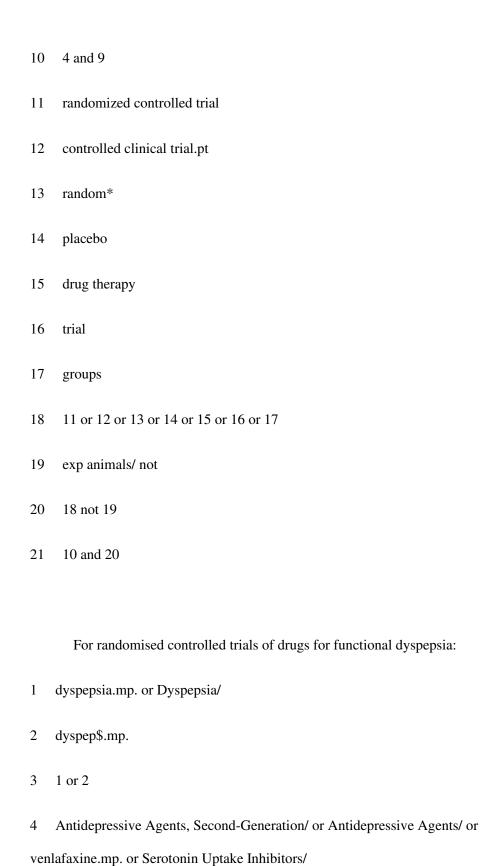
SUPPLEMENT

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 eradication therapy for *H. pylori*-positive functional dyspepsia:

- 1 exp Dyspepsia/
- 2 dyspep* or "NUD" or "FD"
- 3 indigestion or indigestive
- 4 1 or 2 or 3
- 5 exp helicobacter
- 6 exp helicobacter infections
- 7 exp helicobacter pylori
- 8 helicobacter or pylori or pyloridis or "HP" or Campylobacter
- 9 5 or 6 or 7 or 8



- 5 psychotropic drugs.mp. or Psychotropic Drugs/
- 6 antidepressive agents.mp. or Antidepressive Agents/
- 7 Antidepressive Agents, Tricyclic/ or Desipramine/ or tricyclic.mp. or Nortriptyline/ or Serotonin Uptake Inhibitors/ or Imipramine/
- 8 desimipramine.mp.
- 9 doxepin.mp. or Doxepin/
- 10 dothiepin.mp. or Dothiepin/
- 11 Amitriptyline/ or amitryptiline.mp.
- 12 paroxetine.mp. or Paroxetine/
- 13 sertraline.mp. or Sertraline/
- 14 fluoxetine.mp. or Fluoxetine/
- 15 citalopram.mp. or Citalopram/
- 16 trimipramine.mp. or Trimipramine/
- 17 desipramine.mp. or Desipramine/
- 18 imipramine.mp. or Imipramine/
- 19 nortiptyline.mp. or Nortriptyline/
- 20 venlafaxine.mp.
- 21 duloxetine.mp.
- 22 escitalopram.mp.

23	Sulpiride/ or levosulpiride.mp.
24	mirtazapine.mp.
25	pregabalin
26	gabapentin
27	Histamine 2 receptor antagonists.mp.
28	Histamine-2 receptor antagonists.mp.
29	H2 receptor antagonists.mp.
30	H-2 receptor antagonists.mp.
31	famotidine.mp.
32	nizatidine.mp.
33	ranitidine.mp.
34	cimetidine.mp.
35	proton pump inhibitors.mp.
36	PPIs.mp. 35 omeprazole.mp.
37	esomeprazole.mp.
38	lansoprazole.mp.
39	dexlansoprazole.mp.
40	rabeprazole.mp.

pantoprazole.mp.

42	zantac.mp.
43	tagamet.mp.
44	losec.mp.
45	prilosec.mp.
46	zoton.mp.
47	nexium.mp.
48	pariet.mp.
49	protium.mp.
50	mosapride.mp.
51	itopride.mp.
52	Ganaton.mp.
53	acotiamide.mp.
54	Acofide.mp.
55	tegaserod.mp.
56	zelnorm.mp.
57 Reu	serotonin norepinephrine reuptake inhibitors.mp or Serotonin and Noradrenaline ptake Inhibitors/
58	Serotonin 5-HT1 Receptor agonists/ or tandospirone.mp or Receptor, Serotonin, 5
HT1	A/

- 59. buspirone.mp or Buspirone/
- 4 or 5 or 6 or 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 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59
- 61 3 and 60

Supplementary Table 1. Summary of Evidence from Randomised Controlled Trials of Drugs in Functional Dyspepsia.

