomised, double-blind, placebo-controlled trial conducted in patients with refractory FD demonstrated that 12 weeks of treatment with imipramine was significantly more effective than placebo. All enrolled patients had inadequate symptom relief after open-label treatment with 8 weeks of esomeprazole and then 4 weeks of domperidone, had at least moderately severe FD symptoms, and completed a 2-week run-in period to reduce the magnitude of the placebo effect. We used a patient-reported global symptom assessment, asking participants whether they had overall satisfactory relief of global dyspepsia symptoms as the primary endpoint, rather than using multiple endpoints, in order to minimise false positive outcomes. In total, 63.6% of patients receiving imipramine had overall satisfactory relief of global dyspepsia symptoms, based on patient-reported assessment during the 12-week treatment period, as compared with 36.5% of patients receiving placebo. In addition, patients receiving imipramine had significantly lower total HAD scores and anxiety scores after 12 weeks of treatment, and we observed a significant difference in the mean change in total dyspepsia symptom scores between baseline and 12 weeks in patients receiving imipramine, but not with placebo. There was no significant effect on sleep detected. Our findings indicate that imipramine is an effective treatment for patients with refractory FD that has not responded to either PPIs or prokinetics.

There are some limitations of our study. Although it demonstrates that patients with FD are more likely to respond to TCAs, no firm conclusions regarding their efficacy according to FD subtype can be made, due to the relatively small scale of the RCT, and the fact that it was designed and conducted prior to the current Rome IV classification system. In addition, we used a

dichotomous endpoint to assess treatment response, which was in accordance with published recommendations for the design of treatment trials in functional GI disorders at the time this study was conducted. This is not validated, and is not a composite endpoint, but it is important to point out that, unlike in IBS, there are no validated, or Food and Drug administration-approved, dichotomous composite endpoints for trials in FD. Similarly, the dyspepsia symptom score we used has not been validated in a Hong Kong Chinese population. Although response to treatment was superior with imipramine, and there was a significant effect on total dyspepsia symptom scores at 12 weeks and 16 weeks, we also demonstrated a significant effect of imipramine on total HADS scores and anxiety scores. It is suggested that treatment outcomes for functional GI disorders may be influenced by psychosocial stressors²⁸⁻³⁰. A previous study demonstrated that anxiety may have an aetiological role in FD, especially in viscerally hypersensitive patients³¹. Gastric hypersensitivity is implicated in the pathogenesis of FD symptoms such as postprandial epigastric pain, belching²⁵, and several psychologic variables including the presence of anxiety, somatisation, and neuroticism^{32,33}. Some neuromodulators, such as TCAs, may therefore have their beneficial effects in FD via a reduction in psychological symptoms³⁴.

Other limitations include the fact that the dropout rate due to adverse events was higher in the imipramine group, which suggests TCAs are not suitable for all patients with refractory FD. This may have led to unblinding of treatment allocation, although we are unable to assess this, as we did not ask patients to guess whether they were assigned to active therapy or placebo. Severity and causality of adverse events was not assessed, but adverse events leading to withdrawal were

recorded, and all adverse events experienced with imipramine were consistent with its side-effect profile, and resolved upon stopping the drug. In addition, the overall dropout rate of 24.3% in the trial was higher than we had anticipated, which reduces the power of the study for the primary endpoint to 66%. Finally, the population under study consisted of patients who were recruited in Hong Kong, and were all Chinese, thereby limiting the generalisability of the results to patients with FD of other ethnicities, and in different clinical settings.

A recent adequately powered study by Talley *et al.* demonstrated a beneficial effect of amitriptyline, another TCA, compared with placebo in patients with FD, although this was of borderline statistical significance²³. The drug appeared to be of greater benefit in those with epigastric pain syndrome, compared with those with postprandial distress syndrome, although in our trial imipramine had significant effects on epigastric pain, early satiety, and postprandial fullness scores. In their large three-arm multi-centre trial, there was no beneficial effect of escitalopram, a selective serotonin re-uptake inhibitor (SSRI). This is in keeping with the results of an RCT conducted in Chinese patients with FD, which used sertraline, another SSRI³⁵. However, our study design has some differences to that of Talley *et al.* Firstly, we enrolled exclusively patients with refractory FD who had at least moderate severity of symptoms after open-label treatment with 8 weeks of esomeprazole and 4 weeks of domperidone, which mirrors recommendations for the place of TCAs in the treatment of FD. Secondly, in our study, we were deliberately inclusive, and recruited patients irrespective of their scores on the HADS questionnaire, because the co-existence of anxiety and depressive disorders amongst patients with FD is known to

