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Review Article

Design characteristics of comparative effectiveness trials for the relief of symptomatic dyspepsia: A systematic review

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ABSTRACT

Background: Dyspepsia represents a symptom domain rather than a diagnostic condition and covers a wide range of complex, underlying pathophysiologies that are not well understood. The review explores comparative effectiveness interventions for the treatment of symptomatic dyspepsia along a pragmatic-explanatory continuum. The aim is to identify relevant design characteristics applicable to future upper gastrointestinal comparative effectiveness research employing integrative medicine.
Methods: Medline, CINAHL, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL) and WHO Clinical Trials were systematically searched until January 2019. Included articles were original research with two or more comparative intervention arms for the primary outcome; relief of symptomatic dyspepsia. Evaluation of the studies was conducted using the pragmatic-explanatory continuum indicator summary (PRECIS-2) tool.
Results: Thirty-six articles were included in the review. A total of 68 Patient Reported Outcome Measurements (PROMs), utilizing 50 different formats were deployed across the studies. The appraisal process revealed eligibility, flexibility in adherence, flexibility in delivery and organization domains further aligned towards an explanatory design.
Conclusion: This review identified three design characteristics relevant for future comparative effectiveness research for the treatment of upper gastrointestinal disorders in a community setting. Extensive exclusion eligibility criteria limited the generalization of comparative effectiveness study results by removing sub-groups of the target populations more at risk of dyspeptic symptoms. The requirement for entry endoscopy was found to be common and not always pragmatically justifiable. Development of validated PROMs appropriate for a generic application to upper gastrointestinal disorders would be advantageous for future comparative effectiveness research within integrative medicine.

1. Introduction

Symptomatic dyspepsia encompasses a wide range of upper gastrointestinal (GIT) symptoms and overlapping GIT conditions.[1–5] Broadly, dyspepsia is defined as any symptom referable to the upper gastrointestinal tract, including heartburn, reflux, upper abominable or epigastric pain or discomfit.[6] This definition captures variations in terminology, diagnostic criteria and unclassified presentation of symptoms as would be encountered in a community setting. Despite symptoms of dyspepsia being reported by 20.8% of the global population the underlying pathophysiologies are complex and not well understood.[3,4] Pathologies which may result in dyspepsia can include undetected chronic *Helicobacter pylori* infection, peptic ulcer disease, gastric malignancy, duodenal mucosal inflammatory and permeability changes.[3,7] Preliminary research suggests 25% of individuals experience an overlap between both dyspepsia and gastrooesophageal reflux symptoms.[8] Symptoms of dyspepsia may fluctuate over time, aging and with lifestyle factors.[9] Interactions between the GIT and the brain can result in individuals with dyspepsia experiencing increased anxiety and depression,[7,10] reductions in work productivity, and compromised quality of life.[11] In the United States of America, management of dyspepsia is estimated to cost health services over $US 18 billion per annum.[11]

Globally, approximately only 40% of patients with symptomatic dyspepsia utilise a primary health provider for assistance and 15% of these will be referred for secondary care.[3] Clinical management for uninvestigated dyspepsia can include initial treatment with a

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proton-pump inhibitor (PPI),[3,12] despite emerging evidence of PPI ingestion being associated with renal, cardiovascular, gastrointestinal, autoimmune and neurologic adverse effects.[13] Complementary medicine (CM) - a diverse group of non-conventional medical and health practices used together with conventional medical care [14] - is also currently used for the symptomatic treatment of dyspepsia.[15,16] It has been reported more than 50% of those experiencing functional gastrointestinal disorders seek CM in the community setting for the management of their condition.[15] In Australia, a recent study reported 63.5% of those with a diagnosed gastrointestinal disease use CM products and 48.1% have visited a CM practitioner for gastrointestinal (GIT) assistance.[16] The World Gastroenterology Organisation recommends the use of locally available symptomatic remedies for GERD if they are safe, effective and less costly than prescription medications in areas with limited resources.[17] Conversely, the American College of Gastroenterology and the Canadian Association of Gastroenterology has recommended CM is not used for dyspepsia as there is no clear evidence for their effectiveness.[3] To address this discrepancy, research is needed that is appropriately designed to evaluate the effectiveness of complementary medicine compared to other commonly available, and frequently prescribed, treatments.[9]

The heterogeneity of dyspepsia pathophysiology and symptomatology presents obstacles for effective research and clinical management. Classic biomedical research is built upon assessment of efficacy under ideal or controlled conditions.[18] Yet, the more the research design imposes controls on subject selection, eligibility and participation, the greater the risk the results will not apply to the management of dyspepsia among the broader population.[18,19] An alternative approach is Comparative Effectiveness Research (CER). CER is the direct comparison of existing health care interventions to determine which treatment works best, for whom, and under which context.[20] Correspondingly, CER is designed to support a health care provider make an informed decision on the most effective treatment option for their patient's symptoms and resources.[18,19] An important aspect of CER is the concept of pragmatic trials: the interventions are tested in routine, usual care settings.[21] This type of approach lends itself to research examining CM treatments for dyspepsia being undertaken in a CM practitioner setting. CM practitioners commonly utilize health care interventions with a long history of traditional use, which continue to be prescribed in contemporary practice. The intention of this review is to explore pragmatic design characteristics relevant for future CER of CM treatments available to those seeking relief of upper gastrointestinal disorders in a community setting, including undiagnosed and unclassified dyspepsia.

2. Methods

The literature review protocol was developed and implemented using the *Preferred reporting items for systematic review and meta-analysis* protocols (PRISMA-P) 2015 statement.[22] The protocol has been submitted and registered with the International Prospective Register of Systematic Reviews and registration (PROSPERO) (#CRD42020127885).

2.1. Study aim

The systematic review aims to explore the design characteristics of comparative effectiveness trials for the relief of symptomatic dyspepsia.

2.2. Search strategy

The following databases were searched: MEDLINE; CINAHL; SCOPUS; Cochrane Central Register of Controlled Trials (CENTRAL) and WHO Clinical Trials. Date range was January 2014 to January 2019. Medical subject headings and existing literature reviews[8,23] were used to help formulate the following search term strategy: ("dyspepsia" OR "heartburn" OR "gastroesophageal reflux" OR "GERD" OR "GORD" OR "NERD" OR "gastroesophageal-reflux disease" OR "gastrointestinal reflux disease" OR "non-erosive reflux disease" OR "gastro esophageal reflux disease" OR "nonerosive esophagitis" OR "endoscopically negative reflux disease") AND ("treatment" OR "intervention" OR "comparative").

2.3. Eligibility criteria

Included articles were original research with two or more comparative intervention arms for the relief of symptomatic dyspepsia. Articles were included if the subjects were over 18 years old, human and the primary treatment aim was relief of symptomatic dyspepsia. Articles were excluded for: no comparative intervention arm; intervention compared with placebo; treatment of helicobacter pylori intervention arm; or, if an intervention was surgical. No language restrictions were applied.

2.4. Study selection

All identified citations were downloaded to Endnote. After removal of duplicates, the remaining citations were screened by title, abstract and full-text against the eligibility criteria by one researcher (NE) (Fig. 1).[24] In accordance with the AMSTAR 2 appraisal tool for systematic reviews, a sample of eligible studies (20%) was reviewed by one other researcher (BL).[25]

2.5. Data extraction

Data from those studies in English language or translated via Google translation were independently extracted by one researcher (NE) and reviewed by two other researchers (BL and AS). Data from the eight Mandarin manuscripts were independently extracted via a fourth researcher (WP). The data was reviewed and incorporated into the systematic literature review by researcher (NE). Extracted information consists of: authors, publishing date, country, study design and interventions. Additional extracted information was formatted according to PRECIS -2 domain design categories: eligibility, recruitment, setting, organization, flexibility: delivery, flexibility: adherence, follow-up, outcome and primary analysis (Table 1).

2.6. Data extraction process

The criteria used to extract information for the nine PRECIS-2 domain categories were conducted in accordance with the published methodology, with a number of clarifications.[26] Setting included location of measurements, participant testing and place of treatment intervention. It is assumed participants ingest oral interventions within their community setting and return to their site of recruitment for outcome measurements unless specified. Validation status of Patient Reported Outcome Measurements (PROMs) was extracted from a systematic review on gastroesophageal reflux disease questionnaires.[23]

2.7. Methodology for exclusion categories

Exclusion criteria were categorized into; alarm symptoms, co-morbidities, contraindications, demographic, Irritable Bowel

Table 1
Summary of extracted data from reviewed articles: Study design and characteristics of PRECIS -2 domains.

Source: Author Year Country	Study Design	Interventions	Eligibility: *Who is selected to participate in the trial*	Recruitment: *How are participants recruited into the trial?*	Setting: *Where is the trial being done?*	Organization: *What expertise & resources are needed to deliver the intervention?*	Flexibility - delivery: *How should the intervention be delivered?*	Flexibility - adherence: *What measures are in place to make sure the participants adhere to the intervention?*	Follow-up: *How closely are participants followed-up?*	Outcome: *How relevant is it to participants?* *(1) Primary* *(2) Secondary*	Primary analysis: *To what extent are all data included?*
Azimi et al. 2017 Iran	Randomized double-blind trial	(1) *Apium graveolens & Trachyspermum copticom* (oral; 100 mg, bds) or (2) Omeprazole (oral; 20 mg; qds)	*Inclusion:* Rome III criteria FD 2 wk screening period *Total exclusion criteria:* 19	(1) Patient visit; to gastroenterologist; (2) Convenience sampling by gastroenterologist	(1) Community setting (2) Hospital setting	(1) Specialist medical; endoscopy required	Usual care with set protocol; 2 wk screening	*Duration:* 4 wk *Adherence:* 4 clinic visits *Patients excluded:* Non-compliance	*Measurements:* Stangellini's questionnaire: d 0, 14, 28, 56 Rome III questionnaire: d 0, 14, 28, 56 *Follow-up*: 4 wk	(1) Improvement in symptoms	n = 100 n analyzed = 78 *Patients excluded:* (1) Poor compliance (2) Intervention intolerance (3) Using other dyspepsia medications *Adverse events:* Checked
Choi et al. 2015 Korea	Multi center double-blind randomized concealed allocation controlled trial	(1) DA-9701 (plant extract) (oral; 30 mg; tds) or (2) Itopride (oral; 50 mg; tds)	*Inclusion:* Rome II criteria FD *Total exclusion criteria:* 18	(1) Patient visit; hospital or specialist community based clinics (2) Unspecified recruitment method	(1) Community setting (2) Hospital; specialist community based clinic	(1) Specialist medical; endoscopy required	Usual care with set protocol: 2 wk screening 2 wk medication - free	*Duration:* 4 wk *Adherence:* 5 clinic visits *Patients excluded:* Non-compliance $\leq$ 80% Interrupted study meds > 5 d	*Measurements:* Composite symptom score: d -14, 0, 14, 28 OTE: d 28 NDI: d 0, 14, 28 Daily diary: relief *Follow-up:* unspecified	(1) Improvement in symptoms (2) QoL impact	n = 464 n analyzed = 375 *Patients excluded:* (1) Poor compliance (2) Lost to follow-up (3) Prohibited drug use (4) Incorrect randomization (5) Request discontinuation (6) Adverse event *Adverse events:* Reported
Eherer 2014 Austria	Randomized control group open-label	(1) Specialized breathing exercises with relaxing music (30 min daily) or (2) No breathing exercises	*Inclusion:* Rome II criteria FD *Total exclusion criteria:* 2	Unspecified recruitment method	(1) Community setting (2) Medical Dept; university	(1) Physiotherapists; (2) Specialist medical; Manometry pH-metry Endoscopy	Usual care with set protocol: 1 wk wash-out period Participants may continue with on-demand drug therapy for GERD symptoms	*Duration:* 4 wk *Adherence:* 4 trial site visits *Patients excluded:* Unspecified	*Measurements:* QOL - symptom scores: d -7, 28 *Specialist:* pH-metry: d 0, 28 Manometry: Day unspecified *Follow up:* 9 mo	(1) Improvement in symptoms; Improvement in QoL (2) pH-metry improvement	n = unspecified n analyzed = unspecified *Patients excluded:* unspecified *Adverse events:* Unspecified

