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Prokinetics for functional dyspepsia (Protocol)

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[Intervention Protocol]

Prokinetics for functional dyspepsia

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

By meta-analysis and systematic review of randomized controlled trials (RCTs), to evaluate the role of prokinetics in the treatment of functional dyspepsia (FD) as reflected by improvement of either individual or global dyspepsia symptom scores and quality of life scores. The primary comparisons will be as follows.

- Are prokinetic drugs in general better than placebo?
- Which of the individual prokinetic drugs is the most effective?

BACKGROUND

Description of the condition

Dyspepsia is a common condition in gastrointestinal disease with a global prevalence of at least 20% (Ford 2015; Tack 2006). It is defined by epigastric pain or discomfort as described in the Rome criteria definition, which has had four iterations (Stanghellini 2016; Tack 2006; Talley 1991; Tally 1999). Nevertheless, 72% to 82% of patients presenting with dyspepsia have no evidence of structural disease on endoscopic findings (Ford 2010) that is likely to explain the symptom, called functional dyspepsia (FD) (Stanghellini 2016; Tack 2006; Talley 1991; Tally 1999).
The pathophysiology of FD is likely multifactorial and not fully understood (Stanghellini 2016). However, several factors have been identified as relevant, including abnormality of gastroduodenal motor (delayed gastric emptying or impaired gastric accommodation) and sensory (gastric and duodenal hypersensitivity) mechanisms (Stanghellini 2016; Vanheel 2013).
A prokinetic is one of the rescue medications for FD, which according to Lacy and colleagues, aims to improve gastric emptying (Lacy 2012). It provided a significant benefit over placebo with a relative risk reduction of 33% and number needed to treat (NNT) of six but had the major concern of publication bias (Stanghellini 2016). Moreover, Moayyedi and colleagues reported the significant effect of prokinetic treatment in reducing global symptoms of FD with a relative risk of remaining dyspeptic in the prokinetic group of 0.92 (95% CI 0.88 to 0.97) with a NNT of 12.5 (95% CI 8 to 25) (Moayyedi 2017).
Currently, a prokinetic is recommended as the first-line treat-

ment in patients with postprandial distress syndrome (PD) subtype (Stanghellini 2016). On the other hand, it is suggested as the third-line treatment by recent guidelines on dyspepsia from the American College of Gastroenterology (ACG) and the Canadian Association of Gastroenterology (CAG), regardless of FD subtypes (Moayyedi 2017).

Description of the intervention

The intervention addressed in this review is the use of prokinetic agents to treat FD. Prokinetics are agents that accelerate gastric emptying and intestinal transit time.

How the intervention might work

FD is a clinical entity of significant disease and economic burden on both patients and the healthcare system (Lacy 2013; Moayyedi 2002; van Zanten 2011). Its pathophysiology remains elusive and as such so has its appropriate management. However, a subtype of this population (e.g. postprandial distress syndrome (PD)) may experience symptoms secondary to dysmotility, which drives the use of prokinetics as a potential therapeutic intervention (Tally 2005).

Why it is important to do this review

The Cochrane systematic review on the pharmacological Interventions for FD evaluated the effectiveness of six classes of drugs for the treatment of FD since 2006 (Moayyedi 2011). Prokinetics were found to be and efficacious drug class with relative risk reduction 33%; 95% confidence intervals (CI) 18% to 45% (Moayyedi 2011). However, several new prokinetics have since been developed and, added to this, cisapride, the most heavily studied drug of this class, is no longer available in many markets thus necessitating a more up-to-date review.

OBJECTIVES

By meta-analysis and systematic review of randomized controlled trials (RCTs), to evaluate the role of prokinetics in the treatment of functional dyspepsia (FD) as reflected by improvement of either individual or global dyspepsia symptom scores and quality of life scores. The primary comparisons will be as follows.

- Are prokinetic drugs in general better than placebo?
- Which of the individual prokinetic drugs is the most effective?

METHODS

Criteria for considering studies for this review

Types of studies

Any parallel group RCTs comparing one prokinetic with either placebo or another prokinetic of the same or different class for the treatment of FD will be included. Only the first period of cross-over trials will be included.

