

## SUPPLEMENT

### Search Strategy

MEDLINE, EMBASE and EMBASE Classic, and the Cochrane central register of controlled trials were searched. The search was limited to humans. No restrictions were applied with regard to language of publication. A recursive search of the bibliography of relevant articles was also conducted. Conference proceedings from Digestive Diseases Week, Asia Pacific Digestive Week, and United European Gastroenterology Week were searched. The literature search used is given below.

For randomised controlled trials of soluble or insoluble fibre:

- 1 irritable bowel syndrome.mp. or Colonic Diseases, Functional/ or Irritable Bowel Syndrome/
- 2 irritable colon.mp.
- 3 IBS.mp.
- 4 spastic colon.mp.
- 5 (functional adj5 bowel).mp.
- 6 1 or 2 or 3 or 4 or 5
- 7 Dietary Fiber/ or dietary fibre.mp.
- 8 cereals.mp. or Cereals/
- 9 psyllium.mp. or Psyllium/
- 10 sterculia.mp. or Sterculia/

- 11 karaya gum.mp. or Karaya Gum/
- 12 bulking agent.mp. or Cellulose/
- 13 psyllium fibre.mp.
- 14 psyllium fiber.mp.
- 15 dietary fiber.mp.
- 16 fiber.mp.
- 17 fibre.mp.
- 18 husk.mp.
- 19 bran.mp.
- 20 wheat bran.mp.
- 21 ispaghula.mp.
- 22 metamucil.mp.
- 23 fybogel.mp.
- 24 linseeds.mp.
- 25 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 o  
23 or 24
- 26 6 and 25

For randomised controlled trials of low FODMAP diet or gluten-free diet:

- 1 irritable bowel syndrome.mp. or Colonic Diseases, Functional/ or Irritable Bowel Syndrome/
- 2 irritable colon.mp.
- 3 IBS.mp.
- 4 spastic colon.mp.
- 5 (functional adj5 bowel).mp.
- 6 1 or 2 or 3 or 4 or 5
- 7 diet.mp.
- 8 gluten-free.mp.
- 9 gluten.mp.
- 10 FODMAP\$.mp.
- 11 7 or 8 or 9 or 10
- 12 6 and 11

For randomised controlled trials of probiotics:

- 1 irritable bowel syndrome.mp. or Colonic Diseases, Functional/ or Irritable Bowel Syndrome/
- 2 irritable colon.mp.
- 3 IBS.mp.
- 4 spastic colon.mp.
- 5 (functional adj5 bowel).mp.
- 6 1 or 2 or 3 or 4 or 5
- 7 saccharomyces.mp.
- 8 lactobacillus.mp.
- 9 bifidobacterium.mp.
- 10 escherischia coli.mp.
- 11 escherichia coli.mp.
- 12 probiotics.mp.
- 13 7 or 8 or 9 or 10 or 11 or 12
- 14 6 and 13

For randomised controlled trials of antispasmodic drugs:

- 1 irritable bowel syndrome.mp. or Colonic Diseases, Functional/ or Irritable Bowel Syndrome/
- 2 irritable colon.mp.
- 3 IBS.mp.
- 4 spastic colon.mp.
- 5 (functional adj5 bowel).mp.
- 6 1 or 2 or 3 or 4 or 5
- 7 Parasympatholytics.mp. or Parasympatholytics/
- 8 scopolamine.mp. or Scopolamine Hydrobromide/
- 9 scopolamine derivatives.mp. or Scopolamine Derivatives/
- 10 trimebutine.mp. or Trimebutine/
- 11 spasmolytics.mp.
- 12 spasmolytic agents.mp.
- 13 antispasmodics.mp.
- 14 antispasmodic agents.mp.
- 15 mebeverine.mp.
- 16 alverine.mp.
- 17 pinaverium.mp.
- 18 otilonium.mp.

- 19 octilonium.mp.
- 20 cimetropium.mp.
- 21 hyoscine.mp. or Scopolamine Hydrobromide/
- 22 muscarinic antagonists.mp. or Muscarinic Antagonists/
- 23 Butylscopolammonium Bromide.mp. or Butylscopolammonium Bromide/
- 24 hyoscine butyl bromide.mp.
- 25 butylscopolamine.mp.
- 26 dicyclomine.mp. or Dicyclomine/
- 27 dicycloverine.mp.
- 28 propinox.mp.
- 29 rociverine.mp.
- 30 pirenzipine.mp. or Pirenzepine/
- 31 prifinium.mp.
- 32 drotaverine.mp.
- 33 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22  
or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32
- 34 6 and 33

For randomised controlled trials of peppermint oil:

- 1 irritable bowel syndrome.mp. or Colonic Diseases, Functional/ or Irritable Bowel Syndrome/
- 2 irritable colon.mp.
- 3 IBS.mp.
- 4 spastic colon.mp.
- 5 (functional adj5 bowel).mp.
- 6 1 or 2 or 3 or 4 or 5
- 7 peppermint oil.mp. or Menthol/
- 8 peppermint.mp. or Mentha piperita/
- 9 colpermin.mp.
- 10 mintec.mp.
- 11 7 or 8 or 9 or 10
- 12 6 and 11

For randomised controlled trials of gut-brain neuromodulators:

- 1 irritable bowel syndrome.mp. or Colonic Diseases, Functional/ or Irritable Bowel Syndrome/
- 2 irritable colon.mp.
- 3 IBS.mp.
- 4 spastic colon.mp.
- 5 (functional adj5 bowel).mp.
- 6 1 or 2 or 3 or 4 or 5
- 7 psychotropic drugs.mp. or Psychotropic Drugs/
- 8 antidepressive agents.mp. or Antidepressive Agents/
- 9 Antidepressive Agents, Tricyclic/ or tricyclic.mp. or Amitriptyline/
- 10 antidepressants.mp.
- 11 serotonin uptake inhibitors.mp. or Serotonin Uptake Inhibitors/
- 12 serotonin reuptake inhibitors.mp.
- 13 selective serotonin reuptake inhibitors.mp.
- 14 serotonin re-uptake inhibitors.mp.
- 15 selective serotonin re-uptake inhibitors.mp.
- 16 desimipramine.mp.
- 17 doxepin.mp. or Doxepin/
- 18 dothiepin.mp. or Dothiepin/



19 amitriptyline.mp. or Amitriptyline/

20 trimipramine.mp. or Trimipramine/

21 desipramine.mp. or Desipramine/

22 imipramine.mp. or Imipramine/

23 nortriptyline.mp. or Nortriptyline/

24 paroxetine.mp. or Paroxetine/

25 fluoxetine.mp. or Fluoxetine/

26 sertraline.mp. or Sertraline/

27 citalopram.mp. or Citalopram/

28 escitalopram.mp. or Citalopram/

29 venlafaxine.mp.

30 efexor.mp.

31 prozac.mp.

32 seroxat.mp.

33 duloxetine.mp.

34 pregabalin.mp.

35. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or  
23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34

35 6 and 35

For randomised controlled trials of laxatives, 5-HT<sub>4</sub> receptor agonists, and secretagogues:

- 1 irritable bowel syndrome.mp. or Colonic Diseases, Functional/ or Irritable Bowel Syndrome/
- 2 irritable colon.mp.
- 3 IBS.mp.
- 4 spastic colon.mp.
- 5 (functional adj5 bowel).mp.
- 6 1 or 2 or 3 or 4 or 5 (55240)
- 7 laxatives.mp. or Cathartics/ or Anthraquinones/ or Laxatives/ or Phenolphthaleins/ or Indoles/ or Phenols/
- 8 polyethylene glycol.mp. or Polyethylene Glycols/
- 9 lactulose.mp. or Lactulose/
- 10 Serotonin Agonists/ or tegaserod.mp. or Receptors, Serotonin, 5-HT<sub>4</sub>/
- 11 zelnorm.mp.
- 12 Senna Plant/ or Senna Extract/ or senna\$.mp.
- 13 linaclotide.mp.
- 14 prucalopride.mp.
- 15 lubiprostone.mp. or Receptors, Prostaglandin E/
- 16 bisacodyl.mp. or Bisacodyl/

- 17 sodium picosulphate.mp. or Phosphates/
- 18 docusate.mp. or Dioctyl Sulfosuccinic Acid/
- 19 Magnesium/ or milk of magnesia.mp.
- 20 magnesium hydroxide.mp. or Magnesium Hydroxide/
- 21 sorbitol.mp. or Sorbitol/
- 22 danthron.mp.
- 23 poloxalkol.mp. or Poloxamer/
- 24 A3309.mp.
- 25 elobixibat.mp.
- 26 constella.mp.
- 27 linzess.mp.
- 28 amitiza.mp.
- 29 plecanatide.mp.
- 30 trulance.mp.
- 31 tenapanor.mp.
- 32 velusetrag.mp.
- 33 naronapride.mp.
- 34 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22  
or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
- 35 6 and 34

For randomised controlled trials of anti-diarrhoeal drugs and eluxadoline:

- 1 irritable bowel syndrome.mp. or Colonic Diseases, Functional/ or Irritable Bowel Syndrome/
- 2 irritable colon.mp.
- 3 IBS.mp.
- 4 spastic colon.mp.
- 5 (functional adj5 bowel).mp.
- 6 1 or 2 or 3 or 4 or 5
- 7 loperamide.mp.
- 8 immodium.mp.
- 9 eluxadoline.mp.
- 12 viberzi.mp.
- 13 7 or 8 or 9 or 10 or 11 or 12
- 14 6 and 13

For randomised controlled trials of 5-HT<sub>3</sub> receptors antagonists:

- 1 irritable bowel syndrome.mp. or Colonic Diseases, Functional/ or Irritable Bowel Syndrome/
- 2 irritable colon.mp.
- 3 IBS.mp.
- 4 spastic colon.mp.
- 5 (functional adj5 bowel).mp.
- 6 1 or 2 or 3 or 4 or 5
- 7 serotonin antagonists.mp. or Serotonin Antagonists/
- 8 Receptors, Serotonin/ or 5HT3.mp.
- 9 5-HT3.mp. or Serotonin 5-HT3 Receptor Antagonists/ or Receptors, Serotonin, 5-HT3/
- 10 alosetron.mp.
- 11 ramosetron.mp.
- 12 ondansetron.mp.
- 13 7 or 8 or 9 or 10 or 11 or 12
- 14 6 and 13

For randomised controlled trials of antibiotics:

- 1 irritable bowel syndrome.mp. or Colonic Diseases, Functional/ or Irritable Bowel Syndrome/
- 2 irritable colon.mp.
- 3 IBS.mp.
- 4 spastic colon.mp.
- 5 (functional adj5 bowel).mp.
- 6 1 or 2 or 3 or 4 or 5
- 7 anti-bacterial agents.mp.
- 8 penicillins.mp.
- 9 cephalosporins.mp.
- 10 rifamycins.mp.
- 11 quinolones.mp.
- 12 nitroimidazoles.mp.
- 13 tetracycline.mp.
- 14 doxycycline.mp.
- 15 amoxicillin.mp.
- 16 ciprofloxacin.mp.
- 17 metronidazole.mp.
- 18 tinidazole.mp.

19 antibiotic.mp.

20 rifaximin.mp.

21 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20

22 6 or 21

For randomised controlled trials of psychological therapies:

- 1 irritable bowel syndrome.mp. or Colonic Diseases, Functional/ or Irritable Bowel Syndrome/
- 2 irritable colon.mp.
- 3 IBS.mp.
- 4 spastic colon.mp.
- 5 (functional adj5 bowel).mp.
- 6 1 or 2 or 3 or 4 or 5
- 7 behavior therapy.mp. or Behavior Therapy/
- 8 behaviour therapy.mp.
- 9 behavioral therapy.mp.
- 10 behavioural therapy.mp.
- 11 cognitive behavior therapy.mp. or Cognitive Therapy/
- 12 cognitive behavioral therapy.mp.
- 13 cognitive behaviour therapy.mp.
- 14 cognitive behavioural therapy.mp.
- 15 psychotherapy.mp. or Psychotherapy/ or Psychotherapy, Multiple/ or Psychotherapy, Group/ or Psychotherapy, Brief/
- 16 relaxation therapy.mp. or Relaxation Therapy/
- 17 relaxation technique.mp.



- 18 hypnosis.mp. or Hypnosis/
- 19 hypnotherapy.mp.
- 20 stress management.mp.
- 21 Contingency management.mp.
- 22 (Emotional awareness and expression training).mp.
- 23 Mindfulness meditation.mp.
- 24 Dynamic psychotherapy.mp.
- 25 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22  
or 23 or 24
- 26 6 and 25

**Supplementary Table 1. Summary of Evidence from Randomised Controlled Trials of Dietary Therapies, Drugs, and Psychological Therapies in Irritable Bowel Syndrome.**

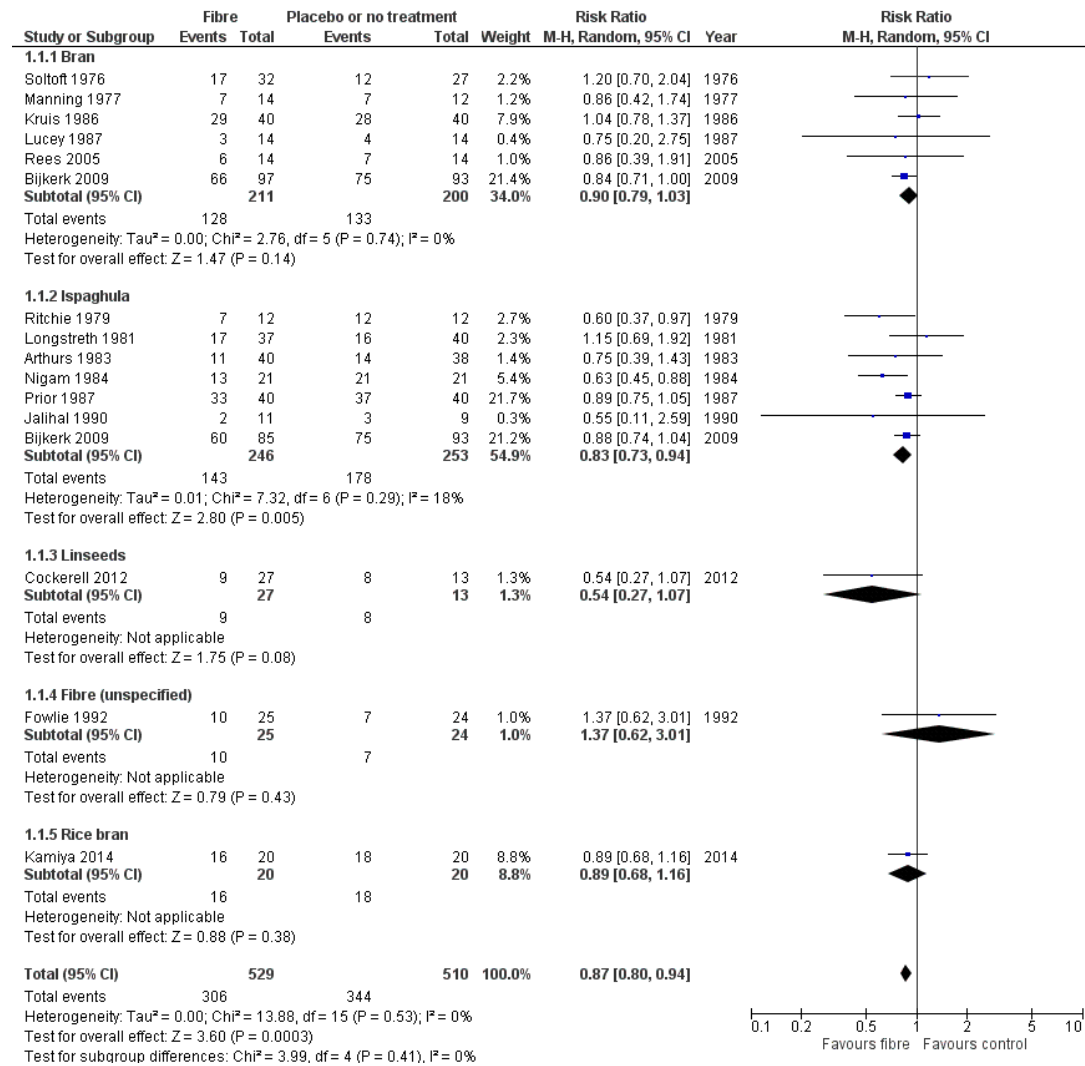
<b>Intervention</b>	<b>Number of RCTs</b>	<b>Number of Patients</b>	<b>IBS Subtype</b>	<b>Relative Risk of Remaining Symptomatic (95% CI)</b>	<b>Recommendation</b>	<b>Quality of Evidence</b>
<b>Ispaghula, but not bran, is effective in IBS</b>	7	499	Not stated	0.83 (0.73 to 0.94)	Strong	Moderate
<b>A low FODMAP diet may be effective in IBS</b>	11	658	Not stated	0.71 (0.61 to 0.83)	Weak	Very low
<b>There is insufficient evidence to recommend a gluten-free diet in IBS</b>	2	111	Not stated	0.42 (0.11 to 1.55)	Weak	Very low
<b>Certain probiotics may be effective in IBS</b>						
Combinations of probiotics	23	2327	Not stated	0.79 (0.70 to 0.89)	Weak	Very low
<i>Lactobacillus</i>	11	1233	Not stated	0.75 (0.60 to 0.94)	Weak	Very low
<i>Bifidobacterium</i>	5	1194	Not stated	0.80 (0.70 to 0.91)	Weak	Very low
<i>Escherichia</i>	2	418	Not stated	0.86 (0.79 to 0.93)	Weak	Very low
<b>Loperamide may be effective for diarrhoea in IBS</b>	2	42	IBS-D or IBS-M	0.44 (0.14 to 1.42)	Strong	Very low

