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TITLE PAGE

Title: Efficacy of Psychotropic Drugs in Functional Dyspepsia: Systematic Review and Meta-analysis.

Short running head: Psychotropic Drugs in Functional Dyspepsia.

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Abbreviations:

5-HT	5-hydroxytryptamine
CI	confidence interval
FD	functional dyspepsia
GI	gastrointestinal
MeSH	medical subject headings
NNH	number needed to harm

NNT	number needed to treat
PPI	proton pump inhibitor
RCT	randomised controlled trial
RR	relative risk
SNRI	serotonin-norepinephrine re-uptake inhibitor
SSRI	selective serotonin re-uptake inhibitor
TCAD	tricyclic antidepressant

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ABSTRACT

Objective: Functional dyspepsia (FD) is a chronic gastroduodenal disorder. Individuals with FD demonstrate visceral hypersensitivity, abnormal central pain processing, and low mood, but it is unclear whether psychotropic drugs are an effective treatment for the condition. We performed a systematic review and meta-analysis of randomised controlled trials (RCTs).

Design: MEDLINE, EMBASE, EMBASE Classic, PsychINFO, and the Cochrane Controlled Trials Register were searched (up to June 2015) for RCTs recruiting adults with FD comparing psychotropic drugs with placebo. We contacted authors directly to maximise trial eligibility and minimise risk of bias for studies. Dichotomous symptom data were pooled to obtain relative risk (RR) of remaining symptomatic after therapy, with 95% confidence intervals (CI).

Results: The search identified 2795 citations; 13 RCTs (1241 patients) were eligible. Ten trials were low risk of bias. The RR of FD symptoms not improving with psychotropic drugs versus placebo was 0.78 (95% CI 0.68-0.91) (number needed to treat = 6; 95% CI 4-16). However, benefit was limited to antipsychotics and tricyclic antidepressants. When only studies that excluded individuals with co-existent mood disorder were considered, there was no benefit. Total numbers of adverse events and adverse events leading to withdrawal were significantly more common, with a number needed to harm of 21 for both.

Conclusion: Psychotropic drugs may be an effective treatment for FD, but the effect appears to be limited to antipsychotics and tricyclic antidepressants with fewer trials for other agents, meaning that firm conclusions for efficacy cannot be made. More data from high quality RCTs are required to support their use in the treatment of FD.

What is already known about this subject?

Functional dyspepsia (FD) is common and difficult to treat.

Helicobacter pylori eradication therapy and proton pump inhibitors are efficacious treatments for FD, but the benefits are modest.

Estimates of the efficacy of psychotropic drugs in FD have been hampered by a paucity of randomised controlled trials (RCTs), and a failure to report extractable dichotomous data.

What are the new findings?

We identified 13 RCTs, and successfully contacted original investigators to obtain supplementary dichotomous data.

Psychotropic drugs were more effective than placebo for the treatment of FD, with a number needed to treat of 6 (95% confidence interval (CI) 4 to 16).

However, this beneficial effect was limited to antipsychotic drugs, such as sulpiride and levosulpiride, and tricyclic antidepressants (TCADs), such as amitriptyline and imipramine.

Adverse events were more common (number needed to harm 21 (95% CI 9 to 597)).

How might it impact on clinical practice in the near future?

Gastroenterologists should consider the use of some psychotropic drugs in FD, particularly TCADs.

Our findings should stimulate further RCTs in this field.

INTRODUCTION

Functional dyspepsia (FD) is a chronic disorder of the gastroduodenal region of the gastrointestinal (GI) tract. The condition is diagnosed using the Rome III criteria, which include the presence of epigastric pain or burning, early satiety during a normal-sized meal, or postprandial fullness, in the absence of an organic disease at upper GI endoscopy that would explain the symptoms. [1] The prevalence of FD in the community is between 5% and 15% using these criteria, [2, 3] and the disorder follows a relapsing and remitting course. [4-6] Functional dyspepsia has a significant impact on individuals, health services, and society, due to consultations with symptoms, [7] investigations, [8] medications, [9] and sickness-related absences from work. [10] A recent burden of illness study estimated that FD costs the USA $18 billion per year, [11] and in the UK direct costs have been reported as being as high as £500 million, and indirect costs £1 billion, per year. [9]

Effective management of the condition is therefore extremely important. Unfortunately, as the exact cause of FD remains obscure, there is no definitive therapy that is of benefit in all individuals. Patients with FD, as with most other functional GI disorders, exhibit higher levels of anxiety, depression, and other psychological conditions than healthy individuals. [2, 12] However, up to 80% of individuals report meal-induced symptoms, [13] and there is also evidence to suggest that delayed gastric emptying, [14] impaired fundal accommodation, [15] visceral hypersensitivity to painful stimuli, [16, 17] and abnormal central processing of pain, [18] are all implicated in the apparently heterogeneous pathophysiology of FD. In addition, recruitment of inflammatory cells, such as eosinophils, and altered mucosal integrity have also been demonstrated in patients with FD, [19, 20] and these types of changes may be associated with psychological stressors. [21]