Types of participants

Adults with dyspepsia, as defined by either Rome Criteria I to IV (Stanghellini 2016; Tack 2006; Talley 1991; Tally 1999) or non-Rome criteria but using the criteria compatible with the Rome criteria. Specifically, we will include studies on adult patients presenting with dyspepsia symptoms who have had negative or insignificant findings on their endoscopy as well as no other organic (pancreato-biliary disease, oesophagitis, peptic ulcer disease and neoplastic disease) and drug-induced (non-steroidal anti-inflammatory drugs) and metabolic disorders. Studies only including participants with primarily reflux or heartburn symptoms will be excluded.

Types of interventions

Only studies that consider the use of prokinetics for the treatment of FD will be considered. Prokinetics will include: erythromycin, metoclopramide, domperidone, cisapride, mosapride, itopride, ABT-229, tandospirone citrate, alosetron, tegaserod, mosapride, and acotiamide, as well as any other prokinetics identified through a literature review. Only studies that provide treatment duration at least seven days will be eligible for inclusion.

Types of outcome measures

Primary outcomes

Global symptoms of dyspepsia, reported as binary outcome (yes or no) or symptom scores. We will use the most stringent definition of not symptom-free or no overall symptom improvement by the patient at the end of treatment. If that is not available we will use overall symptom assessment as assessed by the doctor/researcher. If global symptoms are not reported, we will use epigastric pain/discomfort improvement as the outcome measure, but these studies will be removed in the sensitivity analysis.

Secondary outcomes

- Complete resolution of global symptoms of dyspepsia.
- Quality of life (QoL).
- Adverse events.

Search methods for identification of studies

Electronic searches

In an effort to identify RCTs comparing a prokinetic either with placebo or with another prokinetic of the same or different class, we will search the individual names of prokinetics that are available, have been withdrawn, or are under investigation.
We will search:

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (Appendix 1);
- MEDLINE (Appendix 2);
- Embase (Appendix 3);
- CINAHL (Appendix 4).

Searching other resources

We will search all reference lists of the articles retrieved. Additionally, we will contact experts within the field of FD as well as pharmaceutical companies regarding ongoing clinical trials and relevant unpublished data.

Data collection and analysis

Two review authors will evaluate each retrieved RCT for its eligibility, risk of bias and results.

Selection of studies

Two review authors will independently review studies retrieved by the search strategies and exclude trials based on titles, abstracts, or both. Both study authors will independently review selected studies for complete analysis.

Data extraction and management

A data collection form specifically designed for this review will be used for data collection. One study author will extract data and enter it into RevMan. The other study author will serve to ensure the accuracy of this process.
The data collected will include the following.

- Participant characteristics: demographics, recruitment source, diagnostic criteria used by study authors, symptoms at the trial's start, most prevalent type of dyspepsia.
- Details of interventions: name of medication, dose, schedule.
- Dyspeptic symptoms before and after the intervention: number of patients with dyspepsia symptom, global Dyspepsia Symptom Scores, quality of life, adverse events.

Data will be managed and analyzed according to an intention-to-treat analysis.

Assessment of risk of bias in included studies

All trials will be assessed using Cochrane's 'Risk of bias' tool, which evaluates the following domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data addressed at short and long term (attrition bias), selective reporting (reporting bias) and other bias. Each domain will be described according to what happened in the individual study, followed by a judgment as to the risk of bias relating to that domain. 'Other bias' refers to any other study-specific characteristic that confers a risk of bias on the results (for example, early stopping, baseline imbalance, blocked randomization in unblinded studies, and differential diagnostic activity).

Measures of treatment effect

For the binary outcomes, we will present the results as risk ratio (RR) with 95% confidence interval (CI).
For the continuous outcomes, we will present the results as mean difference (MD) with 95% CI. If all studies have not used the same scales, the results will be presented as a standardized mean difference (SMD) with 95% CI.

Unit of analysis issues

Only a simple parallel group design for clinical trials as well as the first phase of cross-over studies will be included in the analysis such that the number of observations matches the number of individuals randomized.

Dealing with missing data

Any data that are missing will be noted on the data collection form and taken into consideration when evaluating the overall quality of the study. We will also attempt to contact the study authors.