<b>Certain antispasmodics may be effective in IBS</b>						
All antispasmodics	26	2811	Not stated	0.65 (0.56 to 0.76)	Weak	Very low
Otilonium	5	791	Not stated	0.70 (0.54 to 0.90)	Weak	Very low
Pinaverium	4	615	Not stated	0.56 (0.38 to 0.82)	Weak	Very low
Hyoscine	3	426	Not stated	0.63 (0.51 to 0.78)	Weak	Very low
Cimetropium	3	152	Not stated	0.38 (0.20 to 0.71)	Weak	Very low
Drotaverine	2	250	Not stated	0.31 (0.19 to 0.50)	Weak	Very low
Dicycloverine	1	97	Not stated	0.65 (0.45 to 0.95)	Weak	Very low
<b>Peppermint oil may be effective in IBS</b>	8	823	Not stated	0.58 (0.34 to 0.98)	Weak	Very low
<b>Polyethylene glycol may be effective for constipation in IBS</b>	2	181	IBS-C	Data not pooled	Weak	Very low
<b>Tricyclic antidepressants are effective in IBS</b>	12	787	Not stated	0.65 (0.55 to 0.77)	Strong	Moderate
<b>Selective serotonin reuptake inhibitors may be effective in IBS</b>	7	356	Not stated	0.68 (0.51 to 0.91)	Weak	Low
<b>Eluxadoline is effective in IBS-D</b>						
75mg b.i.d.	2	1619	IBS-D	0.89 (0.84 to 0.94)	Weak	Moderate
100mg b.i.d.	4	2312	IBS-D	0.87 (0.83 to 0.91)	Weak	Moderate

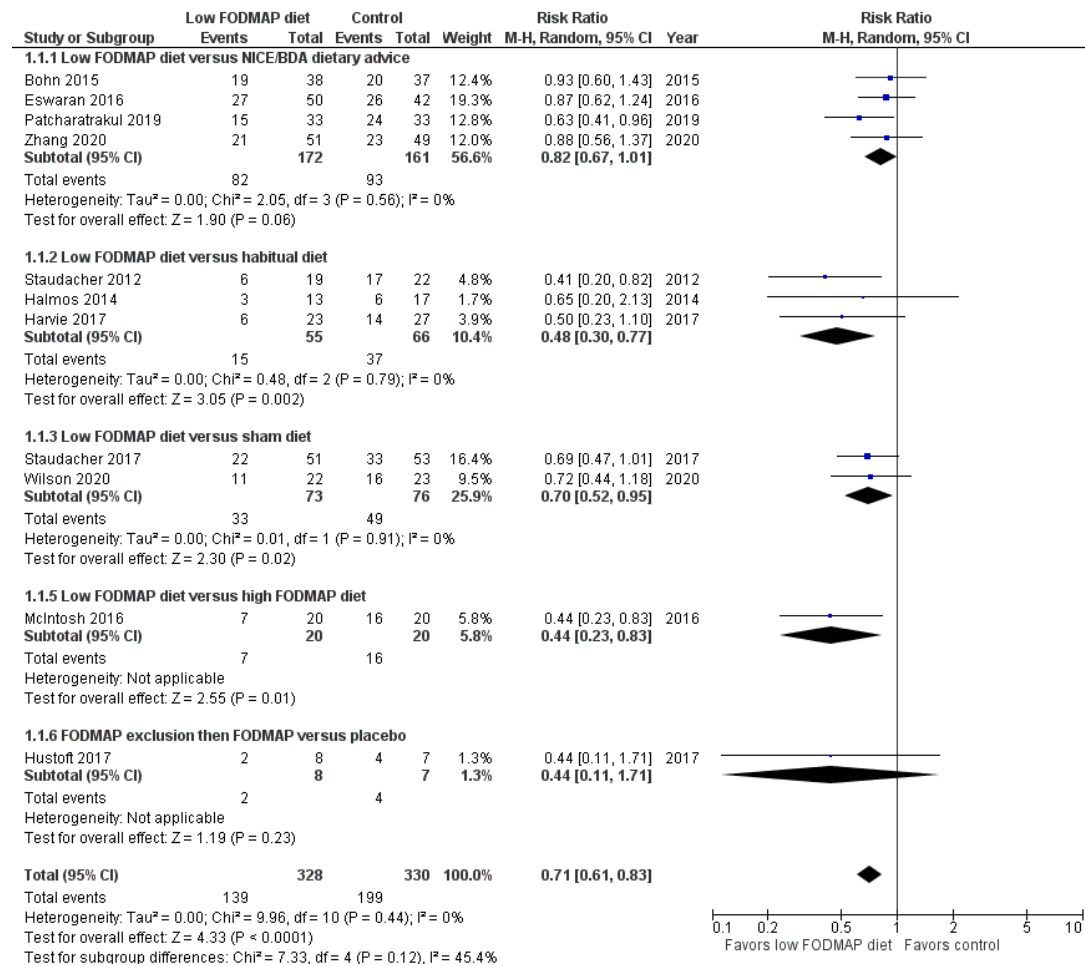
<b>5-HT<sub>3</sub> antagonists are effective in IBS-D</b>						
Alosetron 1mg b.i.d.	3	787	IBS-D	0.69 (0.60 to 0.80)	Weak	High
Ramosetron 2.5mcg o.d.	1	348	IBS-D	0.78 (0.67 to 0.91)	Weak	Moderate
<b>Rifaximin is effective in IBS-D or IBS-M</b>	2	1260	IBS-D or IBS-M	0.92 (0.86 to 0.98)	Weak	Moderate
<b>Linacotide is effective in IBS-C</b>	5	3193	IBS-C	0.82 (0.78 to 0.87)	Strong	High
<b>Lubiprostone is effective in IBS-C</b>	2	452	IBS-C	0.87 (0.78 to 0.96)	Strong	Moderate
<b>Plecanatide is effective in IBS-C</b>						
3mcg o.d.	3	1632	IBS-C	0.88 (0.82 to 0.94)	Strong	High
6mcg o.d.	2	1461	IBS-C	0.87 (0.81 to 0.93)	Strong	High
<b>Tenapanor is effective in IBS-C</b>	3	1428	IBS-C	0.85 (0.79 to 0.92)	Strong	High
<b>Tegaserod is effective in IBS-C</b>	3	2472	IBS-C	0.85 (0.80 to 0.91)	Strong	Moderate
<b>IBS-specific cognitive behavioural therapy may be effective in IBS</b>						
Face-to-face CBT	10	930	Not stated	0.62 (0.48 to 0.80)	Strong	Low
Self-administered/minimal contact CBT	4	434	Not stated	0.61 (0.45 to 0.83)	Strong	Low
Group CBT	2	50	Not stated	0.41 (0.19 to 0.91)	Weak	Low
Telephone-delivered CBT	1	373	Not stated	0.50 (0.29 to 0.84)	Weak	Low