Besides their pain modifying properties, [22, 23] and beneficial effects on mood, psychotropic drugs including tricyclic antidepressants (TCADs), selective serotonin re-uptake inhibitors (SSRIs), 5-hydroxytryptamine (5-HT)-$_{1A}$ receptor agonists, such as buspirone, and benzamides, such as levosulpiride, have all been shown to have effects on gastric motor function, which include increased gastric accommodation, enhanced pre-prandial gastric relaxation, and alterations in gastric emptying rate. [24-28] These effects on GI motility stem from their agonism or antagonism of receptors with an affinity for various neurotransmitters, including 5-HT receptors in the case of 5-HT$_{1A}$ agonists and SSRIs, the dopamine D_2 receptor in the case of benzamides, and 5-HT, dopamine D_2, histamine, and acetylcholine receptors in the case of TCADs. As well as being located in the brain, these receptors are located throughout the GI tract. As a result, these drugs have been proposed as potential treatments for FD for many years, although national guidelines for the management of dyspepsia have highlighted that data to support their use are lacking. [29-31]

In recent years, there have been several randomised controlled trials (RCTs) conducted that have assessed the efficacy of psychotropic drugs in FD, but some studies have been small, and the results have been conflicting. [32-34] In addition, physicians may be reluctant to consider using these drugs due to negative perceptions about their side-effect profile. Their role in the management of FD is therefore unclear at the present time. In an attempt to address this uncertainty, we have conducted a systematic review and meta-analysis of RCTs to estimate the efficacy and tolerability of psychotropic drug therapy in patients with FD.

METHODS

Search Strategy and Study Selection

A search of the medical literature was conducted using MEDLINE (1946 to 30th June 2015), EMBASE and EMBASE Classic (1947 to 30th June 2015), PsychINFO (1806 to 30th June 2015), and the Cochrane central register of controlled trials. Randomised controlled trials examining the effect of psychotropic drugs in adult patients (over the age of 16 years) with FD were eligible for inclusion (Box 1). The first period of cross-over RCTs, prior to cross-over to the second treatment, were also eligible for inclusion. The control arms were required to receive placebo.

Duration of therapy had to be at least 7 days. The diagnosis of FD could be based on either a physician's opinion or symptom-based diagnostic criteria, with a negative upper GI endoscopy excluding an organic cause of dyspepsia. Subjects were required to be followed up for at least 1 week, and studies had to report a global assessment of FD symptom cure or improvement after completion of therapy, preferably as reported by the patient, but if this was not recorded then as documented by the investigator. Where studies did not report these types of data, but were otherwise eligible for inclusion in the systematic review, we attempted to contact the original investigators in order to obtain dichotomous data.

Studies on FD were identified with the term dyspepsia (both as a medical subject heading (MeSH) and a free text term), and dyspep$, satiety, epigastric adj5 pain, upper gastrointestinal symptom$, or upper gastrointestinal adj5 symptoms (as free text terms). These were combined using the set operator AND with studies identified with the terms: antidepressive agents (second generation), antidepressive agents, antidepressive agents (tricyclic), psychotropic drugs, serotonin uptake inhibitors, sulpiride, mianserin,

desipramine, imipramine, trimipramine, doxepin, dothiepin, nortriptyline, amitriptyline, paroxetine, sertraline, fluoxetine, or citalopram (both as MeSH terms and free text terms), and the following free text terms: venlafaxine, duloxetine, escitalopram, levosulpiride, mirtazapine, tricyclic, desimipramine, buspirone, or tandospirone.

There were no language restrictions and abstracts of the papers identified by the initial search were evaluated by two reviewers for appropriateness to the study question, and all potentially relevant papers were obtained and evaluated in detail. Foreign language papers were translated where necessary. Abstract books of conference proceedings from Digestive Diseases Week and United European Gastroenterology Week between 2001 and 2014 were hand-searched to identify potentially eligible studies published only in abstract form. The bibliographies of all identified relevant studies were used to perform a recursive search of the literature. Articles were assessed independently by two reviewers using pre-designed eligibility forms, according to the prospectively defined eligibility criteria. Any disagreement between investigators was resolved by consensus.

Outcome Assessment

The primary outcomes assessed were the effects of psychotropic drugs compared with placebo on global FD symptoms after cessation of therapy. Secondary outcomes included adverse events occurring as a result of therapy, and adverse events leading to study withdrawal.

Data Extraction

All data were extracted independently by two reviewers on to a Microsoft Excel spreadsheet (XP professional edition; Microsoft Corp, Redmond, WA, USA) as dichotomous outcomes (global FD symptoms unimproved) (Box 2), with disagreements resolved by consensus. In addition, the following clinical data were extracted for each trial: setting (primary, secondary, or tertiary care-based), country of origin, dose and class of psychotropic drug administered, duration of therapy, total number of adverse events reported, total number of adverse events leading to withdrawal, criteria used to define FD, primary outcome measure used to define symptom improvement following therapy, and proportion of female patients. Data were extracted as intention-to-treat analyses, with all drop-outs assumed to be treatment failures, wherever trial reporting allowed this.

Assessment of Risk of Bias

This was performed independently by two investigators, with disagreements resolved by consensus. Risk of bias was assessed as described in the Cochrane handbook, [35] by recording the method used to generate the randomisation schedule and conceal allocation, whether blinding was implemented for participants, personnel and outcome assessment, what proportion of subjects completed follow-up, and whether there was evidence of selective reporting of outcomes.

Data Synthesis and Statistical Analysis

Data were pooled using a random effects model, [36] to give a more conservative estimate of the effect of psychotropic drugs, allowing for any heterogeneity between studies. The impacts of different interventions were expressed as a relative risk (RR) of global FD symptoms not improving with psychotropic drugs compared with placebo, with 95% confidence intervals (CI). Adverse events data were also summarised with RRs. The number needed to treat (NNT) and the number needed to harm (NNH), with 95% CIs, were calculated using the formula NNT or NNH = 1 / (control event rate x (1 – RR)).