be common³⁶. As a result, almost 60% of all recruited patients had a HADS anxiety score ≥ 8 , and approximately one-third a HADS depression score ≥ 8 . Finally, our trial provides support for the borderline significant result seen in the RCT by Talley *et al.*, adding clarity to the existing literature, and reproduces the efficacy of a TCA in another geographical region. When data from all three RCTs of TCAs conducted, up to 2016, were pooled in a recent meta-analysis the number needed to treat was estimated at 6, with no heterogeneity between studies³⁷.

Treatment with TCAs may be effective in patients with FD who have not responded to PPI and prokinetics. Given the significant differences in total HADS and anxiety scores at 12 weeks, it may be that low-dose imipramine also has some of its beneficial effects on global symptoms via an improvement in mood, by alleviating anxiety and depressive symptoms. Certainly, the patients who received imipramine demonstrated a significant difference in mean total HADS and anxiety scores between baseline and 12 weeks, and a higher proportion of those with a decrease in HADS score of ≥ 3 at 12 weeks responded to imipramine, although there were fewer patients contributing to this analysis due to missing data. However, mood at baseline was not a predictor of response to imipramine, either in univariate analysis, or based on multivariate logistic regression.

It is important to point out that, at the doses used in most treatment trials in functional GI disorders, centrally acting neuromodulators have limited effects on mood, but do have effects on visceral hypersensitivity, neuroplasticity, and pain modulation^{15,17}. In addition, the direction of effect on mood cannot be uncovered by the design of this trial. It may be that mood scores improved significantly due to an amelioration of GI symptoms. Our findings further highlight the

complex relationship between mood and dyspeptic symptoms and suggest that, similar to IBS³⁸, behavioural therapy may also have a role in the management of FD³⁹, although RCT data to support this approach are sparse^{40,41}.

Adverse events were noted in both the imipramine and placebo groups, but none were serious. The higher dropout rate in the imipramine arm appeared to be explained by adverse events including dry mouth, constipation, drowsiness, and palpitations during the study treatment period. Such anti-muscarinic side effects were also noted in the trial by Talley *et al.*²³, and are seen with older tertiary amine TCAs, such as imipramine and amitriptyline^{15,17}. Newer, secondary amine TCAs, such as nortriptyline or desipramine, may be better tolerated in this regard, and perhaps future RCTs should use one of these drugs, although a recent small RCT of nortriptyline in Thai patients with FD did not demonstrate any beneficial effects⁴².

In our study, adverse drug effects were the cause of study withdrawal in 13.1% (n = 14) of cases. Among the other 12 patients who dropped out, nine (8.4%) were withdrawn from the study due to non-adherence to study medication, and three (2.8%) withdrew consent without giving a reason. Reported adverse events were quite heterogeneous, and were not confined to the imipramine group, so may partly be explained by cultural stigma. A cultural bias against a diagnosis of psychiatric or functional disorders has been reported in some studies conducted in Chinese populations^{43,44}. Dropout rates may therefore have been exacerbated by the potential stigma attached to treatment with a drug perceived as an antidepressant for a functional disorder.

Overall, low-dose imipramine was more effective than placebo for the treatment of refractory

FD, despite higher rates of adverse events. These may be better tolerated with a longer treatment time, or may subside during therapy, and some may not be drug-related, but could relate to cultural factors. TCAs seem to have a positive impact on patients with FD, with a relatively large therapeutic gain, and an improvement in mood. These findings are important, in terms of providing clinicians with a context in which to recommend using neuromodulators, such as TCAs, to treat FD, and despite potential adverse events, which were outweighed by the benefit, with a number needed to treat of 4. However, TCAs should probably not be recommended as a first-line treatment for FD based on our results. Trials of TCAs against established first-line therapies, such as PPI, would be required before it is known whether they should be used earlier in the management of FD. Further studies to elucidate the role of TCAs in various subtypes of FD, and which address the potential pathophysiological mechanisms by which they exert their beneficial effects are also needed.