Table 1 (*Continued*)

Source: Author Year Country	Study Design	Interventions	Eligibility: *Who is selected to participate in the trial*	Recruitment: *How are participants recruited into the trial?*	Setting: *Where is the trial being done?*	Organization: *What expertise & resources are needed to deliver the intervention?*	Flexibility - delivery: *How should the intervention be delivered?*	Flexibility - adherence: *What measures are in place to make sure the participants adhere to the intervention?*	Follow-up: *How closely are participants followed-up?*	Outcome: *How relevant is it to participants? (1) Primary (2) Secondary*	Primary analysis: *To what extent are all data included?*
Hosseini et al. 2018 Iran	Randomized control group blinded	(1) Psyllium seed; (oral; 5 g bds) or (2) Omeprazole; (oral; 20 mg; bds)	*Inclusion:* 3 yr refractory GERD with Rome III functional constipation with Endoscopy confirmed esophagitis *Total exclusion criteria:* 21	(1) Patient visit; hospital (2) Convenience sampling	(1) Community setting (2) Hospital	Specialist medical; endoscopy	Usual care with set protocol: 4 wk wash-out period Set dose Set timing	*Duration:* 8 wk *Adherence:* 14 home visits *Patients excluded:* No improvement at 8 wk	*Measurements:* Clinical evaluation, response to intervention: d 0, 1, 2, 3, 4, 5, 6, 7, 14, 21, 28, 35, 42, 48 (Unspecified measurement instrument, unspecified who performed evaluation) *Follow up:* 3 mo PRO; VAS: weekly	(1) Improvement in symptoms	n = 132 n analyzed = 132 *Patients excluded:* Non-responders *Adverse events:* Unspecified
Jin et al. 2015 China	Randomized single-blinded controlled	(1) Classic acupoint acupuncture with manipulations; (20–60 min; qad) or (2) Nonacupoint acupuncture without manipulation; (20 min; qad)	*Inclusion:* Rome III criteria FD with Endoscopy *Total exclusion criteria:* 9	(1) Patient visit to hospital (2) Recruitment via advertise-ments; hospital website; newspaper; posters	(1) Hospital setting; Dept Acupuncture	Specialist medical; endoscopy, blood tests, equipment	Usual care with set protocol: 1 wk wash-out period	*Duration:* 4 wk *Adherence:* 3 clinic visits *Patients excluded:* Not specified	*Measurements:* Chinese NDI: d 0, 28, 84 DSSS: d 0, 28, 84 QoL; SF-36: d 0, 28 Zung SDS: d 0, 28 Zung SAS: d 0, 28 *Specialist:* Fasting serum gastrin concentration: d 0, 28 Propagation velocity gastric slow waves: d 0, 28 *Follow up:* 3 mo	(1) Improvement in symptoms, QoL & mental status (2) Effects on fasting serum gastrin concentration; Frequency & propagation velocity of gastric slow waves	n = 60 n analyzed = 56 *Patients excluded:* Non-compliant *Adverse events:* Reported

Table 1 (*Continued*)

Source: Author Year Country	Study Design	Interventions	Eligibility: *Who is selected to participate in the trial*	Recruitment: *How are participants recruited into the trial?*	Setting: *Where is the trial being done?*	Organization: *What expertise & resources are needed to deliver the intervention?*	Flexibility - delivery: *How should the intervention be delivered?*	Flexibility - adherence: *What measures are in place to make sure the participants adhere to the intervention?*	Follow-up: *How closely are participants followed-up?*	Outcome: *How relevant is it to participants?* *(1) Primary* *(2) Secondary*	Primary analysis: *To what extent are all data included?*
Kamiya et al. 2017 Japan	Multi center (4) randomized open label	(1) Raberprazole (oral; 10 mg; daily) or (2) Itopride (oral; 50 mg; tds)	*Inclusion:* Rome III criteria FD *Total exclusion criteria:* 19	(1) Patient visit; hospital or specialist community based clinics (2) Unspecified recruitment method	(1) Community setting (2) Unspecified trial site	Unspecified	Usual care with set protocol; 7 d wash-out GIT meds	*Duration:* 4 wk *Adherence:* 3 clinic visits *Patients excluded:* Failure to adhere to protocol	*Measurement:* 1 PRO questionnaire: d 0, 7, 14, 28 *Follow up:* Nil	(1) Improvement of symptoms	n = 155 n analyzed = 116 *Patients excluded:* (1) Withdrew consent (2) Failure to adhere to protocol (3) Lost to follow-up *Adverse events:* Checked
Ko et al. 2016 Korea	Two center randomized wait-list controlled clinical trial	(1) Individualised AT (15 min; 2x wk) or (2) No treatment waitlist	*Inclusion:* Rome III criteria FD VAS score ≥ 40 mm *Total exclusion criteria: 25*	(1) Hospital outpatients contacted from previous trials (2) Advertise-ments at hospital: web-page, notice-board; subways, newspapers	(1) Community setting (2) Hospital based acupuncture clinic	Usual care 10 h additional training for acupuncturist Specialist medical; blood samples	Usual care Partially individualized AT Participants to avoid bad living habits during the study	*Duration:* 8 wk *Adherence:* 2x wk AT *Patients excluded:* Unspecified Illiterate	*Measurements:* AR Question: during AT, 2 x wk NDI-K: d 0,2856 FD-QOL: d 0, 28, 56 BDI: d 0, 28, 56 STAI: d 0, 28, 56 Ghrelin levels: d 0, 28 Acu belief scale: d 0 Acu Credibility test: d 0 *Follow-up:* 4 wk	(1) Improvement of symptoms (2) QoL impact (3) Depression & anxiety impact (4) Ghrelin hormone levels	n = 76 n analyzed = 72 *Patients excluded:* (1) Poor compliance < 80% *Adverse events:* Checked

Table 1 (*Continued*)

Source: Author Year Country	Study Design	Interventions	Eligibility: *Who is selected to participate in the trial*	Recruitment: *How are participants recruited into the trial?*	Setting: *Where is the trial being done?*	Organization: *What expertise & resources are needed to deliver the intervention?*	Flexibility - delivery: *How should the intervention be delivered?*	Flexibility - adherence: *What measures are in place to make sure the participants adhere to the intervention?*	Follow-up: *How closely are participants followed-up?*	Outcome: *How relevant is it to participants? (1) Primary (2) Secondary*	Primary analysis: *To what extent are all data included?*
Li & Bai 2018 China	Randomized controlled trial	(1) acupuncture: (10 acupoints) (needle insertion; 30 min/time, once every other day) (2) Omeprazole capsules (oral; 20 mg/time before breakfast and night sleep, twice/day)	Inclusion: (1) symptomatic GERD accompanied with somnipathy - Subpump inhibitor test confirmed or endoscopic confirmed (2) age: 25−78 years (3) no other clinical trial taken within the last 4 weeks (4) participant's informed consent *Total exclusion criteria: 22*	Out-patients visit of a Chinese medicine hospital	Unspecified	Unspecified	Unspecified	Duration: 8 wk Adherence: N/A Patients excluded: specified	*Measurements:* Reflux Diagnostic Questionnaire (RDQ) score: week 0, 8 GERD symptom scale score: week 0, 8 Pittsburgh Sleep Quality Index (PSQI) score: week 0, 8 *Follow-up:* Intervention free follow-up	(1) Improvement in symptoms	n = 60 n analyzed = 58 *Patients excluded:* Patients with occult gastro-esophageal reflux *Adverse events:* Unspecified
Liang et al. 2017 Taiwan	Multi-center randomized controlled open label	(1) Dexlanso-prazole (oral; 60 mg; daily) or (2) Esomeprazole (oral; 40 mg; daily)	*Inclusion:* Endoscopic confirmed erosive esophagitis GERD diagnosis GERD score > 11 *Total exclusion criteria: 9*	(1) Out-patient visit to hospital (2) Invited to participate	(1) Community setting (2) Hospital	(1) Specialist medical; endoscopy required gastric biopsy blood samples BMI calculated	Usual care with set protocol	*Duration:* 1 wk *Adherence:* Daily diary 4 study site visits *Patients excluded:* Failure to adhere to protocol Compliance <80%	*Measurements:* Chinese GERDQ d 0 Daily & diet diary: d 0 to 7 CSR Survey: d 1, 3, 7 *Follow up:* Unspecified	(1) Complete symptom resolution (2) Improvement of symptoms	n = 175 n analyzed = 162 *Patients excluded:* (1) Poor compliance < 80% *Adverse events:* Checked

Table 1 (*Continued*)

Source: Author Year Country	Study Design	Interventions	Eligibility: *Who is selected to participate in the trial*	Recruitment: *How are participants recruited into the trial?*	Setting: *Where is the trial being done?*	Organization: *What expertise & resources are needed to deliver the intervention?*	Flexibility - delivery: *How should the intervention be delivered?*	Flexibility - adherence: *What measures are in place to make sure the participants adhere to the intervention?*	Follow-up: *How closely are participants followed-up?*	Outcome: *How relevant is it to participants? (1) Primary (2) Secondary*	Primary analysis: *To what extent are all data included?*
Liu et al. 2017 China	Double-blinded Randomized controlled trial (pilot trial)	(1) Acupuncture (acupoints: CV 12 and ST 36) (needle insertion; 30 min/time, once/day) (2) Moxibustion (acupoints: CV 12 and ST 36) (Moxibustion tool box; 30 min/time, once/day)	Inclusion: (1) symptomatic functional dyspepsia – endoscopic confirmed and pathology tests confirmed (2) dextromanuality (3) age: 20−50 years (4) no gastrointestinal stimulants taken or no participation of other clinical trials at least 15 days prior to the commence of the study (5) participant's informed consent *Total exclusion criteria: 15*	(1) Out-patients visit; Dept. Gastroenterology and Dept. Acupuncture (2) poster recruitment in an university	Unspecified	Registered acupuncturist with specific training for this study Both groups will be conducted by the same acupuncturist	Unspecified	Duration: 4 weeks Adherence: N/A Patients excluded: specified	*Measurements:* Leed's dyspepsia questionnaire (LDQ) score: d 0, 28 Nepean dyspepsia index (NDI) score: d 0, 28 Safety evaluation: d 0, 28 *Follow-up:* Intervention free follow-up	(1) Improvement in symptoms	n = 60 n analyzed = 56 *Patients excluded:* failure to participate due to personal reasons; Withdrew consent due to the smell of moxibustion *Adverse events:* Local swelling and pain, local burns/scalds
Meteerattanapipat & Phupong 2017 Thailand	Randomized double-blinded controlled	(1) Alginate-based reflux suppressant (oral; 15 mL; tds) or (2) Magnesium-aluminum antacid gel (oral; 15 mL; tds)	*Inclusion:* Pregnancy ≤ 36 wk Heartburn diagnosis *Total exclusion criteria:* 5	(1) Out-patient visit; hospital based ante-natal care clinic (2) Invited to participate	(1) Community setting (2) Ante-natal clinic visits	(1) Standard care; pharmacist to deliver interventions	Pre-treatment with 1 wk of diet modifications Usual care with set protocol	*Duration:* 2 wk *Adherence:* Daily diary 2 clinic visits *Patients excluded:* Poor compliance Improvement after 1 wk diet modifications	*Measurements:* Daily diary VAS symptom frequency: d 0, 14 VAS symptom severity: d 0, 14 OptumQoL Survey: d 0, 14 SF-12v2: d 0, 14 Maternal satisfaction survey: d 0, 14 *Follow up:* Until delivery	(1) Improvement of symptoms (2) QoL impact (3) Pregnancy & neonatal outcomes	n = 100 n analyzed = 100 *Patients excluded:* Poor compliance *Adverse events:* Checked