Assessment of heterogeneity

We will assess heterogeneity with the Chi^2 test ($P < 0.10$ = significant heterogeneity) and I^2 statistic (> 50% = substantial heterogeneity) using a random-effects model along with visual inspection of the forest plots. Possible sources for heterogeneity will be evaluated by subgroup analyses according to the following criteria.

- Subtypes of functional dyspepsia (postprandial distress syndrome and epigastric pain syndrome).
- Length of follow-up.
- Use of validated dyspepsia questionnaires.
- Studies assessed as hIgh risk of bias versus low or unclear risk of bias.
- Prokinetic subtype and dose.

Assessment of reporting biases

In order to assess the presence of small-study effects in the meta-analysis, a funnel plot will be used. We will assess publication bias by examining the relationship between the treatment effects and the standard error of the estimate using a funnel plot and Egger's test.

Data synthesis

Global symptoms of dyspepsia will be categorized as not symptom-free or no overall symptom improvement (if "not symptom-free" is unavailable, which includes unchanged or worsened symptoms). The relative risk reduction (RR) and 95% CI will be recorded, and number needed to treat (NNT) (if a significant difference is seen) will all be calculated. We will record the mean and SD of global symptom score at pre- and post- treatment as well as mean and SD of change scores from baseline in each group, if available. We will calculate the mean and SD of change scores from baseline if only pre- and post treatment scores are reported, using the methods proposed in the Cochrane Handbook (Higgins 2011b). An analysis based on changes from baseline is preferred as it is more efficient and powerful than a comparison of final values. For studies that do not report change scores from baseline, or for scores which aren't calculable, we will use the final values as the difference in mean final values will on average be the same as the difference in mean change scores in RCTs. Mean difference (MD) and 95% CI will be calculated as the summary statistic for symptom scores, for studies that used the same scales. The standardized mean difference (SMD) and 95% CI will be calculated between two groups if different scales are used in the primary studies. However, final value and change scores will not be combined together as SMD (Deeks 2011).

For adverse events, we will calculate the RR, 95% CI and number need to treat for an additional harm (NNTH) if a significant difference is seen. MD and SMD and 95% CI will be used to report changes of quality scores, for similar or different QOL scales, respectively. A meta-analysis of all data will be conducted, if possible. Mantel-Haenszel (M-H) methods (random-effects model) will be used to synthesize data in the meta-analysis (Mantel 1959).

'Summary of findings' table

We will create 'Summary of findings' tables for the following comparisons:

- prokinetics versus placebo,
- one prokinetic versus another prokinetic.

using the following primary and secondary outcomes:

- global symptom and symptom score of dyspepsia,
- complete resolution of global symptoms of dyspepsia,
- quality of life,
- adverse events.

We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to the studies which contribute data to the meta-analyses for the pre-specified outcomes (GRADEpro GDT). We will use methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a) and using GRADEpro software. We will justify all decisions to down- or up-grade the quality of studies using footnotes and make comments to aid a reader's understanding of the review where necessary. If meta-analysis is not possible, we will present the results in a narrative format. We will consider whether there is any additional outcome information that was not able to be incorporated into meta-analyses and note this in the comments and state if it supports or contradicts the information from the meta-analyses.

Subgroup analysis and investigation of heterogeneity

Subgroups that we plan to analyze include the predominant type of dyspepsia: ulcer-like, dysmotility-like, reflux-like and non-specific. If heterogeneity is substantial (I^2 statistic > 50%, or P value for Chi^2 test < 0.10), we will explore whether it is explained by methodological or clinical heterogeneity, or both, among the trials. Issues that may explain observed heterogeneity include the following.

- Subtypes of functional dyspepsia (postprandial distress syndrome and epigastric pain syndrome)
- Length of follow-up (> one month versus < one month).
- Use of validated versus non-validated dyspepsia questionnaires.
- Studies assessed as hIgh risk of bias versus low or unclear risk of bias.
- Prokinetic subtype, recommended versus below recommended versus above recommended dose as per manufacturer.

Sensitivity analysis

Sensitivity analysis will be conducted depending on study characteristics identified during the review process. Studies using individual symptom improvement as the outcome will be excluded in the sensitivity analysis. Studies with significant clinical heterogeneity will be excluded from the sensitivity analysis. Pre-specified sensitivity analyses include: fixed-effect model analysis, outcomes expressed as odds ratios versus relative risks.