Heterogeneity, which is variation between individual study results arising as a result of either differences in study participants or methodology, was assessed using both the I^2 statistic with a cut off of ≥50%, and the chi-squared test with a P value <0.10, used to define a significant degree of heterogeneity. [37] Where the degree of statistical heterogeneity was greater than this between trial results in this meta-analysis, possible explanations were investigated using subgroup analyses according to type of psychotropic drug used, trial setting, criteria used to define FD, whether individual trials screened for and excluded individuals with co-existent mood disorders, and risk of bias of included trials. These were exploratory analyses only, and may explain some of the observed variability, but the results should be interpreted with caution.

Review Manager version 5.1.4 (RevMan for Windows 2008, the Nordic Cochrane Centre, Copenhagen, Denmark) and StatsDirect version 2.7.7 (StatsDirect Ltd, Sale, Cheshire, England) were used to generate Forest plots of pooled RRs for primary and secondary outcomes with 95% CIs, as well as funnel plots. The latter were assessed for evidence of asymmetry, and therefore possible publication bias or other small study effects,

using the Egger test, [38] if there were sufficient (10 or more) eligible studies included in the meta-analysis, in line with current recommendations. [39]

RESULTS

The search strategy identified a total of 2795 citations, of which 34 published articles appeared to be relevant, and were retrieved for further assessment. Of these 34, 21 were excluded for various reasons leaving 13 eligible studies (Figure 1). [25, 27, 32, 33, 40-48] Agreement between reviewers for assessment of trial eligibility was good (kappa statistic = 0.77). We successfully contacted original investigators to seek clarification on study methodology, and hence reduce risk of bias, or to obtain supplementary dichotomous data for nine trials. [25, 32, 33, 42-46, 48] Three trials used antipsychotic drugs, [27, 40, 41] three trials 5-HT_{1A} receptor agonists, [25, 43, 44] two trials TCADs, [45, 46] one trial SSRIs, [32] one trial tetracyclic antidepressants, [48] one trial serotonin-norepinephrine re-uptake inhibitors (SNRIs), [33] one trial SSRIs or TCADs, [47] and one trial a combination of an antipsychotic drug and a TCAD. [42] Ten of the RCTs were at low risk of bias (Supplementary Table 1). [25, 32, 33, 42-48]

The proportion of female patients recruited by trials ranged from 56.0% to 85.3%. Six trials screened for, and excluded, individuals with co-existent mood disorders. [25, 42, 44, 45, 47, 48] In the trial by Braak et al. seven (10.3%) of 68 screening failures were due to a mood disorder. [45] Among the other studies, three reported reasons for screening failure and none were due to a mood disorder, [25, 42, 44] and two did not report these data. Detailed characteristics of individual RCTs are provided in Table 1.

Table 1. Characteristics of Randomised Controlled Trials of Psychotropic Drugs Versus Placebo in Functional Dyspepsia.

Study name and year	Country	Setting	Diagnostic criteria used for FD	Criteria used to define symptom improvement following therapy	Sample size (% female)	Psychotropic drug used and duration of therapy	Screened for mood disorder prior to entry?	Methodology
Hui 1986 [40]	Hong Kong, China	Tertiary care	Clinical diagnosis and negative investigations	Patient-reported improvement in, or resolution of, dyspeptic symptoms	100 (58.0)	Sulpiride 100mg q.i.d*. for 1 week, then 50mg q.i.d. for 3 weeks	Yes, but not excluded	Method of randomisation and concealment of allocation not stated. Double-blind. Antacids only allowed.

Arienti 1994 [27]	Italy	Tertiary care	Clinical diagnosis and negative investigations	Patient-reported improvement in dyspeptic symptoms using a visual analogue scale	30 (63.3)	Levosulpiride 25mg t.i.d.† for 20 days	No	Method of randomisation and concealment of allocation not stated. Double-blind. No other FD medications allowed.
Song 1998 [41]	South Korea	Tertiary care	Clinical diagnosis and negative investigations, delayed gastric empting present in all patients	Patient-reported global efficacy of treatment rated as excellent or good	42 (78.6)	Levosulpiride 25mg t.i.d. for 3 weeks	No	Method of randomisation and concealment of allocation not stated. Double-blind. No other FD medications allowed.

Hashash 2008 [42]	Lebanon	Tertiary care	Rome III criteria and negative investigations	Patient-reported subjective feeling of global symptom relief	25 (56.0)	Flupenthixol 0.5mg and melitracen 10mg b.i.d.‡ for 2 weeks	Yes, no patients with anxiety recruited	Method of randomisation and concealment of allocation stated. Double-blind. Unclear if other FD medications allowed.
van Kerkhoven 2008 [33]	The Netherlands	Secondary care	Clinical diagnosis and negative investigations	Patient-reported absence of symptoms on a 7-point Likert scale	160 (59.4)	Venlafaxine 75mg o.d.§ for 2 weeks, then 150mg o.d. for 4 weeks, then 75mg o.d. for 2 weeks	Yes, but not excluded	Method of randomisation and concealment of allocation stated. Double-blind. No other FD medications allowed.

Tack 2009 [44]	Belgium, Germany, and The Netherlands	Tertiary care	Rome II criteria and negative investigations	30% improvement in patient assessment of upper GI symptom severity‖	53 (66.0)	R-137696 2mg t.i.d. for 4 weeks	Yes, and excluded	Method of randomisation and concealment of allocation stated. Double-blind. No other FD medications allowed.
Miwa 2009 [43]	Japan	Secondary and tertiary care	Rome II criteria and negative investigations	Patient-reported total abdominal symptom score of 0 or 1 on a modified gastrointestinal symptom rating scale	150 (73.3)	Tandospirone 10mg t.i.d. for 4 weeks	Yes, but not excluded	Method of randomisation and concealment of allocation stated. Double-blind. No other FD medications allowed.