Table 1 (*Continued*)

Source: Author Year Country	Study Design	Interventions	Eligibility: *Who is selected to participate in the trial*	Recruitment: *How are participants recruited into the trial?*	Setting: *Where is the trial being done?*	Organization: *What expertise & resources are needed to deliver the intervention?*	Flexibility - delivery: *How should the intervention be delivered?*	Flexibility - adherence: *What measures are in place to make sure the participants adhere to the intervention?*	Follow-up: *How closely are participants followed-up?*	Outcome: *How relevant is it to participants? (1) Primary (2) Secondary*	Primary analysis: *To what extent are all data included?*
Mizuki et al. 2016 Japan	Multi center prospective randomized open label comparative study	(1) Rabeprazole (oral; 20 mg; daily) or (2) Rabeprazole (oral; 10 mg; bds)	*Inclusion:* Endoscopic defined PPI-refractory GERD GOS score >3 *Total exclusion criteria:* 12	(1) Patient visit; hospital or specialist community based clinic (2) Unspecified recruitment method	(1) Community setting (2) Clinic or hospital	(1) Specialist medical; esophagogas-troduo-denoscopy required	Usual care with set protocol	*Duration:* 8 wk *Adherence:* Weekly GOS scale Monthly survey 3 study site visits *Patients excluded:* Poor compliance	*Measurements:* GOS scale: d 0,714, 21, 28, 35, 42, 49, 56 PSQI: d 0, 28, 56 QoL survey; SF-8: d 0, 28, 56 *Follow-up:* 24 mo (median)	(1) Improvement of symptoms (2) Sleep quality (3) QoL impact	n = 88 n analyzed = 78 *Patients excluded:* (1) Poor compliance (2) AE (3) Withdrew consent *Adverse events:* Checked
Nie & Song 2015 China	Randomized controlled trial	(1) Zhizhu Kuanzhong capsules (oral; 3 capsules/time, 3 times/day) combined with Rabeprazole sodium enteric-coated tablets (oral; 20 mg/time, twice/day: morning and evening) (2) Mosapride citrate tablets (oral; 5 mg/time, 3 times/day) combined with Rabeprazole sodium enteric-coated tablets (oral; 20 mg/time, twice/day: morning and evening)	*Inclusion:* (1) Symptomatic GERD due to deficiency of spleen and stagnation of Qi - endoscopic confirmed (2) GERD questionnaire (GerdQ) score ≥8 (3) age: 18−65 years (4) participant's informed consent *Total exclusion criteria:* 16	Out-patients of a tertiary hospital	Unspecified	Unspecified	Unspecified	*Duration:* 8 weeks *Adherence:* N/A *Patients excluded:* None	*Measurements:* GerdQ score: week 0, 8 SF-36 questionnaire: week 0, 8 Syndrome of deficiency of spleen and stagnation of Qi rating scale: week 0, 8 *Follow-up:* Intervention free follow-up	(1) Improvement in symptoms	n = 100 n analyzed = 100 *Adverse events:* Unspecified

Table 1 (*Continued*)

Source: Author Year Country	Study Design	Interventions	Eligibility: *Who is selected to participate in the trial*	Recruitment: *How are participants recruited into the trial?*	Setting: *Where is the trial being done?*	Organization: *What expertise & resources are needed to deliver the intervention?*	Flexibility - delivery: *How should the intervention be delivered?*	Flexibility - adherence: *What measures are in place to make sure the participants adhere to the intervention?*	Follow-up: *How closely are participants followed-up?*	Outcome: *How relevant is it to participants?* *(1) Primary* *(2) Secondary*	Primary analysis: *To what extent are all data included?*
Ong et al. 2018 Singapore	Waitlist controlled cohort study	(1) Diaphragmatic breathing exercises; 30 min/d, 4x wk or (2) Waitlist group	*Inclusion:* Clinical or endoscopic diagnosed GERD or GERD refractory to PPI Belching VAS score > 6 *Total exclusion criteria: 5*	(1) Patient visit; Gastroenterology hospital clinic (2) Consecutive patients invited to participate	(1) Hospital gastroenterology clinic (2) Community setting	(1) Specialist medical; high resolution esophageal manometry, pH-impedance transnasal catheter (2) Specialist training for speech therapist	Usual care; participants maintained PPI with intervention Set protocol; 7 day wash-out period of GIT meds before study	*Duration:* 4 wk *Adherence:* Weekly clinic visits; 30 min breathing exercises Direct questioning, compliance to home exercises *Patients excluded:* Unspecified	*Measurements:* RDQ: d 0,28, 112 VAS: d 0, RQS: d 0, 28, 112 Qol VAS: d 0, 28, 112 HADS: d 0, 28, 112 Patient Health Questionnaire-15: d 0, 28, 112 *Follow-up:* 4 mo	(1) Improvement in belching VAS $\geq$ 50%	n = 36 n analyzed = 36 *Patients excluded:* None specified *Adverse events:* Unspecified
Oshima et al. 2018 Japan	Two-center randomized double-blind parallel-group comparative	(1) Vonoprazan (oral; 20 mg; daily) or (2) Lansoprazole (oral; 30 mg; daily)	*Inclusion:* 2 factor Grade A - D Erosive esophagitis diagnosis & Heartburn *Total exclusion criteria:* 13	(1) Out-patients visit to hospital (2) Physicians invited patients to participate	(1) Community setting (2) Hospital setting	(1) Specialist medical; endoscopy required blood sample physical examination	Usual care with set protocol	*Duration:* 2 wk *Adherence:* Daily diary 2 study site visits *Patients excluded:* Poor compliance	*Measurements:* Daily diary FSSG: d 0,714 PSQI: d 0, 14	(1) Improvement of symptoms (2) Complete heartburn relief for 7 consecutive days	n = 32 n analyzed = 32 *Patients excluded:* Non-compliance
Panahi et al. 2015 Iran	Randomized open-label positive-controlled	(1) Aloe vera syrup (oral; 10 mL; tds) or (2) Omeprazole; (oral; 20 g; tds) or (3) Ranitidine; (oral; 150 mg; bds)	*Inclusion:* GERD diagnosis *Total exclusion criteria: 16*	(1) Patient hospital visit to endoscopy ward; (2) Unspecified recruitment method	(1) Community setting	Unspecified	Usual care with set protocol	*Duration:* 4 wk *Adherence:* 3 study site visits *Patients excluded:* Dropped out due to AE	*Measurements:* RDQ: d 0, 14, 28 *Follow-up:* Unspecified	(1) Improvement of symptoms	n = 79 n analyzed = 75 *Patients excluded:* Dropped out due to AE *Adverse events:* Reported
Panahi et al. 2016 Iran	Randomized open-label	(1) Aloe vera syrup (oral; 5 mL; bds) & Pantoprazole; (oral; 40 g; daily) or (2) Pantoprazole; (oral; 40 g; daily) or (3) Ranitidine; (oral; 150 mg; bds)	*Inclusion:* GERD diagnosis GERD symptoms Mustard gas exposure > 40 years old Male *Total exclusion criteria:* 14	(1) Patient hospital visit to lung clinic; (2) Unspecified recruitment method	(1) Community setting (2) Hospital setting	Usual care with set protocol	Usual care with set protocol	*Duration:* 6 wk *Adherence:* 3 study site visits *Patients excluded:* Not taking study meds for more than 1 wk	*Measurements:* RSI: d 0, 21, 42 *Follow-up:* Unspecified	(1) Improvement of symptoms	n = 85 n analyzed = 75 *Patients excluded:* Non-compliance *Adverse events:* Reported

Table 1 (*Continued*)

Source: Author Year Country	Study Design	Interventions	Eligibility: *Who is selected to participate in the trial*	Recruitment: *How are participants recruited into the trial?*	Setting: *Where is the trial being done?*	Organization: *What expertise & resources are needed to deliver the intervention?*	Flexibility - delivery: *How should the intervention be delivered?*	Flexibility - adherence: *What measures are in place to make sure the participants adhere to the intervention?*	Follow-up: *How closely are participants followed-up?*	Outcome: *How relevant is it to participants? (1) Primary (2) Secondary*	Primary analysis: *To what extent are all data included?*
Saifullah et al. 2018 Bangladesh	Single-centre Prospective open label non-random consecutive experimental study	(1)Omeprazole; (oral;20 mg;daily) Or (2) Alginate (oral;10 mL;tds)	*Inclusion:* (1)Symptomatic NERD - NERD diagnosis (2) Endoscopic confirmed (3) age: >18 (4) Participants informed consent *Total exclusion criteria:* 18	(1) Out-patient visit; Dept. Gastroenterology	(1) Unspecified	(1) Specialist medical: endoscopy required to exclude erosive GERD & other pathology	Usual care with set protocol	*Duration:* 14 days *Adherence:* 2 clinic visits *Patients excluded:* None	*Measurement:* Symptom assessment questionnaire: d 0, 14 Patient satisfaction assessment: d 14	(1)Improvement of symptoms (2)Patient satisfaction	n = 60 n analyzed = 60 *Adverse events:* No serious adverse events
Sakurai et al. 2018 Japan	Multi-center randomized open-label parallel group	(1) Esomeprazole (oral; 20 mg; daily) or (2) Vonoprazan (oral; 20 mg; daily)	*Inclusion:* 3 factor GERD diagnosis *Total exclusion criteria:*18	1) Patient visit to hospital or specialist community based clinic; (2) Unspecified recruitment method	(1) Community setting (2) 2 trial site visits	(1) Specialist medical; endoscopy required	Usual care with set protocol	*Duration:* 4 wk *Adherence:* 4 clinic visits *Patients excluded:* Dropped out due to improvement Non-compliance	*Measurement:* 15 PRO questionnaires: d 0, 1, 3, 7, 14, 28 *Follow up:* Nil	(1) Improvement of symptoms (2) Complete resolution (3) QoL impact	n = 60 n analyzed = 47 *Patients excluded:* (1) Self-elected to discontinue due to improvement (2) Non-compliant *Adverse events:* Checked
Senay et al. 2016 Turkey	Single-center prospective randomized double-blind controlled trial	(1) Ranitidine (IV infusion; 50 mg) or (2) Pantoprazole (IV infusion; 40 mg)	*Inclusion:* Epigastric pain VAS score over 20 mm *Total exclusion criteria:* 6	(1) In-patients; ED hospital (2) Presented at ED, consecutive enrolment, attending physicians decided eligibility	(1) ED hospital setting	Usual care with set protocol	IV intervention, set delivery	*Duration:* 60 min *Adherence:* NA; IV Drug therapy *Patients excluded:* NA; IV Drug therapy	*Measurement:* VAS; 30 min, 60min *Follow-up:* Unspecified	(1) Improvement in symptoms	n = 72 n analyzed = 68 *Patients excluded:* Different diagnosis from dyspepsia at end of study *Adverse events:* Checked
Setright R 2017 Australia	Multi-center observational study	(1) Formula 1 (*ulmus fulva, metha piperita*) (oral; 12 g) or (2) Formula 2 (U*lmus fulva, Metha piperita, Glycyrrhiza gabra)* (oral; 12 g)	*Inclusion:* Duration condition ≥ 6 mo: Gastric reflux, Unspecified epigastric pain, Gastric ulcer, Duodenal ulcer, IBS, Crohns disease *Total exclusion criteria:* 2	(1) Patient visit; community based clinics (2) Recruited from clinic	(1) Community setting (2) Clinic setting	Usual care	(1) Usual care delivery (2) Flexible; frequency dose duration	*Duration:* 24 mo *Adherence:* None specified *Patients excluded:* None specified	*Measurement:* Unvalidated PRO questionnaire: d 1, 730 *Follow up:* Unspecified	(1) Improvement of symptoms; compare efficacy of two herbal interventions	n = 59 n analyzed = 58 *Patients excluded:* (1) None *Adverse events:* Unspecified