ACKNOWLEDGEMENTS

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REFERENCES

Additional references

Deeks 2011
Deeks JJ, Higgins JPT, Deeks JJ, Altman DG, on behalf of the Cochrane Statistical Methods Group, editors. Chapter 9.4: Analysing data and undertaking meta-analyses. In: Higgins JP, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Ford 2010
Ford AC, Marwaha A, Lim A, Moayyedi P. What is the prevalence of clinically significant endoscopic findings in subjects with dyspepsia? Systematic review and meta-analysis. *Clinical Gastroenterology and Hepatology* 2010;**8**: 830–7.

Ford 2015
Ford AC, Marwaha A, Sood R, Moayyedi P. Global prevalence of, and risk factors for, uninvestigated dyspepsia: a meta-analysis. *Gut* 2015;**64**(7):1049-57.

GRADEpro GDT [Computer program]
GRADE Working Group, McMaster University. GRADE Working Group, McMaster University. GRADEpro GDT. Version (accessed prior to April 22, 2017). Hamilton (ON): GRADE Working Group, McMaster University, 2015.

Higgins 2011a
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Higgins 2011b
Higgins JPT, Deeks JJ, Altman DG, on behalf of the Cochrane Statistical Methods Group, editors. Chapter 16.1.3.2: Imputing standard deviations for changes from baseline. In: Higgins JP, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Lacy 2012
Lacy BE, Talley NJ, Locke GR 3rd, Bouras EP, DiBaise JK, El-Serag HB, et al. Review article: current treatment options and management of functional dyspepsia. *Alimentary Pharmacology & Therapeutics* 2012;**36**(1):3-15.

Lacy 2013
Lacy BE, Weiser KT, Kennedy AT, Crowell MD, Talley NJ. Functional dyspepsia: the economic impact to patients. *Alimentary Pharmacology & Therapeutics* 2013;**38**:170–7.

Mantel 1959
Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *Journal of the National Cancer Institute* 1959;**22**(4):719–48.

Moayyedi 2002
Moayyedi P, Mason J. Clinical and economic consequences of dyspepsia in the community. *Gut* 2002;**50 (suppl 4)**: 10–2.

Moayyedi 2011
Moayyedi P, Soo S, Deeks JJ, Delaney B, Innes M, Forman D. Pharmacological interventions for non-ulcer dyspepsia. *Cochrane Database of Systematic Reviews* 2011, Issue 12. [DOI: 10.1002/14651858.CD001960.pub4

Moayyedi 2017
Moayyedi PM, Lacy BE, Andrews CN, Enns RA, Howden CW, Vakil N. Corrigendum: ACG and CAG clinical guideline: management of dyspepsia. *American Journal of Gastroenterology* 2017;**112**:1484. [DOI: 10.1038/ajg.2017.238

Stanghellini 2016
Stanghellini V, Chan FK, Hasler WL, Malagelada JR, Suzuki H, Tack J, et al. Gastroduodenal disorders. *Gastroenterology* 2016;**150**:1380–92.

Tack 2006
Tack J, Talley MJ, Camilleri M, Holtmann G, Hu P, Malagelada JR, et al. Functional gastroduodenal disorders. *Gastroenterology* 2006;**130**:1466–79.

Talley 1991
Talley NJ, Colin-Jones DG, Koch KL, Koch M, Nyren O, Stanghellini V. Functional dyspepsia: a classification with guidelines for diagnosis and management. *Gastroenterology International* 1991;**4**:145–60.

Tally 1999
Talley NJ, Stanghellini V, Heading RC, Koch KL, Malagelada JR, Tytgat GN. Functional gastroduodenal disorders. *Gut* 1999;**45 (Suppl 2)**:II37–42. MEDLINE: 10457043

Tally 2005
Talley NJ, Vakil NB, Moayyedi P. American gastroenterological association technical review on the evaluation of dyspepsia. *Gastroenterology* 2005;**129**: 1756–80.

van Zanten 2011
van Zanten SV, Wahlqvist P, Talley NJ, Halling K, Vakil N, Lauritsen K, et al. Randomised clinical trial: the burden of illness of uninvestigated dyspepsia before and after treatment with esomeprazole-results from the STARS II

study. *Alimentary Pharmacology & Therapeutics* 2011;**34**(7): 714–23.