Braak 2011 [45]	The Netherlands	Tertiary care	Rome III criteria and negative investigations	30% improvement in patient assessment of upper GI symptom severity‖	38 (60.5)	Amitriptyline 25mg o.d. for 8 weeks	Yes, and excluded	Method of randomisation and concealment of allocation stated. Double-blind. No other FD medications allowed.
Wu 2011 [46]	Hong Kong, China	Tertiary care	Rome II criteria and negative investigations	Patient-reported relief of global symptoms	107 (80.4)	Imipramine 25mg o.d. for 2 weeks, then 50mg o.d. for 10 weeks	Yes, but not excluded	Method of randomisation and concealment of allocation stated. Double-blind. Other FD medications allowed.

Tack 2012 [25]	Belgium	Tertiary care	Rome II criteria and negative investigations	30% improvement in patient-reported dyspepsia symptom severity‖	17 (76.5)	Buspirone 10mg t.i.d. for 4 weeks	Yes, and excluded	Method of randomisation and concealment of allocation stated. Double-blind. No other FD medications allowed.
Tan 2012 [32]	Hong Kong, China	Tertiary care	Rome II criteria and negative investigations	Patient-reported relief of global symptoms	193 (72.0)	Sertraline 50mg o.d. for 8 weeks	Yes, but not excluded	Method of randomisation and concealment of allocation stated. Double-blind. Other FD medications allowed.

Tack 2015 [48]	Belgium	Tertiary care	Rome III criteria and negative investigations, weight loss present in all patients	30% improvement in patient-reported dyspepsia symptom severity‖	34 (85.3)	Mirtazepine 15mg o.d. for 8 weeks	Yes, and excluded	Method of randomisation and concealment of allocation stated. Double-blind. No other FD medications allowed.
Talley 2015 [47]	USA and Canada	Tertiary care	Rome II criteria and negative investigations	Patient-reported adequate relief of global symptoms for 50% of weeks during weeks 3 to 12	292 (75.0)	Amitriptyline 25mg o.d. for 2 weeks, then 50mg o.d. for 10 weeks, or escitalopram 10mg o.d. for 12 weeks	Yes, and excluded	Method of randomisation and concealment of allocation stated. Double-blind. Other FD medications allowed.

*q.i.d.; four times daily

† t.i.d.; thrice-daily

‡ b.i.d.; twice-daily

§o.d.; once-daily

||Dichotomous data obtained from original investigators

Efficacy of Psychotropic Drugs in the Treatment of FD

In total, there were 1241 patients, 673 of whom received active therapy and 568 placebo. Overall, 388 (57.7%) of 673 patients assigned to psychotropic drugs reported persistent or unimproved FD symptoms following therapy, compared with 407 (71.7%) of 568 allocated to placebo. The RR of FD symptoms persisting or not improving after treatment with psychotropic drugs versus placebo was 0.78 (95% CI 0.68 to 0.91), with significant heterogeneity detected between studies (I^2 = 64%, P < 0.001) (Figure 2). There was statistically significant asymmetry in the funnel plot (Egger test, P = 0.003), suggesting publication bias or other small study effects (Supplementary Figure 1). In view of this, we conducted a sensitivity analysis using a fixed effects model, but the results were almost identical (RR = 0.82; 95% CI 0.76 to 0.89). The NNT with psychotropic drugs was 6 (95% CI 4 to 16).

Subgroup analyses were conducted (Table 2). These revealed that the beneficial effect of psychotropic drugs appeared to be limited to antipsychotics and TCADs. In addition, a significant treatment effect was only seen in trials that were conducted in tertiary care, although these constituted the majority of studies. When only studies that screened for and excluded individuals with a co-existent mood disorder were considered in the analysis, there was no longer a significant effect of psychotropic drugs on FD. Importantly, when the analysis was limited to the 10 trials at low risk of bias, the beneficial effect of psychotropic drugs persisted. A summary of the quality of the evidence for the efficacy of psychotropic drugs, using GRADE criteria, [49] is provided in Supplementary Table 2.

Table 2. Subgroup Analyses of Randomised Controlled Trials of Psychotropic Drugs Versus Placebo in Functional Dyspepsia.

	Number of trials	Number of patients	Relative risk of FD symptoms not improving (95% CI)	NNT (95% CI)	I^2 (P value)
All studies	**13**	**1241**	**0·78 (0·68 to 0·91)**	**6 (4 to 16)**	**64% (<0·001)**
Drug class used					
Antipsychotics	3	172	0·50 (0·37 to 0·67)	3 (2 to 4)	0% (0·91)
TCADs	3	339	0·74 (0·61 to 0·91)	6 (4 to 18)	0% (0·73)
5-HT_{1A} receptor agonists	3	220	0·85 (0·62 to 1·18)	Not estimable	65% (0·06)
SSRIs	2	388	1·01 (0·89 to 1·15)	Not estimable	0% (0·91)
SNRIs	1	160	1·02 (0·80 to 1·30)	Not estimable	Not applicable*
Tetracyclic antidepressants	1	34	0·73 (0·50 to 1·08)	Not estimable	Not applicable*
Antipsychotics and TCADs	1	25	0·31 (0·11 to 0·87)	2 (1.5 to 10)	Not applicable*
Setting					
Tertiary care only	11	931	0·74 (0·61 to 0·89)	6 (4 to 13)	68% (<0·001)
Secondary and tertiary care	2	310	0·88 (0·68 to 1·15)	Not estimable	68% (0·08)