Table 1 (*Continued*)

Source: Author Year Country	Study Design	Interventions	Eligibility: *Who is selected to participate in the trial*	Recruitment: *How are participants recruited into the trial?*	Setting: *Where is the trial being done?*	Organization: *What expertise & resources are needed to deliver the intervention?*	Flexibility - delivery: *How should the intervention be delivered?*	Flexibility - adherence: *What measures are in place to make sure the participants adhere to the intervention?*	Follow-up: *How closely are participants followed-up?*	Outcome: *How relevant is it to participants? (1) Primary (2) Secondary*	Primary analysis: *To what extent are all data included?*
Shakeri et al. 2018 Iran	Two-phase randomized active-controlled open-label parallel group	(1) Ranitidine (oral; 150 mg; bds) or (2) Quince sauce (oral; 10 mg; tds)	*Inclusion:* Pregnant 12−34 wk, Non-responsive to 2 wk of lifestyle modifications, 1 symptom GERD ≥ 1x wk, Duration ≥ 4 wk, Pregnancy heartburn *Total exclusion criteria: 9*	(1) Outpatient; community based clinic (2) Unspecified recruitment method	(1) Community setting (2) Clinic setting	Usual care; GP delivery intervention	(1) Usual care delivery (2) Pre-treatment of 2 wk lifestyle modifications	*Duration:* 4 wk *Adherence:* 3 clinic visits *Patients excluded:* Responders to pre-treatments 2 wk lifestyle modifications Non-compliance	*Measurements:* GSS: d 0, 14, 28 MSS: d 0, 14, 28 *Follow-up:* Unspecified	(1) Improvement of symptoms	n = 137 n analyzed = 120 *Patients excluded:* (1) Lost to follow-up (2) Non-compliance (3) Self-elected to discontinue (AE, symptomatic worsening) *Adverse events:* Checked
Shen et al. 2014 China	Randomized controlled trial	(1) Azintamide (oral; 2 tablets /time after meal; 3 times/day) combined with Itopride hydrochloride (1 tablet/time 30 min. before meal, 3 times/day) (2) Azintamide (oral; 2 tablets /time after meal; 3 times/day)	Inclusion: Symptomatic functional dyspepsia - endoscopic confirmed *Total exclusion criteria:* N/A	Out patients visit; Dept. Gastroenterol-ogy	Unspecified	Unspecified	Unspecified	*Duration:* 2 wk *Adherence:* N/A *Patients excluded:* None	*Measurements:* Abdominal distension score: d 0, 14 *Follow-up:* Intervention free follow-up	(1) Improvement in abdominal distension	n = 80 n analyzed = 80 *Adverse events:* Unspecified
Singh et al. 2015 India	Prospective randomized open-label three parallel group comparative study	(1) Levosulpiride (oral; 15 mg; tds) or (2) Domperidone (oral; 10 mg; tds) or (3) Metoclo-pramide (oral; 10 mg; tds)	*Inclusion:* Rome III FD Symptomatic presentation *Total exclusion criteria: 8*	(1) Outpatient visit; teaching hospital (2) Recruitment; medicine outpatient dept.	(1) Community setting (2) Medicine outpatient department	Specialist medical: Clinical evaluation Blood tests ECG	(1) Usual care delivery (2) Wash-out period of 2 wk (3) No smoking or alcohol during study	*Duration:* 4 wk *Adherence:* 2 site visits *Patients excluded:* Unspecified	*Measurements:* SF-LDQ: d 0, 28 Blood tests: d 0, 28 12-lead ECG: d 0, 28 *Follow-up:* Unspecified	(1) Improvement of symptoms	n = 120 n analyzed = 113 *Patients excluded:* (1) Lost to follow-up *Adverse events:* Checked

Table 1 (*Continued*)

Source: Author Year Country	Study Design	Interventions	Eligibility: *Who is selected to participate in the trial*	Recruitment: *How are participants recruited into the trial?*	Setting: *Where is the trial being done?*	Organization: *What expertise & resources are needed to deliver the intervention?*	Flexibility - delivery: *How should the intervention be delivered?*	Flexibility - adherence: *What measures are in place to make sure the participants adhere to the intervention?*	Follow-up: *How closely are participants followed-up?*	Outcome: *How relevant is it to participants? (1) Primary (2) Secondary*	Primary analysis: *To what extent are all data included?*
Sri Roja et al. 2017 India	Prospective randomized open-label comparative	(1) Ilaprazole (oral; 1st 5 mg, 2nd 10 mg) or (2) Omeprazole (oral; 20 mg; daily)	*Inclusion:* In-patients Acid peptic disease: Peptic ulcer Duodenal ulcer GERD Gastritis *Total exclusion criteria:* 5	(1) Inpatient visit; Hospital (2) Patients requiring care	(1) Community setting	Usual care	Usual care	*Duration:* 4 wk *Adherence:* 2 clinic visits *Patients excluded:* Unspecified	*Measurements:* Customized data collection sheet: d 0 SF-12 Questionnaire: d 28 *Follow-up:* Unspecified	(1) Improvement of symptoms; compare efficacy of interventions	n = 100 n analyzed = 100 *Patients excluded:* (1) None specified *Adverse events*: Checked
Takenaka et al. 2016 Japan	Randomized multi-center (15) phase III controlled study	(1) Lafutidine (oral; 10 mg, bds) or (2) Lansoprazole (oral; 30 mg; daily)	*Inclusion:* GERD symptoms; (≥ 3 on ques 2 or 3; GSRS) with endoscopy confirmed; Grade A reflux esophagitis *Total exclusion criteria: 13*	(1) Hospital community based clinic (2) Unspecified recruitment method	(1) Community setting (2) Hospital clinic	Specialist medical; endoscopy, physical exam, blood tests	Usual care with set protocol Phase 2: Flexible dose	*Duration:* 32 wk *Adherence:* 6 clinic visits Daily diary; 8wk *Patients excluded:* Concomitant GIT drugs	*Measurements:* GSRS: d 0 to 56, wk 16, 24, 32 (unclear) VAS: d 0 to 56, wk 16, 24, 32 (unclear) *Follow-up:* Unspecified	(1) Improvement in symptoms (2) Improvement in satisfaction score	Phase 1: n = 53, n analyzed = 45 Phase 2: n = 45, n analyzed = 23 *Patients excluded:* (1) Withdrew consent (2) Lost to follow-up *Adverse events:* Checked
Toseef et al. 2015 Pakistan	Multi center (3) randomized case control	(1) *Pepsil (herbal)* (oral; 2 g, bds) or (2) *Safoof-e-Katira (herbal)* (oral; 2 g; bds) or (3) *Omeprazole* (oral; 20 mg; bds)	*Inclusion:* Chronic GERD Lived locally aged 15–55 yr *Total exclusion criteria: 3*	(1) Outpatient visit; hospital or specialist community based clinic (2) Participants were selected	(1) Community setting (2) Specialist clinic	Usual care Researcher	Usual care with set protocol	*Duration:* 8 wk *Adherence:* 2 clinic visits *Patients excluded:* Non-compliant	*Measurements:* Unvalidated trial data sheet; d 0 completed by participant under supervision d 56 completed by physician after assessment *Follow-up:* Unspecified	(1) Improvement of symptoms (2) Heartburn free days	n = unspecified n analyzed = 100 *Patients excluded:* None specified *Adverse events:* Unspecified

Table 1 (*Continued*)

Source: Author Year Country	Study Design	Interventions	Eligibility: *Who is selected to participate in the trial*	Recruitment: *How are participants recruited into the trial?*	Setting: *Where is the trial being done?*	Organization: *What expertise & resources are needed to deliver the intervention?*	Flexibility - delivery: *How should the intervention be delivered?*	Flexibility - adherence: *What measures are in place to make sure the participants adhere to the intervention?*	Follow-up: *How closely are participants followed-up?*	Outcome: *How relevant is it to participants? (1) Primary (2) Secondary*	Primary analysis: *To what extent are all data included?*
Vedamanickam et al. 2017 India	Double-blind Randomized controlled trial	(1) *Rabeprazole* (oral; 20 mg; daily) or (2) *Omeprazole* (oral; 20 mg; daily)	*Inclusion:* Symptomatic GERD Endoscopic diagnosed Erosive or non-erosive esophagitis *Total exclusion criteria:* 10	(1) Patient visit; medical college at hospital (2) Unspecified recruitment method	(1) Community setting (2) Medical college at hospital	Specialist medical; endoscopy required	Usual care with set protocol of daily delivery for 1 mo, followed by intermittent delivery 4x wk for 6 mo On demand antacid therapy permitted as required	*Duration:* 7 mo *Adherence:* 3 study site visits *Patients excluded:* Refusal of endoscopy	*Measurements:* Clinical severity symptom score: d 0, 28, 196 *Follow-up:* Unspecified	(1) Improvement in symptoms (2) Reduce rate of *h.pylori* infection	n = 60 n analyzed = unspecified *Patients excluded:* None specified *Adverse events:* Reported
Wang et al. 2014 China	Randomized single-center controlled trial	(1) Esomeprazole (oral; 20 mg; bds) & Mosapride (oral; 10 mg; tds) or (2) Esomaprazole (oral; 10 mg; tds)	*Inclusion:* GERD diagnosis Internal Medicine 7th Ed criteria Heartburn occurred within 4 wk of enrolment *Total exclusion criteria:* 9	(1) Inpatients visit; Gastroenterology Dept (2) Unspecified recruitment method	(1) Hospital setting	(1) Specialist medical; peristalsis amplitude of the esophagus, lower esophageal sphincter resting pressure, endoscopic rapid urease test to detect *h.pylori*,	Usual care with set protocol Lifestyle modifications: stop smoking, alcohol & strong tea	*Duration:* 8 wk *Adherence:* 4 clinic visits *Patients excluded:* Unspecified	*Measurements:* GERD-Q: d 0, 14, 28, 56 Physician: Endoscopy score: d 0, 56 *h.pylori* test: d 0, 56 *Follow-up:* Unspecified	(1) Improvement in symptoms (2) Reduce rate of h.pylori infection	n = 116 n analyzed = unspecified *Patients excluded:* None specified *Adverse events:* Unspecified
Wilkie et al. 2018 United Kingdom	Non-randomized comparator	(1) Gaviscon Advance (oral; 10 mL, qds) or (2) *Gaviscon Advance* (oral; 10 mL, qds) & [*Lansoprazole (oral;* 30 mg, bds) or *Omeprazole* (oral; 20 mg, bds)]	*Inclusion:* LPR symptoms RSI score $\geq$ 10 *Total exclusion criteria:* unspecified	(1) Patients visit; specialist community clinic (2) Consecutive patients	(1) Community setting	Usual care	Usual care Previous PPI use was continued Additional guidance; lifestyle, vocal, hygiene, psychological factors	*Duration:* 3 mo *Adherence:* 1 clinic visit Postal questionnaire at 3 mo *Patients excluded:* Non-responders	*Measurements:* PRO RSI: d 0, 84 *Follow-up:* Unspecified	(1) Improvement in symptoms	n = 100 n analyzed = 72 *Patients excluded:* Death Non-responders Withdrew consent *Adverse events:* Unspecified