In conclusion, low-dose imipramine was more effective than placebo for patients with refractory FD who had not responded to PPIs or prokinetics, with a number needed to treat of 4. Some of their efficacy may be explained via an improvement in mood. Although almost one-in-five patients experienced intolerable adverse events, the beneficial effects outweighed these. TCAs should therefore be considered in all patients with FD who have failed first-line medical therapies, particularly in those with co-existent mood disorder.

ACKNOWLEDGEMENTS

None.

AUTHOR CONTRIBUTIONS

Guarantor of the article: JCYW.

JCYW designed the study. JCYW, FKLC and JJYS recruited and followed up patients. PKC and AC coordinated the study. YC and CKYC were responsible for database cleaning. Data analysis was done by PKC and YC. JYLC was responsible for study monitoring. The manuscript was prepared by JCYW, ACF, and PKC without editorial support.

DECLARATION OF INTERESTS

Justin CY Wu has been paid lecture fees (including service on speakers' bureaus) by AstraZeneca, Takeda, Reckitt Benckiser, and Maharini. Francis KL Chan has served as a consultant to Pfizer, Eisai, Takeda, and Otsuka. He has received research funding from Pfizer and has been paid lecture fees by Pfizer, AstraZeneca, and Takeda. The other authors declared no conflicts of interest.

DATA SHARING STATEMENT

Data collected for this study will not be made available to others.

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Table 1. Baseline Characteristics of the 107 Included Patients.

	Imipramine	Placebo
	(n = 55)	(n = 52)
Age (SD)	46.4 (11.8)	46.0 (10.1)
Sex (%)		
Male	10 (18.2)	12 (23.1)
Female	45 (81.8)	40 (76.9)
Duration of dyspepsia (%)		
<2 years	7 (12.7)	10 (19.2)
2-5 years	17 (30.9)	22 (42.3)
5-10 years	12 (21.8)	9 (17.3)
>10 years	19 (34.5)	11 (21.2)
Subtypes of dyspepsia (%)		
Dysmotility-like	32 (58.2)	29 (55.8)
Ulcer-like	11 (20.0)	9 (17.3)
Unspecified	12 (21.8)	14 (26.9)
Prior <i>H. pylori</i> infection (%)	5 (9.1)	10 (19.2)

Concomitant IBS (%)	13 (23.6)	4 (7.7)
<hr/>		
Prevalence of anxiety (HADS-A \geq8) (%)	29 (52.7)	32 (61.5)
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Prevalence of depression (HADS-D \geq8) (%)	15 (27.3)	19 (36.5)
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Sleep disturbance \geq1 day/week (%)	18 (32.7)	14 (26.9)
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*Chi-square test or unpaired student's t-test

Table 2. Mean Total and Individual Dyspeptic Symptom Scores at Baseline, 12 Weeks, and 16 Weeks Among Patients Assigned to Imipramine or Placebo.

Mean score (SD)	Imipramine					Placebo				
	Baseline	12 weeks	P value*	16 weeks	P value*	Baseline	12 weeks	P value*	16 weeks	P value*
Total score	8.04 (3.61)	6.45 (4.78)	0.0010	6.77 (4.54)	0.011	8.42 (4.30)	7.42 (4.77)	0.11	7.41 (4.46)	0.056
Epigastric pain	1.24 (0.79)	0.96 (0.90)	0.026	1.08 (0.85)	0.15	1.13 (0.82)	0.96 (0.80)	0.13	1.00 (0.78)	0.25
Belching	1.22 (0.92)	1.11 (0.89)	0.20	1.11 (0.93)	0.14	1.48 (0.98)	1.16 (0.95)	0.012	1.22 (0.90)	0.015
Epigastric burning	0.71 (0.83)	0.55 (0.72)	0.082	0.72 (0.86)	1.000	0.65 (0.68)	0.62 (0.70)	0.69	0.63 (0.66)	0.69
Bloating	1.75 (0.87)	1.30 (0.95)	<0.0001	1.40 (0.88)	0.0030	1.75 (0.91)	1.55 (0.90)	0.22	1.61 (0.87)	0.43
Postprandial fullness	1.33 (0.98)	0.94 (0.97)	0.039	1.02 (0.99)	0.023	1.40 (1.00)	1.24 (0.99)	0.12	1.16 (1.05)	0.074
Early satiety	1.15 (0.89)	0.70 (0.97)	0.0040	0.77 (0.91)	0.010	1.12 (0.96)	0.92 (0.89)	0.089	0.98 (0.93)	0.21
Nausea	0.47 (0.72)	0.55 (0.87)	0.59	0.47 (0.78)	0.911	0.63 (0.77)	0.63 (0.89)	0.85	0.55 (0.76)	0.25
Vomiting	0.18 (0.55)	0.34 (0.73)	0.046	0.21 (0.57)	0.71	0.25 (0.62)	0.31 (0.65)	0.46	0.27 (0.67)	0.96