Criteria used to define FD					
Rome II	6	812	0·89 (0·77 to 1·03)	Not estimable	54% (0·04)
Clinical diagnosis	4	332	0·62 (0·38 to 1·00)	Not estimable	79% (0·003)
Rome III	3	97	0·67 (0·47 to 0·94)	4 (2 to 20)	28% (0·25)
Screened for and excluded individuals with co-existent mood disorder					
Yes	6	459	0·83 (0·67 to 1·02)	Not estimable	52% (0·05)
No	7	782	0·74 (0·59 to 0·93)	5 (3 to 20)	75% (<0·001)
Risk of bias					
Low	10	1069	0·86 (0·76 to 0·98)	10 (6 to 72)	51% (0·02)
Unclear or high	3	172	0·50 (0·37 to 0·67)	3 (2 to 4)	0% (0·96)

*Too few studies to assess heterogeneity

Adverse Events with Psychotropic Drugs

Data concerning total numbers of adverse events were available for 11 of the trials. [25, 27, 32, 40-45, 47, 48] For five studies, these were obtained by direct contact with the original investigators. [25, 32, 42, 44, 48] There were 118 (21.9%) of 538 patients assigned to psychotropic drugs experiencing any adverse event, compared with 73 (16.7%) of 436 allocated to placebo. When data were pooled, the incidence of adverse events was significantly higher among those taking psychotropic drugs (RR of experiencing any adverse event = 1.28; 95% CI 1.01 to 1.63), with no heterogeneity between results $I^2 = 0\%$, P = 0.47) (Figure 3), and a NNH of 21 (95% CI 9 to 597). When type of psychotropic drug was studied, total adverse events were only significantly higher with TCADs in two trials (RR = 1.65; 95% CI 1.11 to 2.45), [45, 47] with a NNH of 7 (95% CI 3 to 40).

Adverse events leading to withdrawal from each of the trials were available for all included studies. [25, 27, 32, 33, 40-48] For eight RCTs these were obtained by contacting involved investigators. [25, 33, 42-47] In total, 78 (11.6%) of 673 patients assigned to psychotropic drugs experienced adverse events leading to withdrawal, compared with 35 (6.2%) of 568 allocated to placebo. When data were pooled the incidence of adverse events leading to withdrawal was significantly higher among those taking psychotropic drugs (RR of experiencing adverse events leading to withdrawal = 1.76; 95% CI 1.22 to 2.55), again with no heterogeneity between results ($I^2 = 0\%$, P = 0.50) (Figure 4). The NNH was 21 (95% CI 10 to 74). Adverse events leading to withdrawal were significantly higher with SSRIs in two trials (RR = 1.94; 95% CI 1.03 to 3.67, NNH = 16; 95% CI 6 to 492),[32, 47] and SNRIs in one trial

(RR = 4.25; 95% CI 1.50 to 12.07, NNH = 6; 95% CI 2 to 40), [33] but not with any other type of psychotropic drug.

DISCUSSION

This systematic review and meta-analysis has demonstrated that psychotropic drugs appear to be an effective treatment for FD, with an NNT of six when data from all studies were pooled. However, this beneficial effect appeared to be limited to TCADs and antipsychotics, such as levosulpiride. There was no significant difference detected between SSRIs, SNRIs, tetracyclic antidepressants, or 5-HT_{1A} receptor agonists and placebo. With two negative studies of SSRIs, containing almost 400 patients, it would be reasonable to assume that these drugs are of no benefit in FD, but for other agents the total number of trials and included patients were fewer, and in the case of 5-HT_{1A} receptor agonists it should be pointed out that the largest trial, which used tandospirone, demonstrated a significant benefit of this drug. Total numbers of adverse events, and adverse events leading to withdrawal, were significantly higher among those taking psychotropic drugs, with a NNH of 21 for both these endpoints.

This systematic review and meta-analysis used rigorous methodology. We reported our search strategy, which included searching the "grey" literature, and assessment of eligibility and data extraction was performed independently by two reviewers. We used an intention-to-treat analysis and pooled data with a random effects model, to minimise the likelihood that treatment effect of psychotropic drugs in FD would be overestimated. We also contacted investigators of potentially eligible studies to either obtain supplementary dichotomous data for effect of treatment on symptoms and adverse events with therapy that were not reported in the original publications, or to clarify study methodology in order to minimise the risk of bias of included RCTs. This inclusive approach has provided us with access to data for >1200 FD patients treated with psychotropic drugs versus placebo. In addition, we performed

subgroup analyses to explore reasons for heterogeneity between studies, and to assess treatment effect according to individual therapy used, study setting, criteria used to define FD, exclusion of patients with pre-existing mood disorder, and risk of bias of included studies. Finally, we extracted and pooled adverse events data, where reported, and again contacted the original investigators in order to maximise the data available for synthesis.

There are limitations to this systematic review and meta-analysis, some of which arise from the nature of the studies available for synthesis. Three of the included trials were unclear risk of bias, [27, 40, 41] due to a lack of reporting of the methods used to generate the randomisation schedule and conceal allocation, which may lead to overestimation of the treatment effect. However, the difference in favour of psychotropic drugs remained statistically significant when only trials at low risk of bias were included in the analysis. The use of subjective, dichotomous outcomes in all the included trials, rather than mechanistic endpoints, may have led to a higher placebo response rate, similar to that seen in treatment trials in irritable bowel syndrome. [50] In addition, the fact that some studies included individuals with psychological co-morbidity may limit the generalisability of our findings to patients with FD outside of specialist referral centres. Finally, it should be pointed out that the longest duration of therapy in any of the RCTs we identified was 12 weeks, meaning that the longer term efficacy of psychotropic drugs in FD is unknown.