Table 1 (*Continued*)

Source: Author Year Country	Study Design	Interventions	Eligibility: *Who is selected to participate in the trial*	Recruitment: *How are participants recruited into the trial?*	Setting: *Where is the trial being done?*	Organization: *What expertise & resources are needed to deliver the intervention?*	Flexibility - delivery: *How should the intervention be delivered?*	Flexibility - adherence: *What measures are in place to make sure the participants adhere to the intervention?*	Follow-up: *How closely are participants followed-up?*	Outcome: *How relevant is it to participants?* *(1) Primary* *(2) Secondary*	Primary analysis: *To what extent are all data included?*
Yamaji et al. 2014 Japan	Prospective randomized open-label controlled trial	(1) *Mosapride* (oral; 5 mg, tds) with *Omeprazole* (oral; 10 mg; daily) or (2) *Omeprazole* (oral; 10 mg; daily)	*Inclusion:* Reflux symptoms ≥ 2x wk *Total exclusion criteria: 14*	(1) Patients visit; Dept. Gastroenterology University (2) Invited to participate	(1) Community setting (2) Unspecified follow-up site	(1) Specialist medical; endoscopy within 3 mo before enrolment, blood tests physical examination	Usual care Set protocol	*Duration:* 4 wk *Adherence:* 2 study site visit Counting meds *Patients excluded:* Non-compliance ≤ 90%	*Measurements:* PRO FSSG score: d 0, 28 GSRS: d 0, 28 *Follow-up:* Unspecified	(1) Improvement in symptoms	n = 60 n analyzed = 50 *Patients excluded:* Lost to follow-up Withdrew consent Discontinued due to SA Non-compliance *Adverse events:* Unspecified
Yang 2014 China	Randomized controlled trial	(1) Mosapride (oral; 5 mg/time, 3 times/day, 30 min. before meal) combined with Pantoprazole sodium entericcoated tablets (oral; 40 mg/time, once/day, before breakfast) (2) Mosapride (oral; 5 mg/time, 3 times/day, 30 min. before meal)	*Inclusion:* (1) Symptomatic functional dyspepsia – endoscopic confirmed and pathology tests confirmed (2) age: 18−70 years *Total exclusion criteria:* 12	(1)In-patients and out-patients of Dept. Gastroenterology	Unspecified	Unspecified	Lifestyle modification (e.g. no smoking and alcohol drinking), no non-steroidal anti-inflammatory drugs, balanced diet rich in vitamin, individual psychological counselling	*Duration:* 4 wk *Adherence:* 6-month follow-up (location unspecified) *Patients excluded:* None	*Measurements:* Relapse rate: month 2, 4, 7 Functional digestive disorder quality of life questionnaire (FDDQL) score: month 2, 4, 7	(1) Improvement in symptoms (2) side effects	n = 149 n analyzed = 149 *Adverse events:* diarrhea, rash, dizziness, insomnia (both groups)

Table 1 (*Continued*)

Source: Author Year Country	Study Design	Interventions	Eligibility: *Who is selected to participate in the trial*	Recruitment: *How are participants recruited into the trial?*	Setting: *Where is the trial being done?*	Organization: *What expertise & resources are needed to deliver the intervention?*	Flexibility - delivery: *How should the intervention be delivered?*	Flexibility - adherence: *What measures are in place to make sure the participants adhere to the intervention?*	Follow-up: *How closely are participants followed-up?*	Outcome: *How relevant is it to participants? (1) Primary (2) Secondary*	Primary analysis: *To what extent are all data included?*
Yang et al. 2015 China	Randomized controlled trial	(1) Banxia Xiexin Decoction combined with Sini Powder (total: 14 herbs, herbs added or eliminated if symptom changed) (oral; 1 decoction/day, twice/day) (2) Omeprazole (oral; 20 mg/time before breakfast, once/day) combined with Domperidone (oral; 10 mg/time, 3 times/day)	*Inclusion:* (1) Symptomatic flux esophagitis - endoscopic confirmed (2) age: 20–65 years (3) no proton pump inhibitors or H_2 receptor blockers taken 2 weeks prior to the study (4) participant's informed consent *Total exclusion criteria:* 10	In-patients and out-patients of Dept. Chinese medicine	Unspecified	Unspecified	Lifestyle modification, including no smoking and alcohol drinking, no cold food, maintenance of emotional stability, avoiding food that deteriorates gastroe-sophageal reflux	Duration: 3 months Adherence: 6-month follow-up (endoscopic examination every month within these 6 months) *Patients excluded:* None	Measurements: Endoscopic observation: months 4–9 recurrence rate: months 4–9 *Follow-up:* Intervention free follow-up	1. Improved Chinese medicine symptom score (self-determined criteria)	n = 139 n analyzed = 139 *Adverse events:* Unspecified

Table 1 (*Continued*)

Source: Author Year Country	Study Design	Interventions	Eligibility: *Who is selected to participate in the trial*	Recruitment: *How are participants recruited into the trial?*	Setting: *Where is the trial being done?*	Organization: *What expertise & resources are needed to deliver the intervention?*	Flexibility - delivery: *How should the intervention be delivered?*	Flexibility - adherence: *What measures are in place to make sure the participants adhere to the intervention?*	Follow-up: *How closely are participants followed-up?*	Outcome: *How relevant is it to participants? (1) Primary (2) Secondary*	Primary analysis: *To what extent are all data included?*
Ye & Wei 2015 China	Randomized controlled trial	(1) Electro-acupuncture (needle insertion; 6 acupoints. No other information provided) combined with Immature Bitter Orange Chest Draining Decoction (7 herbs. oral; 300 mL/time 30 min. before breakfast and dinner, twice/day) (2) Omeprazole (oral; 20 mg/time before breakfast, once/day) and Domperidone 20 mg (oral; 20 mg/time 30 min. before meal, 3 times/day)	Inclusion: Symptomatic gastroe-sophageal reflux disease due to heat stagnation of the liver and stomach (no details) Total exclusion criteria: N/A	A Chinese medicine hospital	Unspecified	Unspecified	Unspecified	Duration: 30 days Adherence: N/A Patients excluded: None	New Chinese Medicine Clinical Guideline criteria: d 0, 30 Follow-up: Intervention free follow-up	(1) Improvement in symptoms (2) Gastroscopy confirmation	n = 60 n analyzed = 60 Adverse events: Unspecified

Table 1 (*Continued*)

Source: Author Year Country	Study Design	Interventions	Eligibility: *Who is selected to participate in the trial*	Recruitment: *How are participants recruited into the trial?*	Setting: *Where is the trial being done?*	Organization: *What expertise & resources are needed to deliver the intervention?*	Flexibility - delivery: *How should the intervention be delivered?*	Flexibility - adherence: *What measures are in place to make sure the participants adhere to the intervention?*	Follow-up: *How closely are participants followed-up?*	Outcome: *How relevant is it to participants? (1) Primary (2) Secondary*	Primary analysis: *To what extent are all data included?*
Zhang et al. 2017 China	Randomized controlled trial	(1) Oryz-Aspergillus Enzyme and Pancreatin Tablet (oral; 1 tablet/time during meal, 3 times/day) (2) Domperidone Tablet (oral; 1 tablet/time after meal, 3 times/day) (3) Esomeprazole Magnesium Enteric-coated Tablet (oral; 1 tablet/time before meal, once/day)	Inclusion: (1) symptomatic helicobacter pylori negative functional dyspepsia (2) the symptoms occurred 6 months prior to the diagnosis Total exclusion criteria: 5	Out-patients of a tertiary hospital	Unspecified	Unspecified	No other drugs that can affect the effect of these treatments during treatment	Duration: 4 weeks Adherence: N/A Patients excluded: None	Measurements: Dyspeptic symptoms severity: d 1, 28 Follow-up: Intervention free follow-up	(1) Improvement in symptoms (2) adverse events	n = 82 n analyzed = 82 Adverse events: Unspecified
Zohalinezhad et al. 2016 Iran	Double-blind randomized controlled trial	(1) *Myrtus communis L.* (oral; 1000 mg, daily) or (2) *Omeprazole* (oral; 20 mg; daily) or (3) *Myrtus communis L.* (oral; 1000 mg, daily) with *Omeprazole* (oral; 20 mg; daily)	*Inclusion:* Symptomatic GERD Endoscopic confirmed T*otal exclusion criteria: 21*	(1) Out-patients visit; Dept. Gastroenterology (2) Referred by gastroenterologist	(1) Community setting (2) Medical college at hospital	(1) Specialist medical; endoscopy required, gastroenterologist	Usual care with 2 wk screening period with endoscopy Set protocol	*Duration:* 6 wk *Adherence:* 1 study site visit + phone call or 2 study site visits *Patients excluded:* Unspecified	*Measurements:* FSSG score: d 0, 28 GSRS: d 0, 28 *Follow-up:* Intervention free follow-up	(1) Improvement in symptoms	n = 45 n analyzed = 42 *Patients excluded:* Lost to follow-up Withdrew consent *Adverse events:* Unspecified

Acu, acupuncture; AE, adverse effects; AR, adverse reactions; AT, Acupuncture Treatment; BDI, Beck Depressive Inventory; bds, twice daily; BMI, Body Mass Index; CSR, Complete Symptom Resolution; DSSS, dyspeptic symptom sum score; ECG, electrocardiogram; ED, emergency department; FD, functional dyspepsia; FD-QOL, Functional Dyspepsia-Related Quality of Life; FSSG, Frequency Scale for the Symptoms of GERD; GERD, gastroesophageal reflux disease; GERD-Q, Gastroesophageal Reflux Disease Questionnaire; GIT, gastrointestinal tract; GP general practitioner; GOS, Global Overall Symptom; GSRS, Gastrointestinal Symptom Rating Scale; GSS, General Symptom Score; HADS, Hospital Anxiety and Depression Scale; h.pylori, helicobacter pylori; IV, intravenous; LPR, laryngopharyngeal reflux; MSS, Major Symptom Score; NA, not applicable; NDI, Nepean Dyspepsia Index; NDI-K, Nepean dyspepsia index - Korean; OTE, overall treatment effect; PPI, proton pump inhibitor; PRO, patient reported outcomes; PSQI, Pittsburgh Sleep Quality Index; QoL, quality of life; RDQ, Reflux Disease Questionnaire; RQS, Reflux Quality Score; RSI, reflux symptom index; SAS, Self-Rating Anxiety Scale; SDS, Self-Rating Depression Scale; SF-12, Short Form 12 Health Survey; SF-LDQ, Short-Form Leeds Dyspepsia Questionnaire; STAI, State-Trait Anxiety Inventory; tds, three times daily; qad, every other day; qds, four times daily; VAS, visual analogue scale.