<b>Gut-directed hypnotherapy may be effective in IBS</b>	6	639	Not stated	0.67 (0.49 to 0.91)	Strong	Low
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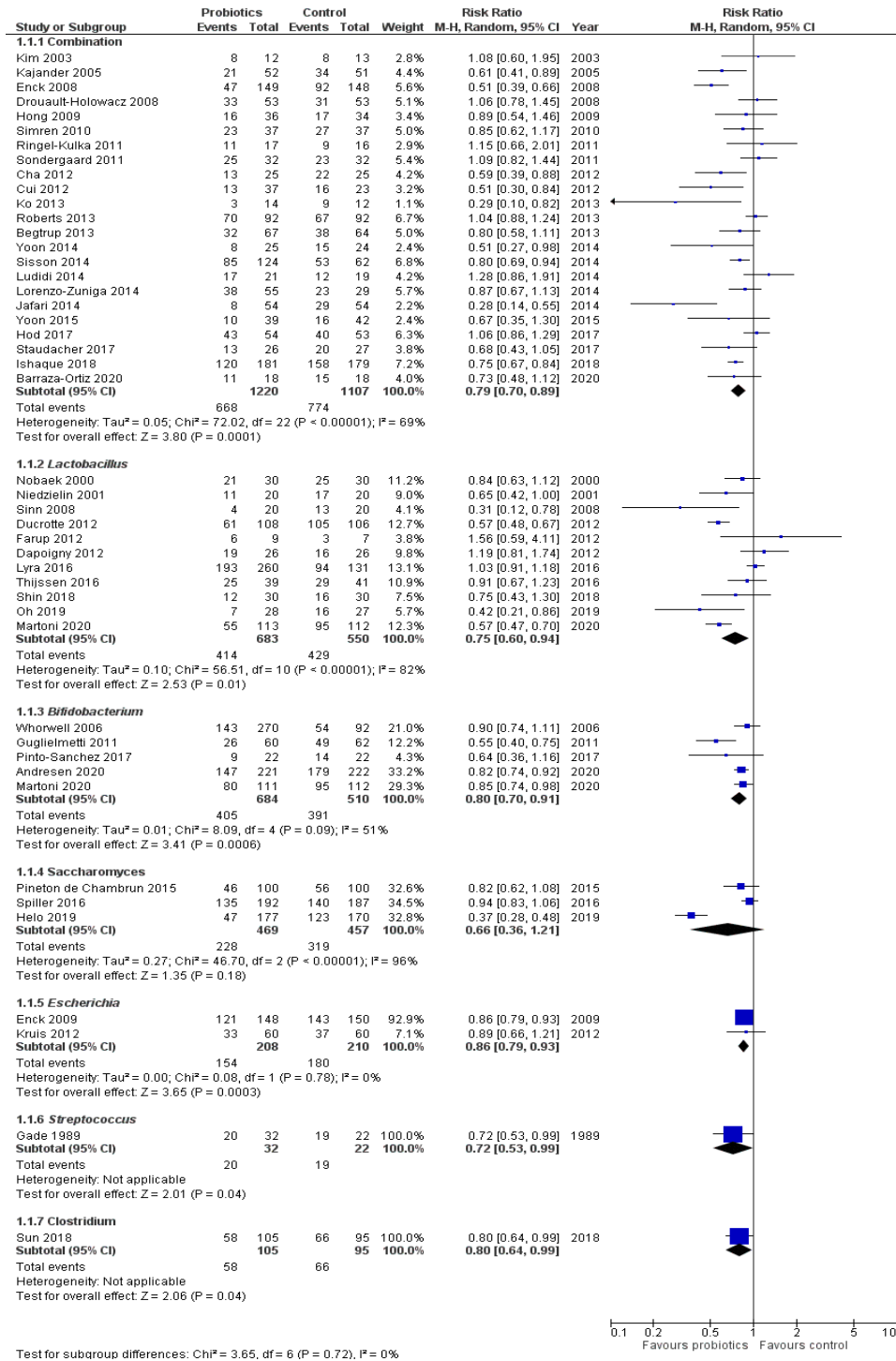
## Supplementary Figure 1. Forest Plot of Randomised Controlled Trials of Fibre in IBS in Terms of Effect on Global Symptoms or Abdominal Pain: Trial-based Meta-analysis.



**Supplementary Figure 2. Forest Plot of Randomised Controlled Trials of a Low FODMAP Diet in IBS in Terms of Effect on Global Symptoms or Abdominal Pain: Trial-based Meta-analysis.**