In terms of limitations of the findings of the meta-analysis itself, there was evidence of heterogeneity between RCTs in our primary analysis, although not when TCADs or SSRIs were considered separately, or when only studies that used the Rome III criteria to define FD were included in the analysis. There was also evidence of publication bias, or other small study effects, when data from all trials were pooled.

If this were due to a genuine failure to publish small negative RCTs of psychotropic drugs in FD, this could mean that the observed treatment effect has been overestimated. We used NNTs and NNHs to summarise efficacy and safety, which are defined as the expected number of people who need to receive the experimental, rather than the comparator, intervention for one additional person to either incur or avoid an event in a given time frame. Their calculation was based on the pooled control event rate and RR. These are time dependent variables and may vary with durations of follow-up. [51] The follow-up duration of included studies in this review ranged from 2 weeks to 12 weeks, therefore, the NNT and NNH and their interval estimations should be interpreted as a range that can be expected within this time frame.

Although proton pump inhibitors (PPIs) and Helicobacter pylori eradication therapy are efficacious treatments for FD, the benefits are modest, [52, 53] and a considerable proportion of patients therefore do not experience relief of their symptoms with either of these approaches. This, together with the fact that most prokinetics are either ineffective, [54] or have been withdrawn or are restricted due to concerns about their safety profile, [55] means that there is a large unmet need for effective therapies in FD. Previous attempts to summarise the literature concerning the role of psychotropic drugs in FD, and to estimate their efficacy, have been hampered by a paucity of trials, and a failure to report extractable dichotomous data, meaning that a formal meta-analysis has not been possible until now. [56, 57] As a result current national guidelines for the management of FD are equivocal concerning the role of psychotropic drugs in FD. [29-31]

This underlines the importance of the current meta-analysis, which has highlighted that antipsychotic drugs and TCADs are more effective than placebo in

FD patients in secondary or tertiary care. However, it remains uncertain whether other psychotropic drugs, including 5-HT_{1A} receptor agonists, tetracyclic antidepressants, or SNRIs are effective treatments in FD. With respect to 5-HT_{1A} receptor agonists, although there have been three trials, [25, 43, 44] each used a different drug, and the results were conflicting. In the case of tetracyclic antidepressants and SNRIs there has been only one trial of each of these drug classes. The trial of mirtazapine suggested a benefit of the drug in FD patients with weight loss (the inclusion criterion), but was relatively small and not powered for a dichotomous endpoint. [48] The RCT of venlafaxine was larger, [33] but has been criticised for its use of an agent with an adverse side-effect profile, leading to a high dropout rate, and the dosing regimen used, which included titration of the dose up to 150mg daily over the first 6 weeks, followed by a reduction to 75mg once daily during the last 2 weeks. [58]

The mechanism of action for the beneficial effect of some psychotropic drugs in FD may arise from their effects on neurotransmitters in the brain, through their local actions in the GI tract, or both. TCADs target serotonergic neurotransmission, while antipsychotic agents are D_2 receptor antagonists, among other actions. The intestinal enterochromaffin cells contain 90% of the body's total stores of 5-HT, [59, 60] which is integral to GI motility. Antagonism of D_2 receptors in the myenteric plexus promotes gastric emptying, pyloric relaxation, and increased lower oesophageal sphincter tone, [61] which may explain the beneficial effects of benzamides such as sulpiride and levosulpiride, and suggests that the efficacy of drugs with a better side-effect profile but with a similar mechanism of action should be explored in FD. Finally, central inhibitory effects of TCADs on 5-HT and norepinephrine re-uptake may lead to their visceral analgesic properties, while their

anticholinergic effects may alter GI motility, [62] although this was not observed with low-dose amitriptyline. [47]

Whether these drugs are effective in patients with FD in primary care, and also whether they are more effective than established drugs, such as PPIs, for the treatment of the condition cannot be determined from this meta-analysis. There is also uncertainty as to whether some of the benefit of psychotropic drugs in FD arises from the treatment of co-existent mood disorder, with a larger treatment effect observed in studies that did not exclude patients with co-existent mood disorder. For SSRIs, this theory is plausible, as the doses used in the two trials were close to those used to treat depression, but this would seem less likely for TCADs, where the doses used were considerably lower than the therapeutic range considered as effective for the treatment of mood disorders. The efficacy of these therapies according to FD subtype (epigastric pain syndrome or post-prandial distress syndrome) has not been well-studied. Future trials should be undertaken in primary care, and could stratify patients according to presence or absence of co-existent mood disorder, and FD subtype, in order to explore these unresolved questions. Finally, the long-term side-effects of TCADs were not able to be considered, although there may be risks. [63]

In summary, this systematic review and meta-analysis has demonstrated that, overall, psychotropic drugs are more effective than placebo for the treatment of FD. However, this beneficial effect was limited to antipsychotic drugs, such as sulpiride and levosulpiride, and TCADs, such as amitriptyline and imipramine. This has implications for the management of a condition that clinicians often find challenging, and should encourage appropriate use of these agents by gastroenterologists, and stimulate further RCTs in this field.