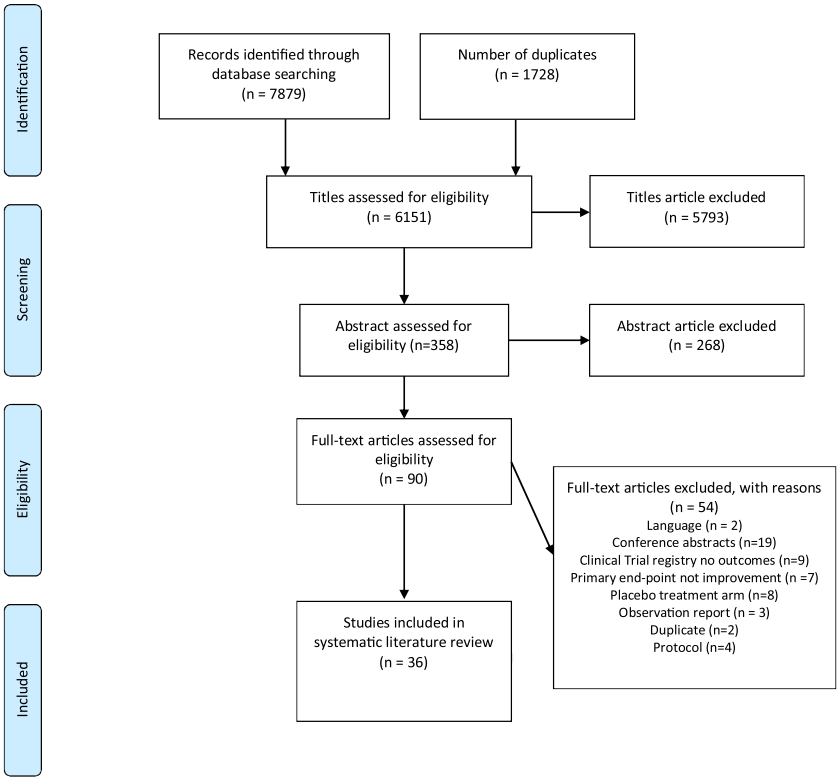

Fig. 1. Preferred Reporting Items for Systematic reviews and Meta Analyses (PRISMA) flow diagram. Starting with 7879 citations identified in the database, 36 articles were included in the final systematic literature review.

Syndrome (IBS), GIT conditions, GIT surgery, lifestyle, medications and others (Table 2). The number of defined items listed within each category is identified. Details of exclusions categorized as 'other' are stated in the comments section.

2.8. Evaluation of studies against PRECIS-2 domains

As the focus for this review is to explore design characteristics of comparative effectiveness trials for symptomatic dyspepsia and not their clinical decision; the risk of bias was not assessed. Instead, an appraisal was conducted utilizing the PRECIS-2 tool (Table 3).[26] Although this tool was originally designed to assist in the construction of trials, more recently it has been used as a tool for assessment of trial design characteristics.[19,27,28] Furthermore, evaluation of studies against PRECIS-2 domains may uncover significant, domain specific factors and highlight important subgroup considerations, relevant for future comparative effectiveness research design.[19,27] The methodology for the appraisal process followed previous published research.[19] A phase of calibration to ensure consistency in scoring across each PRECIS-2 domain occurred between the three researchers (NE, BL and AS) before commencement. A score of over three was classified as a pragmatic approach using an approach adopted by previous research.[26,27] A domain score was left blank if there was insufficient information in the article to inform the scoring process.

3. Results

Primary search returned 7879 articles (Fig. 1). After excluding duplicates (n = 1728), 6151 studies were screened by title / abstracts and 90 articles selected for further assessment. Of those articles, 54 were excluded: symptomatic dyspepsia improvement was not the primary endpoint (n = 7), study protocol (n = 4), registered clinical trials with no stated outcomes (n = 9), conference abstracts (n = 19), placebo treatment arm (n = 8), observation report (n = 3), duplicate (n = 2) and translation with the web-based interface; 'Google Translation', was unsuccessful (n = 2).[29,30]

3.1. Study characteristics

Table 1 shows extracted data from the 36 studies. Thirty two were randomised and[31–62] thirteen studies were open-label.[33,36,38,40,42–44,46–48,53,63,64] The sample size ranged from 32 to 464 participants (mean = 98). One study did not list the sample size and the author has been contacted.[33] Two studies were on pregnant women.[39,46] Included studies were conducted across 14 countries within the following World Health Organisation regions: Eastern Mediterranean (n = 7),[31,34,42,43,46,50,54] Western-Pacific region (n = 20),[35,36,38–41,44,49,52,53,55–61,62,63,65] South-East Asia (n = 6)[32,39,47,48,51,64] and Europe (n = 3).[33,45,66] Treatment duration ranged from one day[45] to 24 months[63] (mean = 50 days). Nineteen studies employed complementary medicine interventions; plant medicines (n = 11),[31,32,34,42,43,46,50,54,57,60,63] acupuncture (n = 5),[35,37,55,56,61] breathing exercises (n = 2)[33,65] and digestive enzymes (n = 1).[62]

3.2. PRECIS-2 Eligibility – who is selected to participate in the trial

Many participants were required to pass one or more gastrointestinal inclusion criteria assessments; endoscopy (n = 23),[31–36,38,40,41,44,49,51–60,64,65] Rome diagnostic criteria for Functional Dyspepsia (FD) (n = 8),[31–37,47] gastrointestinal symptom score patient questionnaires (n = 10)[37,38,40,44,45,49,57,64–66] and / or biological measurements (n = 7).[33,35,52,55,56,59,65] Two studies required participants to be pregnant.[39,46] Six studies required participants to be under 66 years of age (n = 9).[31,43,48,50,54,56,57,60,65]

There were 390 reported eligibility exclusion criteria across the studies (mean = 11). These are categorised and summarized in

Table 2
Categorized analysis of the reported eligibility exclusion criteria per study.

Source	Country	Alarm features	Co-morbidities	Contra-indications to treatment	Demographic	IBS	GIT conditions excluding IBS	GIT surgery	Lifestyle factors	Medications	Other	Total categories for exclusion	Comments
Azimi et al. 2017	Iran	1	3	–	3	1	5	3	1	2	–	19	History of reflux disease excluded
Choi et al. 2015	Korea	–	2	–	3	1	6	1	1	4	–	18	Participants with primary symptom as heart-burn excluded
Eherer 2014	Austria	–	–	1	–	–	1	–	–	–	–	2	–
Hosseini et al. 2018	Iran	–	6	–	1	1	3	–	1	1	–	13	Excluded if history of smoking
Jin et al. 2015	China	–	2	–	3	–	–	–	–	4	–	9	–
Kamiya et al. 2017	Japan	–	8	2	3	–	–	1	1	3	1	19	Other: alcohol or substance abuse
Ko et al. 2016	Korea	3	12	–	2	1	2	–	–	1	4	25	Other: excluded for GERD, maldigestion or malabsorption
Liang et al. 2017	Taiwan	–	3	1	2	–	1	1	–	1	–	9	GIT conditions: peptic ulcer disease
Li & Bai 2018	China	9	6+	–	–	–	5	2	–	–	–	22	Part of the co-morbidities were described as 'Serious heart, lung, kidney, pancreas, liver and nervous system diseases'
Liu et al. 2017	China	7	8+	–	–	–	–	–	–	–	–	15	Part of the co-morbidities were described as 'severe heart, liver, kidney, endocrine and blood diseases' and 'progressive cancer'
Meteerattanapipat & Phupong 2017	Thailand	–	–	2	2	–	–	–	–	–	1	5	Other: participants required to undergo 7 day lifestyle modifications, symptom improvement led to exclusion
Mizuki et al. 2016	Japan	–	3	1	4	–	2	1	–	1	–	12	Participant undergone *h.pylori* TMT prior 3 months were excluded
Nie & Song 2015	China	5	8+	–	–	–	3	–	–	–	–	16	Part of the co-morbidities were described as 'severe heart, liver, kidney, endocrine and blood diseases'
Ong et al. 2018	Singapore	–	2	–	2	–	–	1	–	–	–	5	–

Table 2 (*Continued*)

Source	Country	Alarm features	Co-morbidities	Contra-indications to treatment	Demographic	IBS	GIT conditions excluding IBS	GIT surgery	Lifestyle factors	Medications	Other	Total categories for exclusion	Comments
Oshima et al. 2018	Japan	–	2	2	1	–	2	1	–	4	1	13	Other: abnormal lab values
Panahi et al. 2015	Iran	2	3	1	3	1	4	–	–	1	1	16	GIT conditions: malnutrition syndrome Other: TMT resistant GERD
Panahi et al. 2016	Iran	2	3	1	3	1	2	–	–	1	1	14	Required to be participating in another study or excluded
Saifullah et al. 2018	Bangladesh	–	3	1	2	–	7	–	–	4	1	18	Other: debilitated patient
Sakurai et al. 2018	Japan	–	5	1	1	–	8	1	–	4	–	20	Exclude: acute gastritis with current use of antacids; study required discontinuation GIT meds 8wks prior to onset
Senay et al. 2016	Turkey	–	–	2	2	–	–	–	–	1	1	6	–
Setright R 2017	Australia	–	–	–	–	–	–	–	–	2	–	2	–
Shakeri et al. 2018	Iran	–	1	2	1	–	1	–	3	–	1	9	Excluded if history of heartburn prior to pregnancy Other; high risk pregnancy
Shen et al. 2014	China												Unspecified
Singh et al. 2015	India	–	3	1	3	–	1	–	–	–	–	8	Excluded; history of peptic ulcer

Table 2 (*Continued*)

Source	Country	Alarm features	Co-morbidities	Contra-indications to treatment	Demographic	IBS	GIT conditions excluding IBS	GIT surgery	Lifestyle factors	Medications	Other	Total categories for exclusion	Comments
Sri roja et al. 2017	India	–	–	1	3	–	1	–	–	–	–	5	Exclude; complex ulcer
Takenaka et al. 2016	Japan	–	4	1	1	–	3	1	–	2	1	13	Other; conditions considered unsuitable for participation
Toseef et al. 2015	Pakistan	–	3	–	–	–	–	–	–	–	–	3	–
Vedamanickam et al. 2017	India	–	6	–	2	–	1	–	–	2	–	10	Exclude GIT conditions; known gastric or duodenal ulcer on long-term PPI
Wang et al. 2014	China	–	2	1	1	–	2	1	–	2	–	9	
Wilkie et al. 2018	United Kingdom	–	–	–	–	–	–	–	–	–	–	–	Exclusions not specified
Yamaji et al. 2014	Japan	–	3	–	3	–	1	1	2	3	1	14	Other; abnormal lab values Exclude; history of peptic ulcer diseases
Yang 2014	China	2	4+	4+	–	–	–	2	–	–	–	12	Did not specify all co-morbidities and conditions contra-indications to treatment
Yang et al. 2015	China	2	7+	–	–	–	–	–	–	–	1	10	Did not specify all co-morbidities Other: participation in another drug trial within 3 months
Ye & Wei 2015	China												Unspecified
Zhang et al. 2017	China	1	2	–	–	–	1	1	–	–	–	5	
Zohalinezhad et al. 2016	Iran	–	5	2	4	–	3	1	–	3	3	21	Other; (1) Significant abnormal lab findings (2) Acute childhood illness (3) Participation in another drug trial
Total:		**8**	**81**	**22**	**53**	**6**	**49**	**14**	**9**	**42**	**16**	**299**	

Eligibility exclusion criteria as described in the studies were categorized into 10 groups.
Contra-indications to treatment included intolerance to the intervention medication.
Demographic included age, women of reproductive age, non-pregnant women, pregnancy and lactation.
Each co-morbidity detailed in the study was counted as one item in the co-morbidity category.
Each medication group was counted as one item under the medications category.
Each GIT condition described in the study was counted as one item for this category, excluding IBS.
Details of the 'Other' category is described in the comments column.