Vanheel 2013

Vanheel H, Farré R. Changes in gastrointestinal tract function and structure in functional dyspepsia. *Nature Reviews. Gastroenterology & Hepatology* 2013;**10**:142-9.

References to other published versions of this review

Bollegala 2011

Bollegala NP, Khanna R, Moayyedi P, Leontiadis GI. Prokinetics for functional dyspepsia. *Cochrane Database of Systematic Reviews* 2011, Issue 11. [DOI: 10.1002/14651858.CD009431

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. CENTRAL search strategy (Ovid)

1. exp Dyspepsia/
2. (dyspep* or "NUD" or "FD").tw,kw.
3. (indigestion or indigestive).tw.
4. or/1-3
5. (prokinetic* or gastroprokinetic* or gastrokinetic* or gastro-kinetic*).tw,kw.
6. (antiemetic* or anti-emetic).tw,kw.
7. exp Benzamides/
8. (Benzoic Acid Amide or Amides or Phenyl Carboxyamide or Benzamide* or Benzoylamide or benzoates).tw,kw.
9. (Phenylcarboxyamide or Phenylcarboxamide or Benzenecarboxamide or Amid kyseliny benzoove).tw,kw.
10. exp Domperidone/
11. (domperidon* or domidon or Domperi or Domstal or evoxin or gastrocure or motilium or motilium).tw,kw.
12. (motis or nauzelin or Motinorm Costi or Nomit or Brulium or Molax).tw,kw.
13. exp Antiemetics/
14. exp Metoclopramide/
15. (Metoclopramide or cerucal or clopra or gastrese or gastrobid or gastroflux or gastromax or maxolon).tw,kw.
16. (metaclopramide or metozolv or metramid or migravess or mygdalon or octamide or parmid).tw,kw.
17. (primperan or reglan or reliveran or rimetin or Degan or Maxeran or Pylomid or Pramin).tw,kw.
18. exp Cisapride/
19. (Cisapride or alimix or Prepulsid or Propulsid).tw,kw.
20. exp Cholinesterase Inhibitors/
21. (Itopride or ganaton).tw,kw.
22. Mosapride.tw,kw.
23. exp Erythromycin/
24. (erythromycin or aknemycin or emcin or emgel or emycin or eryderm or erygel or erymax).tw,kw.
25. (erymin or eryped or gallimycin or ilosene or ilosone or ilotycin or lauromicina or maracyn).tw,kw.
26. (monomycin or ornacyn or retcin or rommix or romycin or roymicin or staticin or stiemycin or theramycin or tiloryth or wyamycin).tw,kw.
27. (Motilin adj3 (receptor* or agonist*)).tw,kw.
28. ((5HT3 or 5HT 3 or 5-HT3 or 5-HT 3) adj3 antagonist*).tw,kw.

29. ((5HT or 5-HT or 5-hydroxytryptamine*) adj3 (agonist* or antagonist*)).tw,kw.
30. ((5-HT1A or 5HT1A or 5-HT 1A or 5HT 1A) adj3 agonist*).tw,kw.
31. exp Serotonin Antagonists/
32. exp Serotonin 5-HT3 Receptor Antagonists/
33. exp Serotonin 5-HT4 Receptor Agonists/
34. exp Serotonin 5-HT1 Receptor Agonists/
35. (serotonin adj3 receptor adj3 (agonist* or antagonist* or block*)).tw,kw.
36. (tegaserod or Zelnorm or Zelmac).tw,kw.
37. ABT-229.tw,kw.
38. (Tandospirone or Sediel or metanopirone or buspirone).tw,kw.
39. (alosetron or Lotronex).tw,kw.
40. (Acotiamide or YM-443 or Z-338D).tw,kw.
41. (acetylcholinesterase inhibitor* or cholinesterase Inhibitor* or anti-cholinesterase* or anticholinesterase*).tw,kw.
42. ((5HT-4 or 5HT4 or 5-HT 4 or 5-HT4) adj3 agonist*).tw,kw.
43. or/5-42
44. 4 and 43