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CONFLICTS OF INTEREST/STUDY SUPPORT

Guarantor of the article: ACF is guarantor.

Specific author contributions: ACF, PL, JT, GEB, PM, and NJT conceived the study. ACF and PL collected all data. ACF and PL analysed and interpreted the data. ACF drafted the manuscript. All authors commented on drafts of the paper. All authors have approved the final draft of the manuscript.

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Box 1. Eligibility criteria.

Randomised controlled trials

Adults (participants aged > 16 years)

Diagnosis of functional dyspepsia based on either a clinician's opinion, or meeting specific diagnostic criteria*, supplemented by negative endoscopy.

Compared psychotropic drugs with placebo.

Minimum duration of therapy 7 days.

Minimum duration of follow-up 7 days.

Dichotomous assessment of response to therapy in terms of effect on global functional dyspepsia symptoms following therapy at study end.†

*Rome I, II, or III criteria.

†Preferably patient-reported, but if this was not available then as assessed by a physician.

Box 2. Data extraction methodology.

Outcome of interest: improvement in global functional dyspepsia symptoms.

Reporting of outcomes: patient-reported preferable, if not available then investigator-reported.

Time of assessment: at last point of follow-up whilst still on therapy.

Denominator used: true intention-to-treat analysis, if not available then all evaluable patients.

Cut off used for dichotomisation: any improvement in global functional dyspepsia symptoms or abdominal pain for Likert-type scales, investigator-defined improvement for continuous scales.

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FIGURE LEGENDS

Figure 1. Flow Diagram of Assessment of Studies Identified in the Systematic Review and Meta-analysis.

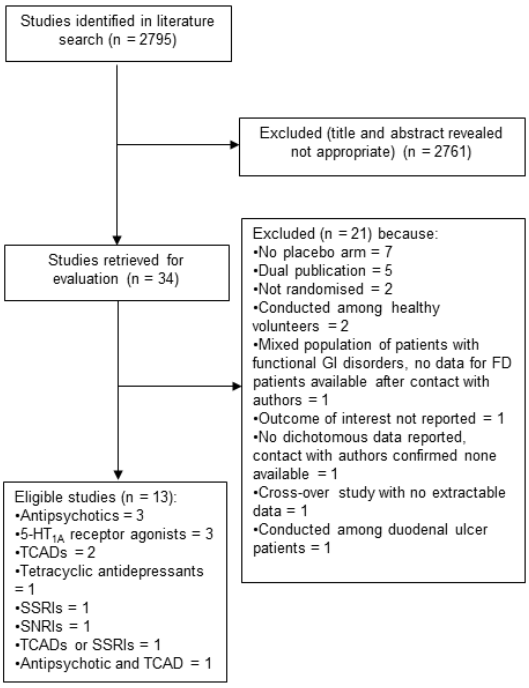

Figure 2. Forest Plot of Efficacy of Psychotropic Drugs Versus Placebo in Randomised Controlled Trials in Functional Dyspepsia.