Intervention	Number of	Number of	FD Subtype	Relative Risk of Symptoms	Recommendation	Quality of
	RCTs	Patients		not Improving (95% CI)		Evidence
H. pylori eradication therapy is effective in	29	6781	Not stated	0.87 (0.83 to 0.92)	Strong	High
FD						
Histamine-2-receptor antagonists may be	12	2268	Not stated	0.79 (0.68 to 0.92)	Weak	Low
effective in FD						
Proton pump inhibitors are effective in FD						
Any dose	16	6017	Not stated	0.88 (0.83 to 0.93)	Strong	High
High dose	5	1627	Not stated	0.86 (0.74 to 1.01)	Strong	High
Standard dose	9	2890	Not stated	0.86 (0.78 to 0.95)	Strong	High
Low dose	9	2755	Not stated	0.89 (0.81 to 0.97)	Strong	High

Prokinetics may be effective in FD						
Acotiamide	6	2429	Mainly PDS	0.89 (0.78 to 1.00)	Weak	Low
Itopride	5	1854	Not stated	0.88 (0.77 to 1.01)	Weak	Low
Mosapride	1	589	Not stated	0.99 (0.80 to 1.23)	Weak	Low
Tegaserod	2	2667	Not stated	0.89 (0.82 to 0.96)	Strong	Moderate
Antipsychotic drugs (sulpiride and levosulpiride) may be effective in FD	3	172	Not stated	0.50 (0.37 to 0.67)	Weak	Low
Tricyclic antidepressants are effective in FD	4	400	Not stated	0.75 (0.62 to 0.90)	Strong	Moderate
Selective serotonin reuptake inhibitors are not effective in FD	2	388	Not stated	1.01 (0.89 to 1.15)	Weak	Moderate
Serotonin norepinephrine reuptake inhibitors are not effective in FD	1	160	Not stated	1.02 (0.80 to 1.30)	Weak	Low
Tandospirone may be effective in FD	1	150	Not stated	0.79 (0.66 to 0.94)	Weak	Low
Buspirone is not effective in FD	1	16	Not stated	0.48 (0.20 to 1.15)	Weak	Low

Pregabalin may be effective in FD	1	72	Not stated	0.53 (0.29 to 0.96)	Weak	Low

Supplementary Table 2. Total Number of Trials of Each Treatment, and Total Number of Included Patients Assigned to Each Drug and Placebo in the Network Meta-analysis of Drugs Used First or Second Line in FD.

Treatment	Number of RCTs	Total Number of Patients
H ₂ -receptor antagonists	16	1293
Itopride	13	1653
Standard dose proton pump inhibitors	11	1693
Low dose proton pump inhibitors	10	1431
Mosapride	8	908
High dose proton pump inhibitors	7	1288
Domperidone	7	587
Acotiamide	6	1540
Tricyclic antidepressants	5	228
5-HT _{1A} agonists	5	158
Selective serotonin reuptake inhibitors	3	216
Antipsychotics	3	86
Tegaserod	2	1337
Mirtazapine	2	37
Serotonin norepinephrine reuptake inhibitors	1	80
Pregabalin	1	38

Placebo	55	6742

Supplementary Figure 1. Forest Plot of Randomised Controlled Trials of Eradication Therapy in *H. pylori*-positive FD in Terms of Effect on Cure or Improvement of Symptoms: Pairwise Meta-analysis.