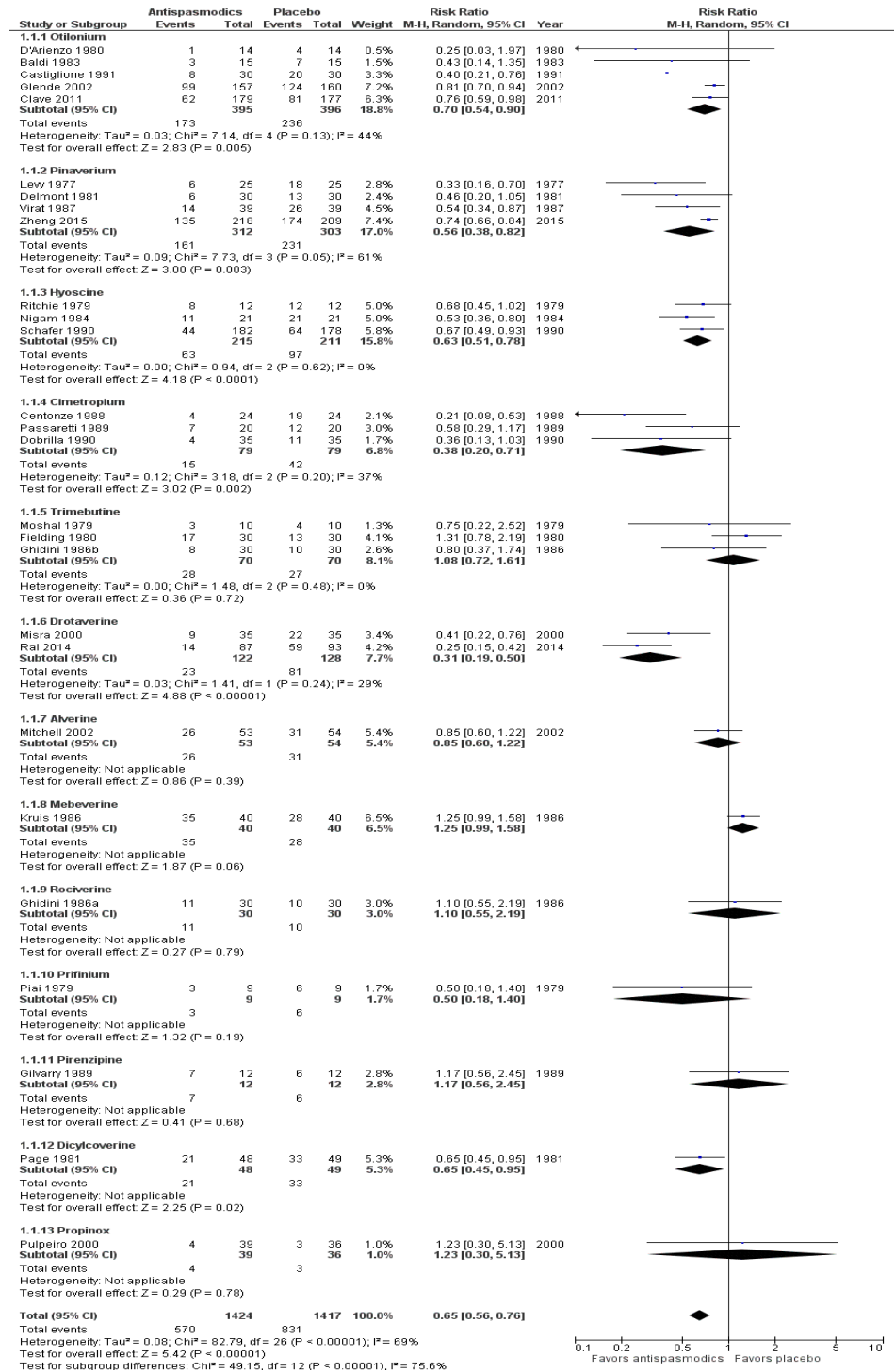


### Supplementary Figure 3. Forest Plot of Randomised Controlled Trials of Probiotics in IBS in Terms of Effect on Global Symptoms or Abdominal Pain: Trial-based Meta-analysis.

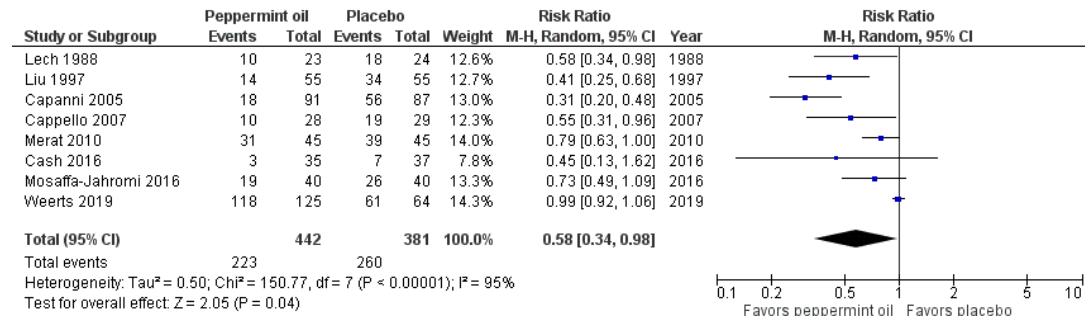




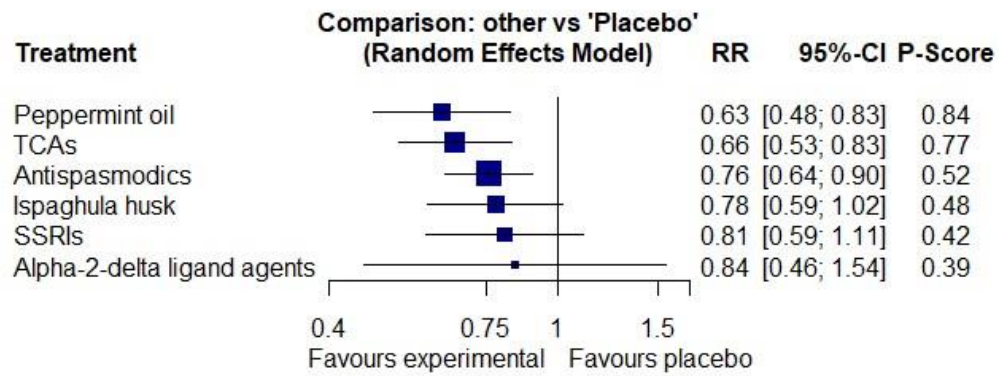
### Supplementary Figure 4. Forest Plot of Randomised Controlled Trials of Antispasmodics in IBS in Terms of Effect on Global Symptoms or Abdominal Pain: Trial-based Meta-analysis.



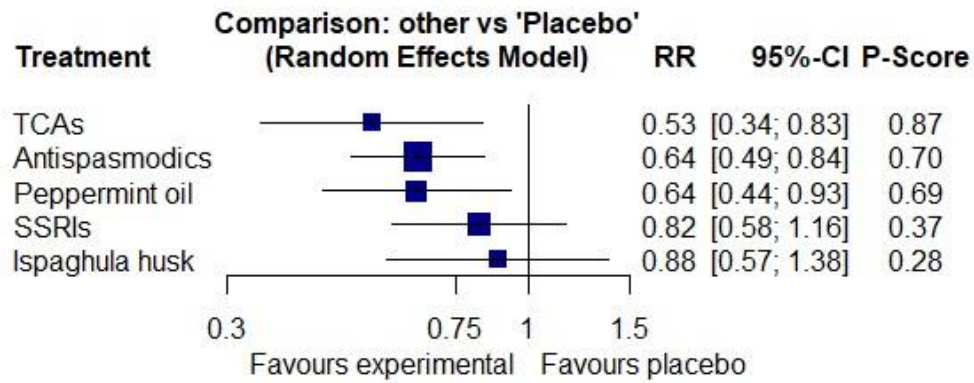
**Supplementary Figure 5. Forest Plot of Randomised Controlled Trials of Peppermint Oil in IBS in Terms of Effect on Global Symptoms or Abdominal Pain: Trial-based Meta-analysis.**



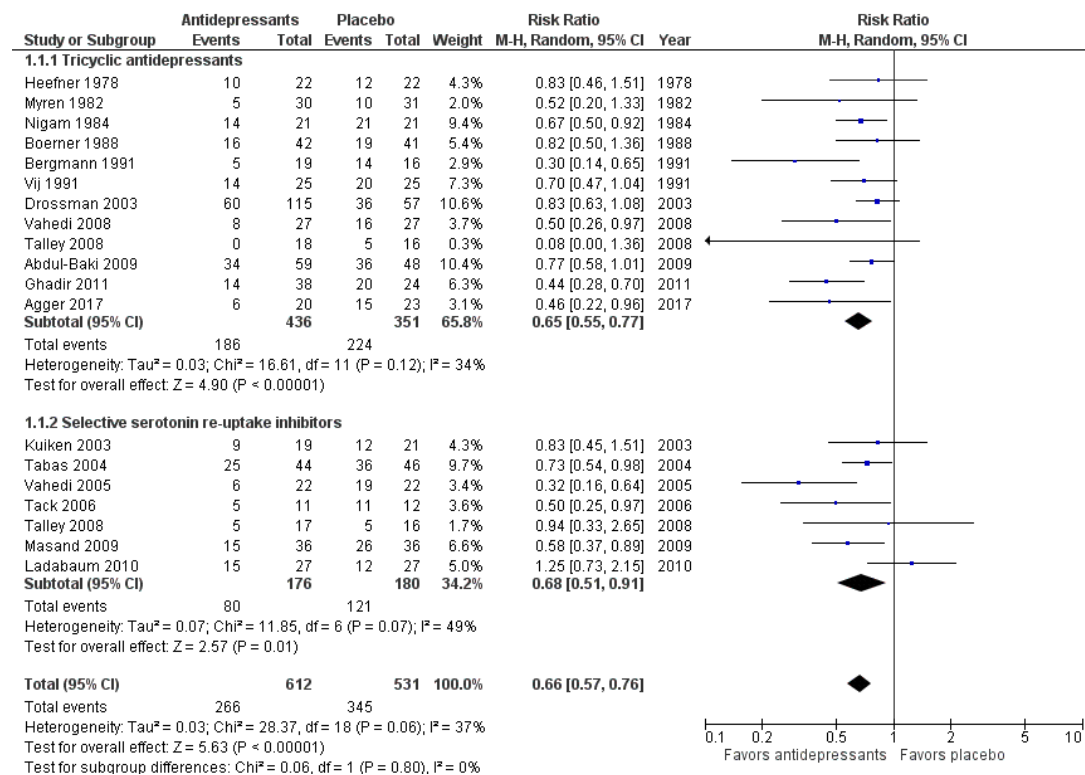
**Supplementary Figure 6. Forest Plot of Unlicensed or “Traditional” Treatments in IBS  
in Terms of Effect on Global Symptoms: Network Meta-analysis.**