* Compared with baseline, using Wilcoxon signed rank testing

Table 3. Mean Hospital Anxiety and Depression Scale Scores at Baseline and 12 Weeks Among Patients Assigned to Imipramine or Placebo.

	Imipramine			Placebo		
Mean score (SD)	Baseline	12 weeks	P value*	Baseline	12 weeks	P value*
Total HADS score	13.6 (6.70)	11.0 (6.66)	0.049	14.9 (6.56)	15.2 (7.72)	0.83
HADS-A score	8.00 (3.86)	6.45 (3.88)	0.035	8.27 (3.84)	8.63 (4.40)	0.88
HADS-D score	5.62 (3.53)	4.50 (3.26)	0.089	6.62 (3.41)	6.51 (4.26)	0.67

* Compared with baseline, using Wilcoxon signed rank testing

Table 4. Mean Total and Individual Dyspeptic Symptom Scores at Baseline, 12 Weeks, and 16 Weeks Among Patients Assigned to Imipramine or Placebo: Sensitivity Analysis Without Imputation.

Mean score (SD)	Imipramine					Placebo				
	Baseline	12 weeks	P value*	16 weeks	P value*	Baseline	12 weeks	P value*	16 weeks	P value*
Total score	8.04 (3.61)	5.92 (3.761)	0.0030	6.46 (4.30)	0.051	8.42 (4.30)	7.44 (4.82)	0.046	7.49 (4.47)	0.056
Epigastric pain	1.24 (0.79)	0.87 (0.83)	0.047	1.05 (0.79)	0.43	1.13 (0.82)	0.95 (0.81)	0.062	1.00 (0.78)	0.15
Belching	1.22 (0.92)	1.05 (0.86)	0.80	1.08 (0.90)	0.80	1.48 (0.98)	1.10 (0.89)	0.003	1.17 (0.83)	0.0030
Epigastric burning	0.71 (0.83)	0.51 (0.64)	0.041	0.77 (0.84)	1.000	0.65 (0.68)	0.65 (0.70)	1.00	0.66 (0.66)	1.00
Bloating	1.75 (0.87)	1.18 (0.94)	0.0010	1.33 (0.87)	0.012	1.75 (0.91)	1.46 (0.93)	0.062	1.54 (0.90)	0.16
Postprandial fullness	1.33 (0.98)	0.82 (0.89)	0.076	0.95 (0.94)	0.060	1.40 (1.00)	1.29 (0.98)	0.21	1.20 (1.05)	0.12
Early satiety	1.15 (0.89)	0.62 (0.94)	0.0030	0.69 (0.86)	0.0070	1.12 (0.96)	0.95 (0.89)	0.082	1.02 (0.94)	0.20
Nausea	0.47 (0.72)	0.54 (0.85)	0.38	0.44 (0.72)	0.97	0.63 (0.77)	0.71 (0.93)	0.84	0.61 (0.77)	0.23
Vomiting	0.18 (0.55)	0.33 (0.74)	0.014	0.14 (0.49)	0.32	0.25 (0.62)	0.34 (0.66)	0.46	0.29 (0.68)	0.96

* Compared with baseline, using Wilcoxon signed rank testing