Appendix 2. MEDLINE search strategy

1. exp Dyspepsia/
2. (dyspep* or "NUD" or "FD").tw,kw.
3. (indigestion or indigestive).tw.
4. or/1-3
5. (prokinetic* or gastroprokinetic* or gastrokinetic* or gastro-kinetic*).tw,kw.
6. (antiemetic* or anti-emetic).tw,kw.
7. exp Benzamides/
8. (Benzoic Acid Amide or Amides or Phenyl Carboxyamide or Benzamide* or Benzoylamide or benzoates).tw,kw.
9. (Phenylcarboxyamide or Phenylcarboxamide or Benzenecarboxamide or Amid kyseliny benzoove).tw,kw.
10. exp Domperidone/
11. (domperidon* or domidon or Domperi or Domstal or evoxin or gastrocure or motilium or motilium).tw,kw.
12. (motis or nauzelin or Motinorm Costi or Nomit or Brulium or Molax).tw,kw.
13. exp Antiemetics/
14. exp Metoclopramide/
15. (Metoclopramide or cerucal or clopra or gastrese or gastrobid or gastroflux or gastromax or maxolon).tw,kw.
16. (metaclopramide or metozolv or metramid or migravess or mygdalon or octamide or parmid).tw,kw.
17. (primperan or reglan or reliveran or rimetin or Degan or Maxeran or Pylomid or Pramin).tw,kw.
18. exp Cisapride/
19. (Cisapride or alimix or Prepulsid or Propulsid).tw,kw.
20. exp Cholinesterase Inhibitors/
21. (Itopride or ganaton).tw,kw.
22. Mosapride.tw,kw.
23. exp Erythromycin/
24. (erythromycin or aknemycin or emcin or emgel or emycin or eryderm or erygel or erymax).tw,kw.
25. (erymin or eryped or gallimycin or ilosene or ilosone or ilotycin or lauromicina or maracyn).tw,kw.
26. (monomycin or ornacyn or retcin or rommix or romycin or roymicin or staticin or stiemycin or theramycin or tiloryth or wyamycin).tw,kw.
27. (Motilin adj3 (receptor* or agonist*)).tw,kw.
28. ((5HT3 or 5HT 3 or 5-HT3 or 5-HT 3) adj3 antagonist*).tw,kw.
29. ((5HT or 5-HT or 5-hydroxytryptamine*) adj3 (agonist* or antagonist*)).tw,kw.
30. ((5-HT1A or 5HT1A or 5-HT 1A or 5HT 1A) adj3 agonist*).tw,kw.
31. exp Serotonin Antagonists/
32. exp Serotonin 5-HT3 Receptor Antagonists/

33. exp Serotonin 5-HT4 Receptor Agonists/
34. exp Serotonin 5-HT1 Receptor Agonists/
35. (serotonin adj3 receptor adj3 (agonist* or antagonist* or block*)).tw,kw.
36. (tegaserod or Zelnorm or Zelmac).tw,kw.
37. ABT-229.tw,kw.
38. (Tandospirone or Sediel or metanopirone or buspirone).tw,kw.
39. (alosetron or Lotronex).tw,kw.
40. (Acotiamide or YM-443 or Z-338D).tw,kw.
41. (acetylcholinesterase inhibitor* or cholinesterase Inhibitor* or anti-cholinesterase* or anticholinesterase*).tw,kw.
42. ((5HT-4 or 5HT4 or 5-HT 4 or 5-HT4) adj3 agonist*).tw,kw.
43. or/5-42
44. 4 and 43
45. randomized controlled trial.pt.
46. controlled clinical trial.pt.
47. random*.mp.
48. placebo.ab.
49. drug therapy.fs.
50. trial.ab.
51. groups.ab.
52. or/45-51
53. exp animals/ not humans.sh.
54. 52 not 53
55. 44 and 54