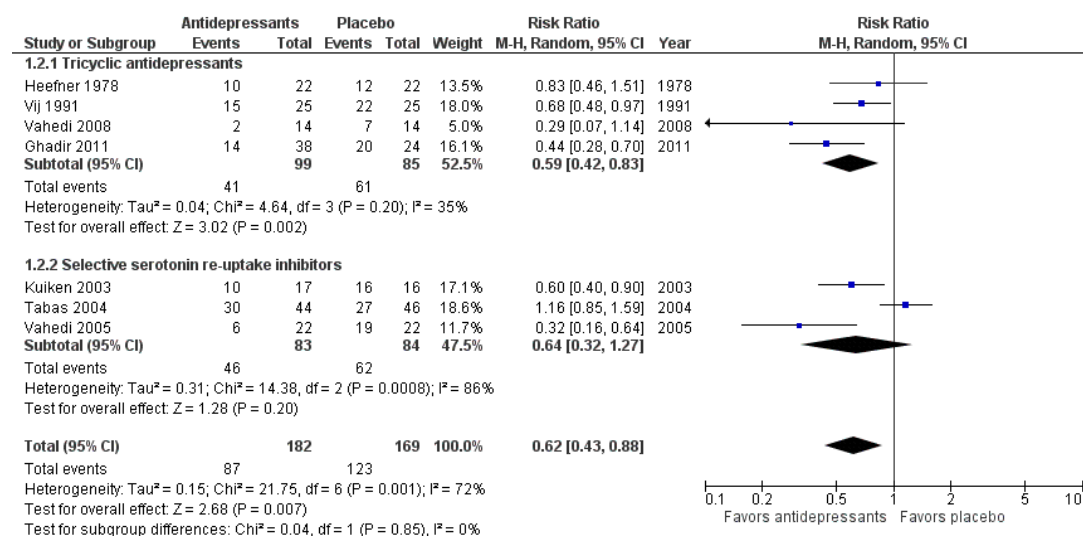
**Supplementary Figure 7. Forest Plot of Unlicensed or “Traditional” Treatments in IBS in Terms of Effect on Abdominal Pain: Network Meta-analysis.**



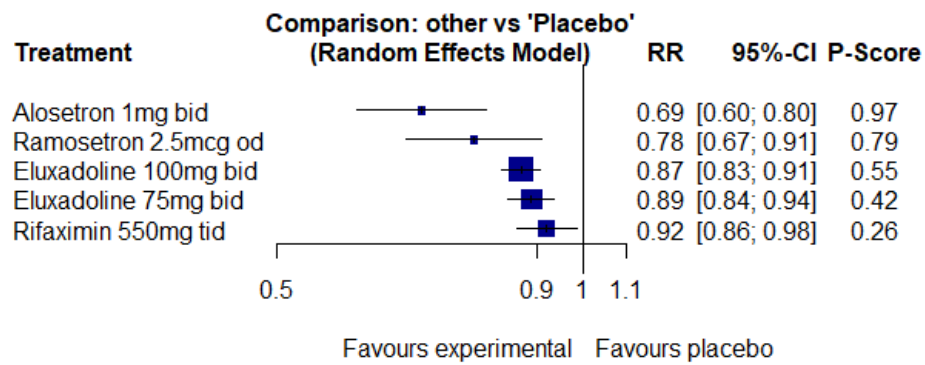
**Supplementary Figure 8. Forest Plot of Randomised Controlled Trials of Tricyclic Antidepressants and Selective Serotonin Reuptake Inhibitors in IBS in Terms of Effect on Global Symptoms or Abdominal Pain: Trial-based Meta-analysis.**



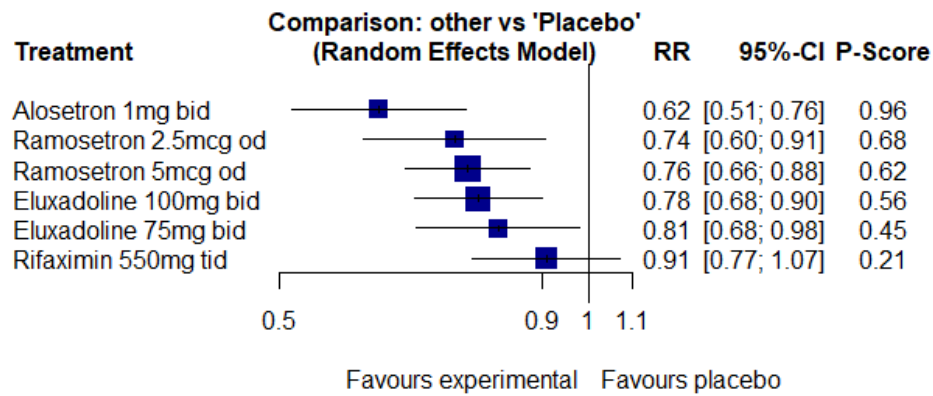
**Supplementary Figure 9. Forest Plot of Randomised Controlled Trials of Tricyclic Antidepressants and Selective Serotonin Reuptake Inhibitors in IBS in Terms of Effect on Abdominal Pain: Trial-based Meta-analysis.**



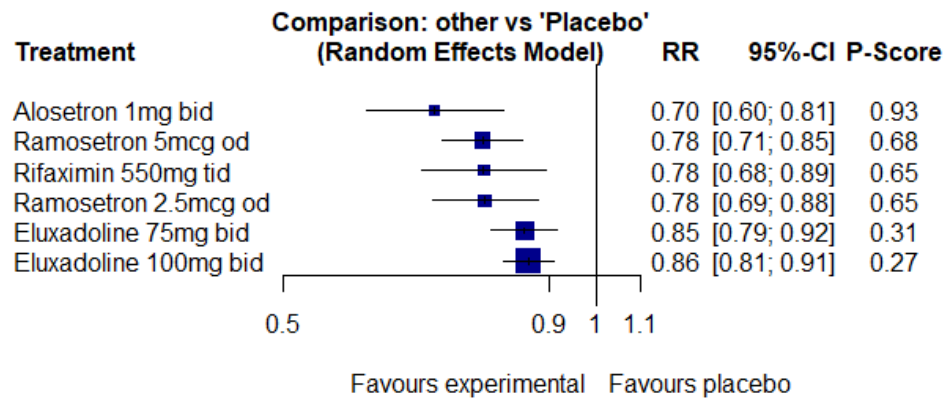
**Supplementary Figure 10. Forest Plot of Randomised Controlled Trials of 5-HT<sub>3</sub> Antagonists, Eluxadoline, and Rifaximin in IBS in Terms of Effect on a Composite Endpoint of Improvement in Abdominal Pain and Stool Consistency: Network Meta-analysis.**