	H. pylori eradicat	ion Rx	Contr	ol		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% CI
Blum 1998	119	164	130	164	4.6%	0.92 [0.81, 1.03]	1998	-
McColl 1998	127	160	147	158	5.3%	0.85 [0.78, 0.93]	1998	-
Talley (ORCHID) 1999	115	135	127	143	5.3%	0.96 [0.88, 1.05]	1999	-
Talley (USA) 1999	128	170	134	167	4.8%	0.94 [0.84, 1.05]	1999	-
Dhali 1999	6	32	20	30	0.4%	0.28 [0.13, 0.60]	1999	
Miwa 2000	35	50	31	40	2.5%	0.90 [0.71, 1.16]	2000	
Bruley des Varannes 2001	74	129	86	124	3.3%	0.83 [0.68, 1.00]	2001	-
Hsu 2001	34	81	36	80	1.5%	0.93 [0.66, 1.33]	2001	
Froehlich 2001	77	92	75	88	4.6%	0.98 [0.87, 1.11]	2001	+
Koskenpato 2001	61	77	63	74	4.1%	0.93 [0.80, 1.08]	2001	-
Alizadeh-Naeeni 2002	72	84	65	73	4.7%	0.96 [0.85, 1.08]	2002	-
Malfertheiner 2003	338	534	177	266	5.0%	0.95 [0.85, 1.06]	2003	+
Koelz 2003	67	89	73	92	3.9%	0.95 [0.81, 1.11]	2003	-
Veldhuyzen van Zanten 2003	31	75	42	82	1.6%	0.81 [0.57, 1.14]	2003	
Gisbert 2004	13	34	8	16	0.5%	0.76 [0.40, 1.46]	2004	
Gonzalez Carro 2004	22	47	31	46	1.4%	0.69 [0.48, 1.00]	2004	
Martinek 2005	5	20	9	20	0.3%	0.56 [0.23, 1.37]	2005	
Ruiz Garcia 2005	46	79	64	79	2.9%	0.72 [0.58, 0.89]	2005	
Ang 2006	49	71	45	59	3.0%	0.90 [0.73, 1.12]	2006	+
Mazzoleni 2006	39	46	42	45	4.1%	0.91 [0.79, 1.05]	2006	-
Shi 2006	65	88	77	86	4.2%	0.82 [0.71, 0.95]	2006	
Gwee 2009	31	41	38	41	3.2%	0.82 [0.67, 0.99]	2009	
VVu 2010	55	100	79	100	3.1%	0.70 [0.57, 0.85]	2010	
Lan 2011	86	98	94	97	5.5%	0.91 [0.83, 0.98]	2011	
Mazzoleni 2011	166	201	175	203	5.5%	0.96 [0.88, 1.04]	2011	-
Sodhi 2013	185	280	204	276	4.9%	0.89 [0.80, 1.00]	2013	
Xu 2013	105	262	66	134	2.7%	0.81 [0.65, 1.02]	2013	
Liu 2014	100	200	174	200	4.1%	0.57 [0.50, 0.67]	2014	-
Yazdanbod 2015	99	186	90	173	3.2%	1.02 [0.84, 1.25]	2015	_
Total (95% CI)		3625		3156	100.0%	0.87 [0.83, 0.92]		•
Total events	2350		2402					
Heterogeneity: Tau² = 0.01; Ch	i² = 77.80, df = 28 (f	o.000	01); $I^2 = 6$	i4%				0.1 0.2 0.5 1 2 5 10
Test for overall effect: Z = 5.47	(P < 0.00001)							Favours eradication Rx Favours control

Supplementary Figure 2. Forest Plot of Randomised Controlled Trials of Eradication Therapy in *H. pylori*-positive FD in Terms of Effect on Cure or Improvement of Symptoms in Patients with Successful Eradication of *H. pylori*: Pairwise Meta-analysis.

	H. pylori eradicat	ion Rx	Contr	ol	Risk Ratio			Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% CI			
Blum 1998	89	129	130	164	8.2%	0.87 [0.76, 1.00]	1998	-			
Talley (ORCHID) 1999	84	119	71	100	7.9%	0.99 [0.84, 1.18]	1999	+			
Talley (USA) 1999	65	124	71	142	7.2%	1.05 [0.83, 1.33]	1999				
Miwa 2000	27	41	28	37	6.6%	0.87 [0.65, 1.16]	2000				
Bruley des Varannes 2001	10	63	23	82	3.1%	0.57 [0.29, 1.10]	2001				
Koelz 2003	13	46	19	78	3.5%	1.16 [0.63, 2.12]	2003				
Gisbert 2004	10	26	8	16	2.9%	0.77 [0.39, 1.53]	2004				
Gonzalez Carro 2004	13	33	31	46	4.6%	0.58 [0.37, 0.93]	2004				
Ruiz Garcia 2005	38	64	64	79	7.2%	0.73 [0.58, 0.92]	2005				
Shi 2006	65	88	77	86	8.2%	0.82 [0.71, 0.95]	2006				
Gwee 2009	16	26	38	41	6.2%	0.66 [0.48, 0.91]	2009				
Wu 2010	41	84	77	98	7.1%	0.62 [0.49, 0.79]	2010				
Lan 2011	61	72	86	89	8.5%	0.88 [0.79, 0.97]	2011	-			
Sodhi 2013	46	116	108	180	7.0%	0.66 [0.51, 0.85]	2013				
Xu 2013	41	126	66	134	6.4%	0.66 [0.49, 0.90]	2013				
Liu 2014	24	120	134	160	5.7%	0.24 [0.17, 0.34]	2014				
Total (95% CI)		1277		1532	100.0%	0.74 [0.64, 0.85]		•			
Total events	643		1031								
Heterogeneity: Tau² = 0.06; 0	chi ² = 85.12, df = 15	$(P \le 0.00]$	0001); l ^z =	82%				0.1 0.2 0.5 1 2 5 10			
Test for overall effect: Z = 4.1	7 (P < 0.0001)							0.1 0.2 0.5 1 2 5 10 Favours eradication Rx Favours control			