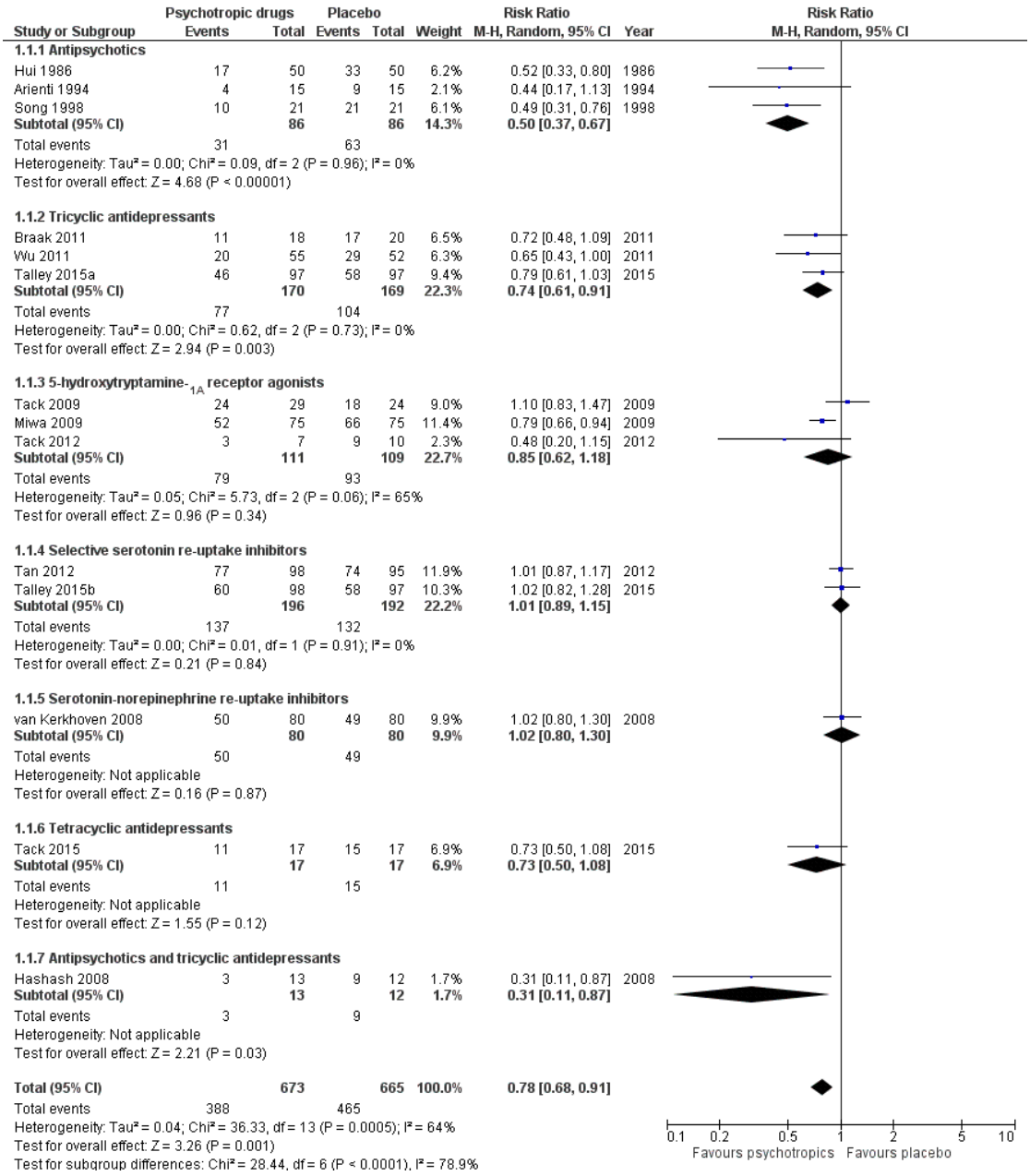

Figure 3. Forest Plot of Adverse Events with Psychotropic Drugs Versus Placebo in Randomised Controlled Trials in Functional Dyspepsia.

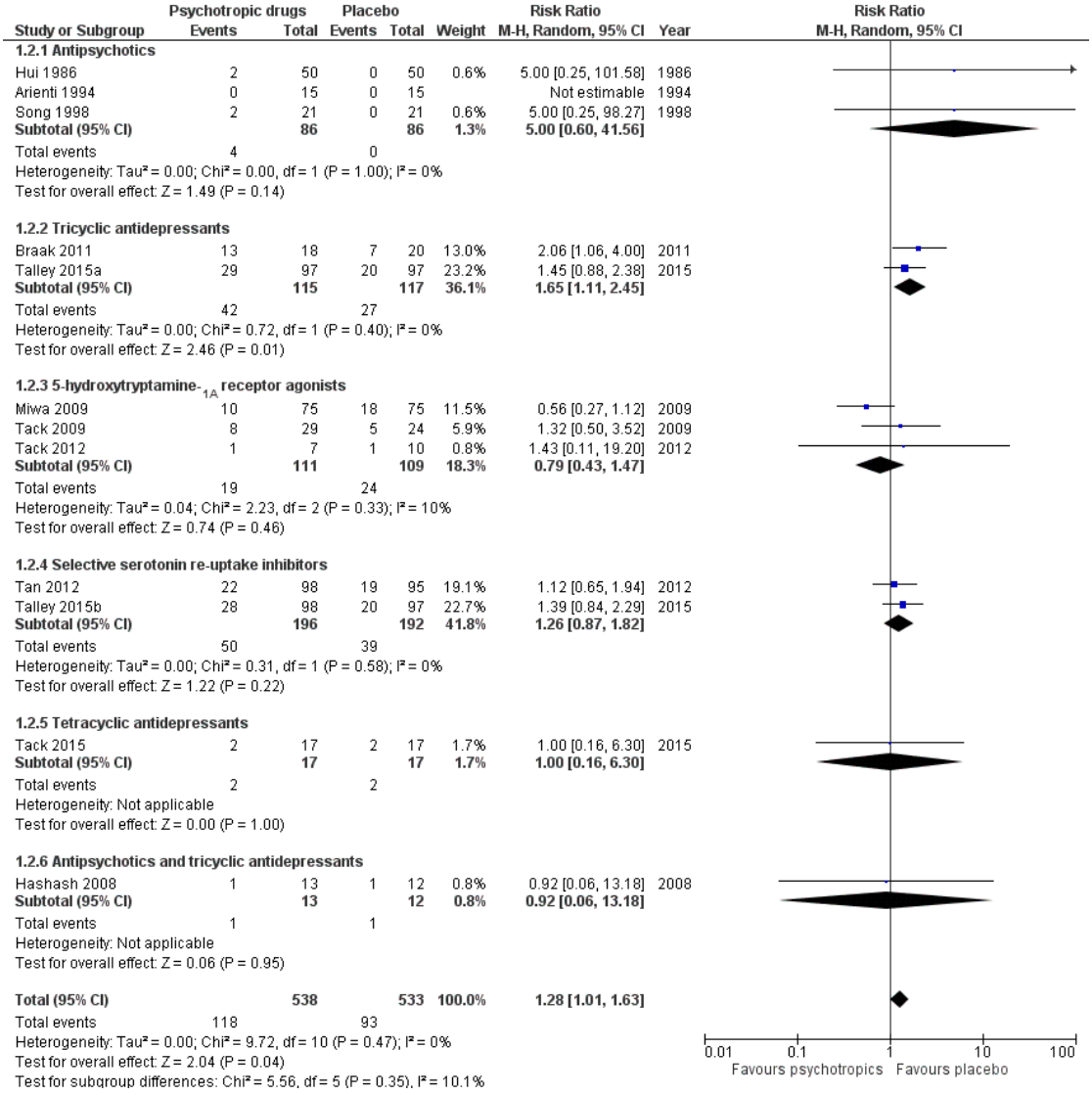

Figure 4. Forest Plot of Adverse Events Leading to Withdrawal with Psychotropic Drugs Versus Placebo in Randomised Controlled Trials in Functional Dyspepsia.