Table 3
Critical appraisal summary table using PRECIS-2 domain scores.

Source	Year	PRECIS-2 Domain Score											
		Eligibility	Recruitment	Setting	Organization	Flexibility: delivery	Flexibility: adherence	Follow-up	Primary Analysis	Primary Outcome	Average Score	Average Excl. Primary Outcome	Pragmatic Classification
Sakurai et al.	2018	1	4	4	2	2	2	2	2	3	2.44	2.37	E
Wang et al.	2014	2	3	5	1	2	2	2	–	5	2.75	2.43	E
Yang et al.	2015	2	4	5	1	2	1	1	5	1	2.33	2.5	E
Jin et al.	2015	2	1	5	2	2	3	2	2	3	2.44	2.62	E
Mizuki et al.	2016	1	3	5	3	3	2	2	2	4	2.77	2.62	E
Choi et al.	2015	1	3	5	3	2	2	3	2	4	2.77	2.62	E
Liang et al.	2017	2	3	4	2	3	2	2	3	5	2.88	2.62	E
Liu et al.	2017	1	3	5	1	1	1	5	4	5	2.88	2.62	E
Singh et al.	2015	3	3	3	2	2	3	2	3	5	2.89	2.63	E
Takenaka et al.	2016	2	3	5	2	3	2	2	3	5	3	2.75	E
Azimi et al.	2017	1	3	4	3	4	2	3	2	5	3	2.75	E
Hosseini et al.	2018	1	4	5	2	3	2	2	3	5	3	2.75	E
Eherer	2014	4	–	3	2	3	2	3	–	4	3	2.83	E
Kamiya et al.	2017	2	3	5	3	3	2	3	2	5	3.11	2.87	E
Panahai et al.	2015	2	3	5	–	4	2	3	2	5	3.25	3	P
Yamaji et al.	2014	2	3	4	3	3	2	4	3	5	3.22	3	P
Oshima et al.	2018	2	4	4	3	3	1	3	4	5	3.22	3	P
Yang	2014	1	5	5	3	2	2	1	5	4	3.11	3	P
Ko et al.	2016	2	2	5	2	3	4	2	3	4	3	3.12	P
Ong et al.	2018	1	5	5	2	3	2	2	5	5	3.33	3.12	P
Zohalinezhad et al.	2016	2	3	3	3	3	4	3	4	5	3.33	3.13	P
Vedamanickam et al.	2017	2	4	3	3	4	–	–	–	3	3.17	3.17	P
Panahai et al.	2016	2	3	5	4	4	4	3	2	5	3.5	3.28	P
Shakeri et al.	2018	3	4	5	4	4	2	3	2	5	3.55	3.37	P
Li & Bai	2018	2	4	5	1	2	4	5	4	5	3.44	3.37	P
Meteerattanapipat & Phupong	2017	5	3	5	4	4	2	2	4	5	3.78	3.63	P
Senay et al.	2016	4	5	5	4	2	–	3	4	5	4	3.86	P
Zhang et al.	2017	2	5	5	5	1	3	5	5	4	3.88	3.87	P
Toseef et al.	2015	4	3	5	4	4	4	4	4	5	4.11	4	P
Wilkie et al.	2018	3	5	5	4	5	3	4	3	5	4.11	4	P
Ye & Wei	2015	2	4	5	3	–	4	5	5	2	3.75	4	P
Nie & Song	2015	1	5	5	3	–	4	5	5	5	4.12	4	P
Saifullah et al.	2018	3	5	5	4	5	4	4	5	4	4.22	4.12	P
Sri Roja et al.	2017	5	3	4	4	4	4	4	5	4	4.11	4.12	P
Shen et al.	2014	5	5	5	3	–	3	5	5	5	4.5	4.42	P
Setright	2017	4	5	5	5	3	4	5	5	5	4.56	4.5	P
Average		**2.33**	**3.66**	**4.61**	**2.82**	**2.97**	**2.65**	**3.11**	**3.55**	**4.39**	**3.35**	**3.22**	

(Table 2). History of GIT surgery was a cause for exclusion across fifteen of the included articles.[31,32,36,38,40,41,44,49,52–55,59,62,65] Exclusion due to GIT co-morbidities encompassed: IBS (n = 6),[31,32,34,37,42,43] treatment resistant GERD (n = 3),[34,40,43] history of reflux disease (n = 2),[32,37] maldigestion (n = 2),[37,43] gastritis as primary symptom with concurrent antacid use (n = 1),[44] gastric or duodenal ulcer on long-term PPI (n = 1),[51] *Helicobacter pylori* treatment in the past three months (n = 1)[40] and heartburn as primary symptom (n = 1).[32]

Other causes for exclusion were; reproductive women who may fall pregnant (n = 3),[32,36,54] abnormal laboratory findings (n = 2),[53,54] history of smoking (n = 1),[34] childhood illness (n = 1),[54] extreme body mass index (n = 1),[65] night-shift worker (n = 1)[40] and illiterate (n = 1).[45]

3.3. PRECIS-2 Recruitment - how are participants recruited into the trial?

Participants were recruited from patient visit to hospital (n = 28),[31,32,34–38,40–45,47–52,55–60,64,65,67] medical college (n = 2)[51,53] or specialist community based clinic (n = 13)[32,34,36,39,40,44,46,49,50,52,63,64,66] or both. Method of recruitment; unspecified (n = 15),[32,33,36,40,42–44,46–52,63] invitation (n = 6),[37–39,41,53,65] advertising (n = 3),[35,37,56] consecutive patients presenting for care (n = 3)[64–66] and convenience sampling (n = 1).[34]

3.4. PRECIS-2 Setting - where is the trial being done?

Screening and initial prescription phase occurred in specialist clinics (n = 11),[32,34,36,39,40,44,46,49,50,63,66] hospital (n = 23),[36–38,40–45,47–49,51,55–62,64,65] and university departments (n = 3).[33,53,54] Treatment intervention occurred in; community settings (n = 24),[31–34,36–44,46,47,49–54,63,65,66] acupuncture clinic (n = 2)[35,37] and hospital setting (n = 2).[45,48] The setting of Patient Response to Outcome Measurements (PROMs) was unclear. One study conducted PROMs by phone call and postal questionnaire.[66]

3.5. PRECIS-2 Organisation-What expertise and resources are needed to deliver the intervention?

Endoscopy was required in 23 studies.[31–36,38,40,41,44,49,51–60,64,65] The studies did not specify how the endoscopies were performed. An endoscopy involves the passing of a camera on a lighted tube into the body to provide a direct view of internal organs while a patient is sedated.[68] Although, a variety of novel endoscopic techniques and equipment, including video capsule endoscopy (VCE) have also emerged.[69] In Australia, specialised medical and nursing staff, facilities, endoscopic equipment, accessories, sterilization, monitoring and resuscitation equipment must all meet a minimum standard.[70]

Other medical procedures and expertise required among the studies included blood tests (n = 10),[35,38,41,47,49,50,53,56,59] measurement of peristalsis amplitude of the esophagus (n = 1),[52] ECG (n = 1),[47] esophageal manometry and 24 -h pH/impedance measurement testing (n = 2),[33,65] and additional training (n = 3).[33,37,56]

3.6. PRECIS-2 Flexibility: delivery - how should the intervention be delivered?

Method of delivery was presented as usual care with a structured protocol for dose, duration and frequency of intervention (n = 26).[31–34,36–44,46,48–54,63–67] A wash-out period was required in ten studies.[31–34,36,44,54–56,60] One study described flexibility in selection of acupuncture points for the individual.[37] Another provided flexibility in dose, duration and frequency for participants.[63] Alternatively, one study amended the herbal decoction intervention formula in response to the participant's changing symptoms.[60] Ten studies specified lifestyle modifications during intervention period; no smoking (n = 4),[47,52,59,60] no GI meds (n = 6),[31,44,56,59,60,62] no alcohol (n = 4),[47,52,59,60] diet improvement (n = 5)[37,46,59,60,66] and psychological counselling (n = 1).[59]

3.7. PRECIS-2 Flexibility: adherence -What measures are in place to make sure the participants adhere to the intervention?

Study design encouraging adherence involved; more than one follow-up visit to the study site for participant response measurements (n = 15),[31–36,38,40,42–44,46,49,52,65] exclusion for non-compliance (n = 14),[31,32,35–42,44,46,50,53] counting medications (n = 3),[36,39,41] and daily diaries (n = 3).[38,39,41]

3.8. PRECIS-2 follow-up: how closely are participants followed-up?

A total of 68 Patient Reported Outcome Measurement (PROMs), utilizing 50 different formats were applied among the 36 studies. Among the outcome measurement instruments there were: disease-specific symptom assessments,[31,35,37–44,47,52–54,56,57,65,66] customised composite symptom questionnaires,[32–35,39,41,46,48,50,51,63] quality of life (QoL) surveys[32,33,35,37,39,40,59,65] gastrointestinal-generic symptom assessments,[36,48,49,53,54,60–62,64] visual analogue scales (VAS),[34,39,45,49,65] overall treatment effect surveys,[32,40,44] cultural adaptations of the Nepean Dyspeptic Index (NDI),[32,35,37] daily diary formats,[38,39,41] psychological health questionnaires,[35,37,65] complete symptom resolution surveys,[38] patient satisfaction survey,[64] sleep quality index score[55] and a diet diary.[38] The validated gastrointestinal-generic instrument; Gastrointestinal Symptom Rating Scale (GSRS) was the most frequent instrument employed (n = 4).[36,49,53,54] A mixture of validated and unvalidated PROMs was the most popular approach (n = 15).[31,32,35,38,39,41,44,48,49,53–57,65] Biological measurements were employed across six studies.[33,35,37,47,52,58]

There was variability in the frequency of measurement timepoints during the study period. Follow-up patient response outcome measurements were taken at the following intervals; daily (n = 6)[32,34,38,39,41,49] one week (n = 8),[34,36,38,40,41,44,45,49] two weeks (n = 14),[31,32,34,36,39–42,44,46,49,52,58,64] four weeks (n = 21),[31–37,40,42,44,46–49,51–54,59,61,65] eight weeks (n = 5)[31,37,49,50,52] or longer (n = 8).[34,35,49,51,60,63,65,66] Four studies were two weeks or less in duration.[38,39,41,45]

3.9. PRECIS-2 Outcome: how relevant is it to participants?

Improvement of symptoms was a primary outcome across all studies in accordance with the inclusion criteria for this review. The evaluation of clinical efficacy of intervention was listed as a subsequent primary outcome for two studies[48,63] Secondary outcomes included: QoL (n = 7),[32,33,35,37,39,40,44] biomedical measurements (n = 4),[33,35,37,52] clinical efficacy (n = 1),[49] side effects (n = 2),[59,62] patient satisfaction (n = 1)[64] and pregnancy outcomes (n = 1).[39]

3.10. PRECIS-2 Primary analysis: to what extent are all data included?

Participants were excluded from primary analysis for: non-compliance (n = 14),[31,32,35–42,44,46,50,53] lost to follow-up (n = 8),[32,44,46,47,49,53,54] withdrew consent (n = 10),[32,36,40,43,46,49,53,54,56,66] adverse effect

(n = 7),[31,32,40,43,46,53,55] non-responders (n = 2),[34,66] incorrect diagnosis (n = 1).[45]

3.11. Evaluation of studies against PRECIS-2 domains

The outcomes of the appraisal process are reported in (Table 3). Eligibility criteria for inclusion in the review required the primary treatment aim was relief of symptomatic dyspepsia. Accordingly, the PRECIS-2 domain, 'Primary outcome' received a score of 4.39 out of 5, a very pragmatic result, illustrating the outcome, symptom improvement replicates a usual care context.