Supplementary Figure 3. Forest Plot of Randomised Controlled Trials of Eradication Therapy in *H. pylori*-positive FD in Terms of Effect on Cure of Symptoms: Pairwise Meta-analysis.

	H. pylori eradicat	ion Rx	Contr	ol	Risk Ratio			Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% CI			
McColl 1998	127	160	147	158	10.7%	0.85 [0.78, 0.93]	1998	-			
Talley (ORCHID) 1999	115	135	127	143	10.4%	0.96 [0.88, 1.05]	1999	- +			
Talley (USA) 1999	128	170	134	167	6.9%	0.94 [0.84, 1.05]	1999	-+			
Miwa 2000	35	50	31	40	1.6%	0.90 [0.71, 1.16]	2000				
Bruley des Varannes 2001	74	129	86	124	2.7%	0.83 [0.68, 1.00]	2001				
Hsu 2001	34	81	36	80	0.8%	0.93 [0.66, 1.33]	2001				
Alizadeh-Naeeni 2002	72	84	65	73	6.5%	0.96 [0.85, 1.08]	2002				
Malfertheiner 2003	338	534	177	266	7.8%	0.95 [0.85, 1.06]	2003				
Koelz 2003	67	89	73	92	3.8%	0.95 [0.81, 1.11]	2003	-			
Veldhuyzen van Zanten 2003	31	75	42	82	0.8%	0.81 [0.57, 1.14]	2003				
Ang 2006	49	71	45	59	2.2%	0.90 [0.73, 1.12]	2006				
Mazzoleni 2006	39	46	42	45	4.4%	0.91 [0.79, 1.05]	2006	+			
Shi 2006	65	88	77	86	4.5%	0.82 [0.71, 0.95]	2006	-			
Gwee 2009	31	41	38	41	2.5%	0.82 [0.67, 0.99]	2009				
Wu 2010	55	100	79	100	2.3%	0.70 [0.57, 0.85]	2010				
Lan 2011	86	98	94	97	12.5%	0.91 [0.83, 0.98]	2011	•			
Mazzoleni 2011	166	201	175	203	12.0%	0.96 [0.88, 1.04]	2011	*			
Sodhi 2013	185	280	204	276	7.5%	0.89 [0.80, 1.00]	2013	-			
Total (95% CI)		2432		2132	100.0%	0.91 [0.88, 0.94]		•			
Total events	1697		1672								
Heterogeneity: Tau² = 0.00; Ch	i ^z = 18.21, df = 17 (P = 0.38);	$I^2 = 7\%$					0.1 0.2 0.5 1 2 5 10			
Test for overall effect: $Z = 6.10$	(P < 0.00001)							Favours eradication Rx Favours control			

Supplementary Figure 4. Forest Plot of Randomised Controlled Trials of Histamine-2-Receptor Antagonists in FD in Terms of Effect on Improvement of Symptoms: Pairwise Meta-analysis.