**Supplementary Figure 11. Forest Plot of Randomised Controlled Trials of 5-HT<sub>3</sub> Antagonists, Eluxadoline, and Rifaximin in IBS in Terms of Effect on Global Symptoms: Network Meta-analysis.**



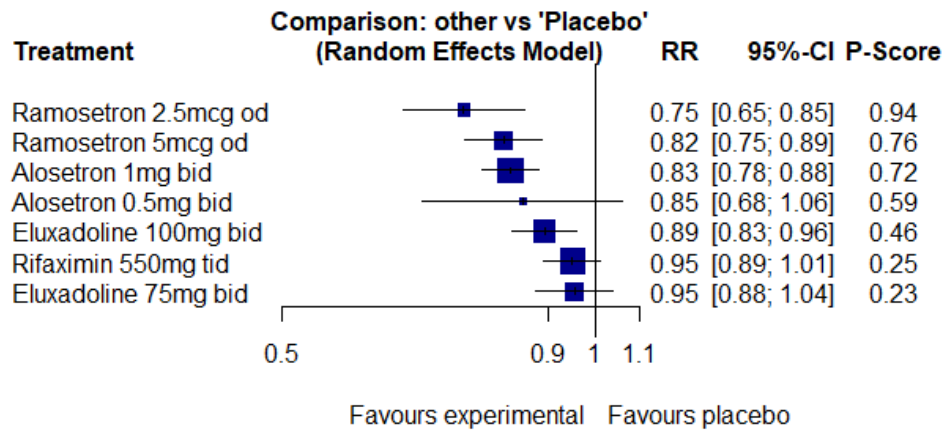


**Supplementary Figure 12. Forest Plot of Randomised Controlled Trials of 5-HT<sub>3</sub>****Antagonists, Eluxadoline, and Rifaximin in IBS in Terms of Effect on Stool****Consistency: Network Meta-analysis.**

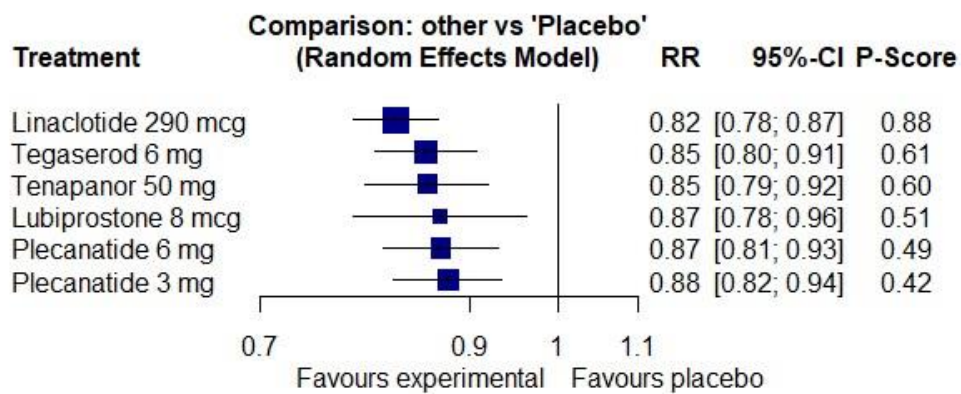
### Supplementary Figure 13. Forest Plot of Randomised Controlled Trials of 5-HT<sub>3</sub>

Antagonists, Eluxadoline, and Rifaximin in IBS in Terms of Effect on Abdominal Pain:

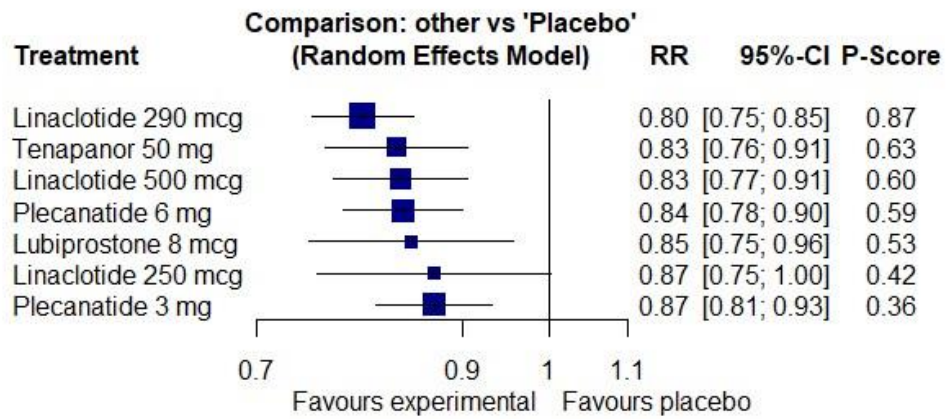
Network Meta-analysis.



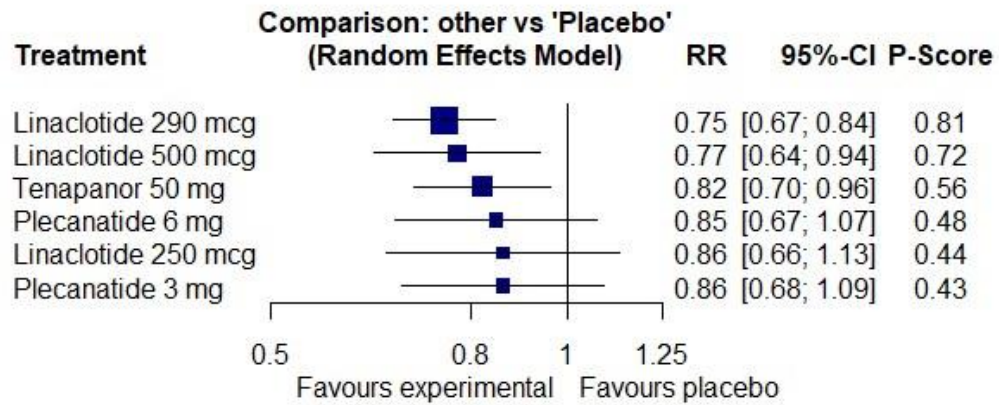
**Supplementary Figure 14. Forest Plot of Randomised Controlled Trials of Linaclotide, Lubiprostone, Plecanatide, Tenapanor, and Tegaserod in IBS in Terms of Effect on a Composite Endpoint of Improvement in Abdominal Pain and an Increase of  $\geq 1$  Complete Spontaneous Bowel Movements Per Week from Baseline: Network Meta-analysis.**