In contrast, the PRECIS-2 domains; 'eligibility' (score = 2.33), 'flexibility in adherence' (score = 2.65), 'organization' (score = 2.82) and 'flexibility in delivery' (score = 2.97) were aligned to an explanatory research design.[26] An explanatory design will often select for ideal patients, is highly controlled for an intervention,[71,72] and will generally require more resources than usual care.

A score of 3.0 is considered an equally pragmatic and explanatory score.[26,27] The mean PRECIS-2 score for the trials was 3.22, (SD 0.61) indicating the included papers for comparative effectiveness trials incorporated a distribution of pragmatic and explanatory design characteristics.

4. Discussion

This review provides an overview of methodological strengths and weakness of published comparative effectiveness trials for symptomatic dyspepsia and provides a number of insights to the design of future trials, particularly for researchers examining CM interventions.

4.1. Exclusion criteria

The extensive application of exclusion criteria notably affected the pragmatic ranking of the trials utilizing a PRECIS-2 assessment. Many of the exclusion criteria removed participants with clinical features linked to a higher incidence of dyspepsia. These clinical features include; IBS,[1] GERD,[8] gastritis,[12] heartburn,[1,3] non-steroidal anti-inflammatory drug use,[4] older than 60 years;[3] reproductive females,[4] mental health co-morbidities[9] and history of GIT surgery.[73] The justification for these exclusions was rarely described and excluding such conditions may hinder CM practitioners whose patient population is characterised by a greater proportion of women,[74] GIT,[16] mental health co-morbidities[75] and chronic, complex conditions.[16] For example, no included articles justified the rationale for IBS exclusion. Prior research has shown IBS patients have a lower resting pressure of the lower oesophageal sphincter,[1] hyperalgesia of the oesophagus[76] and 50% of IBS patients have pathologic reflux.[1] It has been reported participants with overlap in dyspepsia and IBS may represent those with more severe symptom manifestations.[2]

The studies on pregnant women[39,46] employed pre-trial lifestyle modifications and those who improved were excluded. This approach is prescriptive and may or may not reflect usual care in Iran[46] and Thailand,[39]where the studies were conducted. The exclusion represents a loss of informative data and it remains unknown if a relapse occurred. A separate study excluded participants from follow-up if they did not improve.[34] It is problematic to exclude for lifestyle criteria such as drinking alcohol,[47,52,59,60] strong tea,[52] smoking,[47,52,59,60] and 'bad living habits',[37,60] as it remains unknown if these sub-groups will be responsive to the intervention. There are some instances where exclusions may be justified, for example, GIT surgery causing anatomical changes affecting intervention efficacy[65] or a participant on multiple medications which may be contraindicated with the treatment intervention. However, extensive exclusion criteria have the potential to limit trial findings to a subset of the dyspeptic population.

Previous research comparing trial designs has concluded explanatory trials, when grouped and analysed together, regularly report larger effect sizes than similar pragmatic trials.[27] The measured efficacy of one intervention in a homogenised sample may be diluted once applied to the general population experiencing these symptoms. Ideally, a pragmatic approach would limit exclusions to specific contra-indications and include all participants in primary analysis to enhance transferability of outcomes to a real-life context. This would require increased organisation, collection and reporting of participant information to account for the myriad of individual variables observed in usual care. Further incorporation of pragmatism may benefit future CM research. Pragmatic design provides an opportunity to incorporate patient demographics and co-morbidities common in CM practice. This may provide further insight into the comparative effectiveness of different interventions, and which of those are better suited to a heterogeneous or subset population group. Admittedly, relaxation of the condition of entry and extension of the target population would allow many variables to enter the study and influence results. These factors would need to be taken into account and results cautiously interpreted.

4.2. Endoscopy as inclusion criteria

This review identified endoscopy as a common eligibility requirement in comparative effectiveness research for the treatment of symptomatic dyspepsia. Some included papers employed Rome inclusion criteria, which require an upper endoscopy to diagnose FD, although, past popularity of the Rome criteria as a diagnostic and clinical trial tool has been questioned.[2,3] A recent review demonstrated only 54% of clinical trials strictly adhered to the Rome eligibility inclusion criteria.[77] Additionally, in participants with FD, endoscopy does not quantify symptom severity, frequency or impact of the symptoms on the individual. It has been reported, for some individuals, there is no association between symptom severity and endoscopic findings.[3,78] Moreover, endoscopy is not required for diagnosis or commencement of treatment for symptomatic dyspepsia,[17] however, its inclusion may be considered pragmatic when applied as usual care, based on the socio-cultural context of the healthcare policy and the studied population. Recent guidelines for the management of dyspepsia recommend the use of endoscopic investigation in patients who report alarm features and; or are over 60 years of age.[3] Within the included studies, the majority of participants were under 65 years of age or excluded if presenting with alarm features. Entry endoscopy as a trial requirement is costly,[12] disadvantageous for researchers with limited resources and access to medical expertise and excludes participant groups unwilling to undergo endoscopy.[79] An endoscopy is relevant if seeking to classify a condition, identify physiological change such as mucosal erosion, or aligns with routine clinical care and characteristics of the studied population. For instance in Japan, an endoscopic investigation may be a justifiable component of a pragmatic trial design, due to a higher incidence of gastric cancer, resource allocation and recommendation for this procedure in real-world settings.[12,17] A pragmatic trial design, authentic to sample populations, genotypes, cultural, geographical and resource differences is better equipped to reproduce intervention results in a real-world context. A pragmatic design reflective of usual care offers researchers an opportunity to provide measurable results without incumbent and high resource procedures.

4.3. Instruments of measurement

No single common tool or methodology was identified among the included studies to measure patient outcomes for dyspepsia. Similarly, this finding has been noted in prior published research.[23,73,77,80] To illustrate, a recent review identified 65 questionnaires in use for the assessment of symptoms and outcome measures in GERD intervention trials alone.[73]

This review evaluated comparative intervention studies for symptomatic dyspepsia that encompassed various conditions including FD, dyspepsia, belching, heart-burn, gastritis, GERD, erosive esophagitis, duodenal ulcer, gastric ulcer, IBS and non-erosive reflux disease. This has contributed to the multiple PROMs observed in the results but does not fully explain the diversity observed. For instance, within any given condition, an assortment of PROMs was employed. A broader international movement towards development of meaningful, standardised Core Outcome Measurements in Effectiveness Trials (COMET) through expert consensus has yet to decide on a universal set of measures for dyspepsia.[81]

More specifically, there exists no preferred, single, validated patient reported outcome tool to measure symptom change and furthermore, research on methodological aspects of PROMs development for dyspepsia symptoms is minimal.[80] A consensus statement on clinical trial design for GERD stated PROMs should be in electronic format, to increase ease of use, reduce the need for return follow-up assessment and minimise bias.[73] Pictograms have been promoted as a tool to assist symptom identification overcoming the potential for misunderstanding the terminology by participants.[82] This would also prevent participant exclusion based on literacy as occurred in one of the included studies.[45] The challenge for future research is to develop a validated PROM tool which captures symptom improvement across a heterogeneous population and does not become overly cumbersome for a participant to complete, leading to increased risk of drop-off. The lack of consensus on a validated PROM instrument hinders the ability to effectively compare interventions between research trials.

4.4. Limitations

This study has several limitations. Variations in standard care practice across regional and socioeconomic lines, created challenges with maintaining consistency in the PRECIS-2 evaluation process. For example, endoscopy could be classified as explanatory or pragmatic, dependent upon the chosen scope defining usual care.[12,83–85] Furthermore, PRECIS-2 assessors were required to be familiar with routine care practice across fourteen countries. Consequently, a potential deficit in their knowledge may affect accuracy of the pragmatic score for trial design. Missing or unclear data items within the included articles may have affected consistent assessment and calculation of PRECIS-2 summary scores. Two articles were unable to be translated and could not be included in the results.[29,30] Lastly, design characteristics were assessed for their pragmatism and not their effect on statistical analyses or trial results.

4.5. Future directions

This review uncovered several insights relevant for future CER, in the treatment of upper gastrointestinal conditions. Further investigation into the influence of eligibility requirements on the studied population and trial results is warranted. Does requirement for endoscopy affect study recruitment and introduce a selection bias into the study design? For instance, a study on the prevalence and impact of IBS and dyspepsia in China reported 67.3% of participants refused to undergo an endoscopy.[79] Furthermore, does the exclusion of age, lifestyle habits, common co-morbidities and clinical features linked to a higher incidence of dyspepsia affect results and subsequently health care provider decisions upon an appropriate treatment for their patient?

Development of standard, validated PROMs appropriate for a generic application to upper gastrointestinal disorders would benefit comparative research in a community setting. Specifically, a pragmatic PROM tool focussed on patient outcomes and symptom improvement, which is simple to use and encompasses overlapping gastrointestinal conditions and a variety of presenting symptoms. A potential add-on is the inclusion of patient satisfaction as a measurement outcome,[64] and incorporation of electronic data collection formats with pictograms to increase participant adherence and reduce the need for return to study site.

Future research into pragmatic design characteristics would benefit from inclusion of published study protocols to provide further details about trial design, and clear categorisation of the disease group and local standard of care, to minimise variables and help clarify the effectiveness of a intervention in a real-world, context.

4.6. Conclusion

This review identified three key design characteristics pertinent for future comparative effectiveness research for the treatment of upper gastrointestinal disorders. Extensive exclusion eligibility criteria limits the generalization of comparative effectiveness study results by removing sub-groups of the target populations more at risk of dyspeptic symptoms. An ongoing lack of consensus on a validated measurement tool for patient reported outcomes in symptomatic dyspepsia was reflected in the multiple PROMs utilized by the included studies. The trial requirement for entry endoscopy was common; however a majority of sufferers do not seek treatment for their dyspepsia from their primary healthcare provider. In this context, the pragmatic justification for endoscopy as an eligibility requirement to commence treatment will differ across socio-cultural characteristics, their preferred treatment pathway and the country's healthcare policy.

Author contributions

Conceptualization: NE and AS. Methodology: NE. Software: NE. Validation: NE, AS and BL. Formal Analysis: NE, AS and BL. Investigation: NE. Resources: NE. Data Curation: NE and WP. Writing – Original Draft: NE. Writing – Review & Editing: NE, AM, BL and PW. Visualization: NE & AS. Supervision: AS & BL.

Conflict of interest

Natalie Elliott works for the Blackmores Institute.

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This research did not require an ethical approval as it does not involve any human or animal experiment.

Data availability

The data will be made available upon request.

Supplementary material

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