Appendix 3. Embase search strategy

1. exp dyspepsia/
2. (dyspep* or "NUD" or "FD").tw,kw.
3. (indigestion or indigestive).tw.
4. or/1-3
5. (prokinetic* or gastroprokinetic* or gastrokinetic* or gastro-kinetic*).tw,kw.
6. (antiemetic* or anti-emetic).tw,kw.
7. exp benzamide derivative/
8. (Benzoic Acid Amide or Amides or Phenyl Carboxyamide or Benzamide* or Benzoylamide or benzoates).tw,kw.
9. (Phenylcarboxyamide or Phenylcarboxamide or Benzenecarboxamide or Amid kyseliny benzoove).tw,kw.
10. exp domperidone/
11. (domperidon* or domidon or Domperi or Domstal or evoxin or gastrocure or motilium or motilium).tw,kw.
12. (motis or nauzelin or Motinorm Costi or Nomit or Brulium or Molax).tw,kw.
13. exp antiemetic agent/
14. exp metoclopramide/
15. (Metoclopramide or cerucal or clopra or gastrese or gastrobid or gastroflux or gastromax or maxolon).tw,kw.
16. (metaclopramide or metozolv or metramid or migravess or mygdalon or octamide or parmid).tw,kw.
17. (primperan or reglan or reliveran or rimetin or Degan or Maxeran or Pylomid or Pramin).tw,kw.
18. exp cisapride/
19. (Cisapride or alimix or Prepulsid or Propulsid).tw,kw.
20. exp cholinesterase inhibitor/
21. (Itopride or ganaton).tw,kw.
22. exp mosapride/
23. Mosapride.tw,kw.
24. exp erythromycin/
25. (erythromycin or aknemycin or emcin or emgel or emycin or eryderm or erygel or erymax).tw,kw.
26. (erymin or eryped or gallimycin or ilosene or ilosone or ilotycin or lauromicina or maracyn).tw,kw.

27. (monomycin or ornacyn or retcin or rommix or romycin or roymicin or staticin or stiemycin or theramycin or tiloryth or wyamycin).tw,kw.
28. exp motilin receptor agonist/
29. (Motilin adj3 (receptor* or agonist*)).tw,kw.
30. ((5HT3 or 5HT 3 or 5-HT3 or 5-HT 3) adj3 antagonist*).tw,kw.
31. ((5HT or 5-HT or 5-hydroxytryptamine*) adj3 (agonist* or antagonist*)).tw,kw.
32. ((5-HT1A or 5HT1A or 5-HT 1A or 5HT 1A) adj3 agonist*).tw,kw.
33. exp serotonin antagonist/
34. exp serotonin 3 antagonist/
35. exp serotonin 4 agonist/
36. exp serotonin 1 agonist/
37. (serotonin adj3 receptor adj3 (agonist* or antagonist* or block*)).tw,kw.
38. exp tegaserod/
39. (tegaserod or Zelnorm or Zelmac).tw,kw.
40. ABT-229.tw,kw.
41. exp tandospirone/
42. (Tandospirone or Sediel or metanopirone or buspirone).tw,kw.
43. exp alosetron/
44. (alosetron or Lotronex).tw,kw.
45. exp acotiamide/
46. (Acotiamide or YM-443 or Z-338D).tw,kw.
47. (acetylcholinesterase inhibitor* or cholinesterase Inhibitor* or anti-cholinesterase* or anticholinesterase*).tw,kw.
48. ((5HT-4 or 5HT4 or 5-HT 4 or 5-HT4) adj3 agonist*).tw,kw.
49. or/5-48
50. 4 and 49
51. random*.mp.
52. placebo:.mp.
53. clinical trial:.mp.
54. double-blind:.mp. or blind:.tw.
55. or/51-54
56. exp animal/ not human/
57. 55 not 56
58. 50 and 57
59. remove duplicates from 58

Appendix 4. CINAHL Search strategy

1. (MH "Dyspepsia") or TX (dyspep* or "NUD" or "FD")
2. TX prokinetic* or gastroprokinetic* or gastrokinetic* or gastro-kinetic*
3. TX antiemetic* or anti-emetic
4. TX Benzoic Acid Amide or Amides or Phenyl Carboxyamide or Benzamide* or Benzoylamide or benzoates
5. TX Phenylcarboxyamide or Phenylcarboxamide or Benzenecarboxamide or Amid kyseliny benzoove
6. TX domperidon* or domidon or Domperi or Domstal or evoxin or gastrocure or motilium or motilium
7. TX motis or nauzelin or Motinorm Costi or Nomit or Brulium or Molax
8. TX Metoclopramide or cerucal or clopra or gastrese or gastrobid or gastroflux or gastromax or maxolon
9. TX metaclopramide or metozolv or metramid or migravess or mygdalon or octamide or parmid
10. TX primperan or reglan or reliveran or rimetin or Degan or Maxeran or Pylomid or Pramin
11. TX Cisapride or alimix or Prepulsid or Propulsid
12. TX Itopride or ganaton
13. TX Mosapride
14. TX erythromycin or aknemycin or emcin or emgel or emycin or eryderm or erygel or erymax
15. TX erymin or eryped or gallimycin or ilosene or ilosone or ilotycin or lauromicina or maracyn