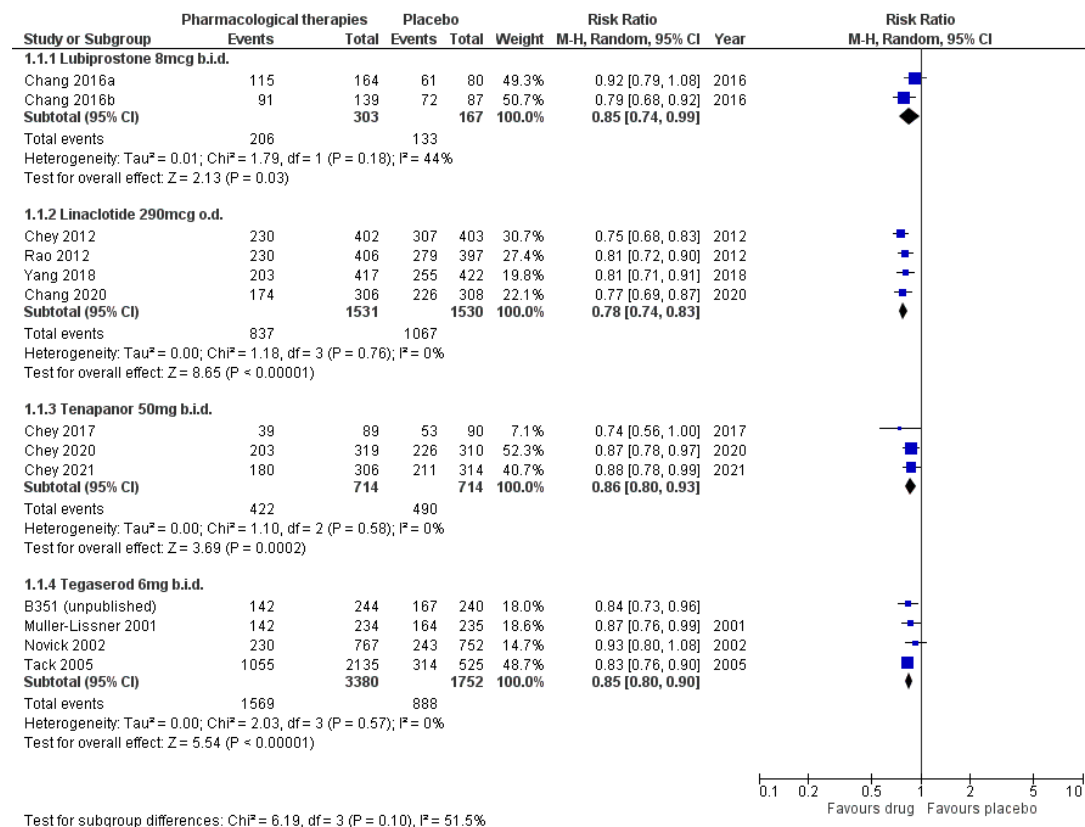
**Supplementary Figure 15. Forest Plot of Randomised Controlled Trials of Linaclotide, Lubiprostone, Plecanatide, and Tenapanor in IBS in Terms of Effect on Abdominal Pain: Network Meta-analysis.**



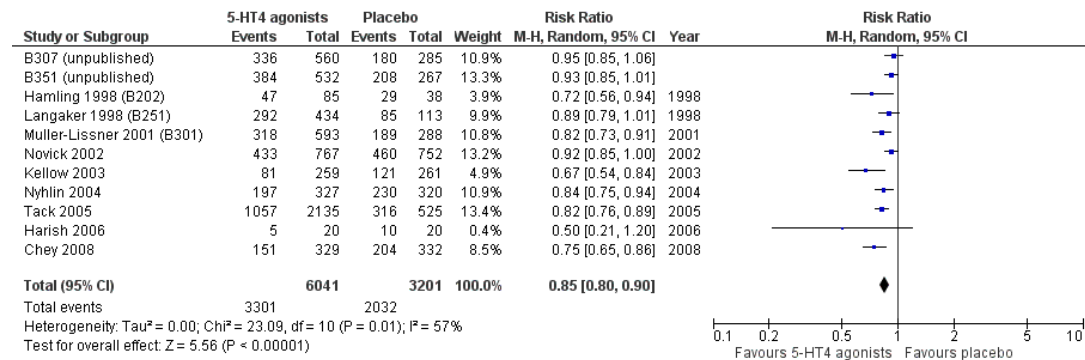
**Supplementary Figure 16. Forest Plot of Randomised Controlled Trials of Linaclotide, Lubiprostone, Plecanatide, and Tenapanor in IBS in Terms of an Increase of  $\geq 1$  Complete Spontaneous Bowel Movements Per Week from Baseline: Network Meta-analysis.**



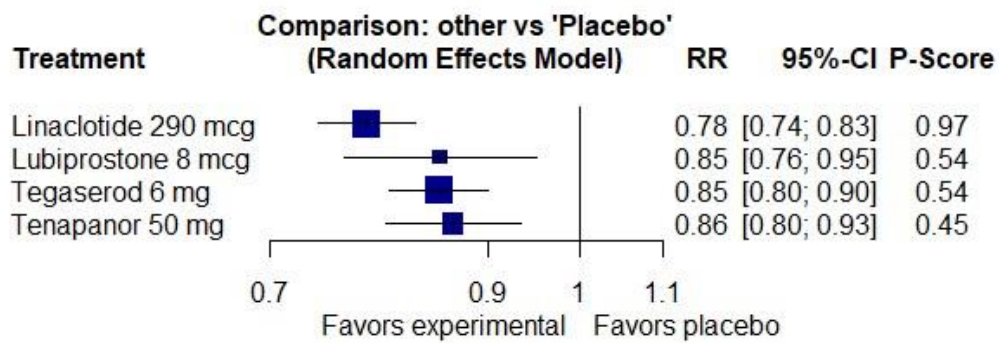
## Supplementary Figure 17. Forest Plot of Randomised Controlled Trials of Linaclotide, Lubiprostone, Tegaserod, and Tenapanor in IBS in Terms of an Improvement in Abdominal Bloating: Trial-based Meta-analysis.



**Supplementary Figure 18. Forest Plot of Randomised Controlled Trials of Tegaserod in IBS in Terms of Effect on Global Symptoms or Abdominal Pain: Trial-based Meta-analysis.**

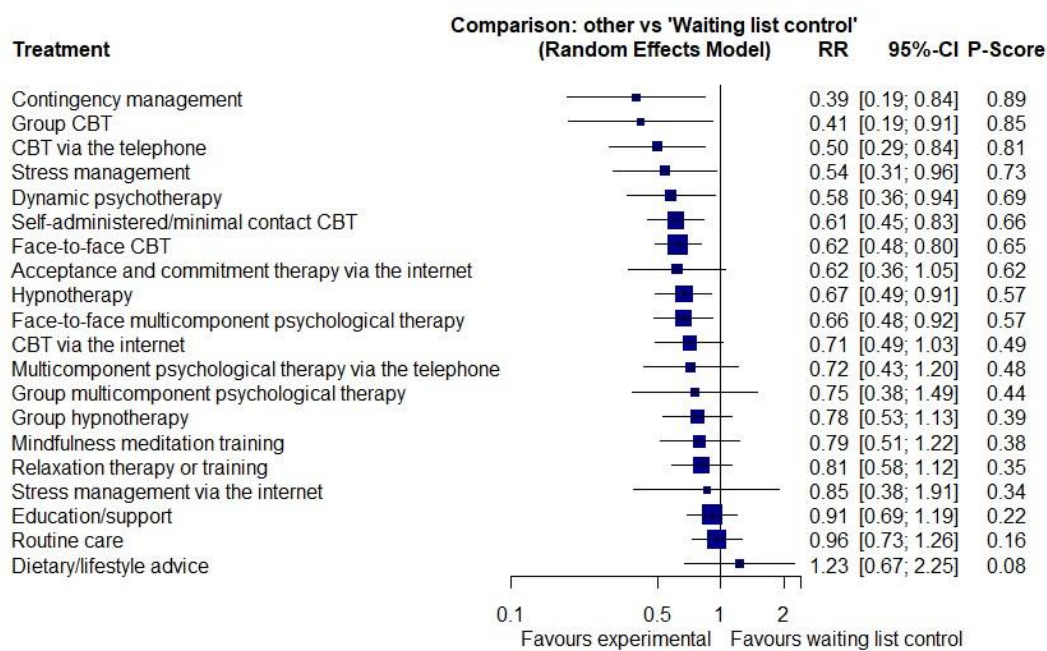


**Supplementary Figure 19. Forest Plot of Randomised Controlled Trials of Linaclotide, Lubiprostone, Tegaserod, and Tenapanor in IBS in Terms of an Improvement in Abdominal Bloating: Network Meta-analysis.**





**Supplementary Figure 20. Forest Plot of Randomised Controlled Trials of Psychological Therapies in IBS in Terms of Effect on Global Symptoms or Abdominal Pain: Network Meta-analysis.**





**Supplementary Figure 22. Forest Plot of Randomised Controlled Trials of Psychological Therapies in IBS in Terms of Effect on Global Symptoms or Abdominal Pain at 12-month Follow-up: Network Meta-analysis.**