16. TX monomycin or ornacyn or retcin or rommix or romycin or roymicin or staticin or stiemycin or theramycin or tiloryth or wyamycin
17. TX Motilin and (receptor* or agonist*)
18. TX (5HT3 or 5HT 3 or 5-HT3 or 5-HT 3) and antagonist*
19. TX (5HT or 5-HT or 5-hydroxytryptamine*) and (agonist* or antagonist*)
20. TX (5-HT1A or 5HT1A or 5-HT 1A or 5HT 1A) and agonist*
21. TX serotonin and receptor and (agonist* or antagonist* or block*)
22. TX tegaserod or Zelnorm or Zelmac
23. TX ABT-229
24. TX Tandospirone or Sediel or metanopirone or buspirone
25. TX alosetron or Lotronex
26. TX Acotiamide or YM-443 or Z-338D
27. TX acetylcholinesterase inhibitor* or cholinesterase Inhibitor* or anti-cholinesterase* or anticholinesterase*
28. TX (5HT-4 or 5HT4 or 5-HT 4 or 5-HT4) and agonist*
29. (MH "Serotonin Agonists+")
30. S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29
31. S1 and S31

WHAT'S NEW

Date	Event	Description
10 October 2017	New citation required and major changes	New author team formed and protocol updated to include new interventions

CONTRIBUTIONS OF AUTHORS

RP: drafted the revised protocol

YY: revised the protocol

NB: drafted the first version of the protocol

RK: drafted the first version of the protocol

GL: supervising author

PM: supervising author

DECLARATIONS OF INTEREST

RP: none known.

YY: none known.

NB: has received speaker honoraria, consulting and reimbursement for expenses from AbbVie.

RK: has received fees for consulting from Takeda, AbbVie, Jansen, Shire and Pfizer.

GL: none known.

PM: chair at McMaster University partly funded by an unrestricted donation by AstraZeneca, and has received consultants' and speakers' bureau fees from AstraZeneca, AxCan Pharma, Nycomed, and Johnson and Johnson.

SOURCES OF SUPPORT

Internal sources

- McMaster University, Canada.

External sources

- No sources of support supplied

NOTES

A new review team was formed and the following protocol sections updated.

- Background: recent citations to support this section were included.
- Methods

○ Types of participants: ROME criteria were expanded to 1 to 4 (from 1 to 3) since the new Rome IV criteria was published in 2016 after Rome III in 2006 (Stanghellini 2016)

○ Types of outcome measures: we revised the primary outcome from "proportion of patients with any improvement of symptoms" to "global symptoms of dyspepsia" (using the most stringent definition of not symptom-free or not overall symptom improvement given by the patient at the end of treatment), because overall symptom improvement is a more reliable measure than one or more symptoms when assessing the treatment efficacy; using the unfavourable outcome (not symptom-free or not improved) makes the risk ratio (RR) easier to be interpreted by clinicians.

- Search methods: we updated the search strategies to include the most recent filters and capture new drugs.
- Data collection and analysis

○ We removed individual symptom scores from the outcome because overall symptom improvement is a more reliable measure than improvement of a single symptom.

○ Assessment of risk of bias in included studies: we included the most recent version of the 'Risk of bias' domains to be assessed.

○ Subgroup analysis and investigation of heterogeneity: we included a subgroup to stratify studies according to their 'Risk of bias' assessment.

○ Sensitivity analysis: we will exclude studies with significant clinical heterogeneity in sensitivity analysis, and exclude studies that only assessed individual symptoms without data for overall symptom improvement in the sensitivity analysis.