	H2RA	s	Place	bo		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% CI
Delattre 1985	48	209	88	205	9.4%	0.54 [0.40, 0.72]	1985	
Kelbaek 1985	11	24	10	26	4.1%	1.19 [0.62, 2.29]	1985	
Nesland 1985	29	50	36	50	9.4%	0.81 [0.60, 1.08]	1985	
Saunders 1986	33	115	66	136	8.5%	0.59 [0.42, 0.83]	1986	
Olubuyide 1986	22	23	21	22	12.8%	1.00 [0.88, 1.14]	1986	+
Gotthard 1988	36	70	50	71	9.8%	0.73 [0.56, 0.96]	1988	
Singal 1989	15	33	23	34	6.7%	0.67 [0.43, 1.04]	1989	
Hadi 1989	1	26	17	26	0.6%	0.06 [0.01, 0.41]	1989	←
Muller 1994	134	261	162	250	12.4%	0.79 [0.68, 0.92]	1994	
Hansen 1998	51	111	42	110	9.0%	1.20 [0.88, 1.64]	1998	+-
Blum 2000	143	194	170	203	13.2%	0.88 [0.79, 0.98]	2000	-
Kato 2005	5	9	8	10	4.0%	0.69 [0.36, 1.35]	2005	
Total (95% CI)		1125		1143	100.0%	0.79 [0.68, 0.92]		•
Total events	528		693					
Heterogeneity: Tau² =	0.05; Chi	$i^2 = 47.$	78, df = 1	1 (P < 0	0.00001);	I ² = 77%		0.1 0.2 0.5 1 2 5 10
Test for overall effect:	Z = 2.94 ((P = 0.0	003)					Favours H2RAs Favours placebo

Supplementary Figure 5. Forest Plot of Randomised Controlled Trials of Histamine-2-Receptor Antagonists in FD in Terms of Effect on Cure of Symptoms: Pairwise Meta-analysis.

	H2RAs Placebo		Risk Ratio			Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% CI	
Kelbaek 1985	18	24	18	26	9.4%	1.08 [0.77, 1.53]	1985		
Saunders 1986	33	115	66	136	9.7%	0.59 [0.42, 0.83]	1986		
Olubuyide 1986	22	23	21	22	15.3%	1.00 [0.88, 1.14]	1986	+	
Gotthard 1988	52	70	65	71	14.6%	0.81 [0.69, 0.95]	1988	-	
Hadi 1989	6	26	26	26	4.2%	0.25 [0.13, 0.48]	1989		
Muller 1994	134	261	162	250	14.7%	0.79 [0.68, 0.92]	1994		
Hansen 1998	102	111	99	110	16.2%	1.02 [0.94, 1.11]	1998	†	
Blum 2000	143	194	170	203	15.8%	0.88 [0.79, 0.98]	2000	-	
Total (95% CI)		824		844	100.0%	0.83 [0.71, 0.98]		•	
Total events	510		627						
Heterogeneity: Tau² = 0.04; Chi² = 54.09, df = 7 (P < 0.00001); l² = 87%								0.1 0.2 0.5 1 2 5 10	
Test for overall effect: Z = 2.26 (P = 0.02)								Favours H2RAs Favours placebo	

Supplementary Figure 6. Forest Plot of Randomised Controlled Trials of Proton Pump Inhibitors in FD in Terms of Effect on

Improvement of Symptoms: Pairwise Meta-analysis.

	PPIs		Place	bo		Risk Ratio		Risk Ratio		
Study or Subgroup					Weight I	M-H, Random, 95% CI	Year	M-H, Random, 95% CI		
2.1.1 High dose PPIs	Lveiks	. ottai	Lveins	rotai	TTCIGITE I	, ramaom, 33% cr	- Cui	m-11, 1 tall tall 1, 55 % Cl		
Bolling-Sternevald 2002	71	100	80	97	4.8%	0.86 [0.74, 1.01]	2002	-		
van Zanten 2006	49	109	62	115	2.8%	0.83 [0.64, 1.09]	2002			
	653	853	84	111			2006	\perp		
Talley 2007		84		85	5.8%	1.01 [0.90, 1.13]				
lwakiri 2013	55		63		3.9%	0.88 [0.72, 1.08]	2013	[_]		
Majewski 2016 Subtotal (95% CI)	11	38 1184	23	35 443	0.9% 18.3 %	0.44 [0.25, 0.77] 0.86 [0.74, 1.01]	2016	•		
Total events	839		312							
Heterogeneity: Tau ² = 0.02	2 ; $Chi^2 = 1$	1.53, d	f = 4 (P =	0.02);1	² = 65%					
Test for overall effect: Z = 1.84 (P = 0.07)										
2.1.2 Standard dose PPIs										
Talley 1998a	126	219	162	219	5.2%	0.78 [0.68, 0.89]	1998			
Talley 1998b	134	202	141	203	5.3%	0.96 [0.84, 1.09]	1998			
Blum 2000	126	193	170	203	5.6%	0.78 [0.69, 0.88]	2000			
Wong 2002	114	149	107	152	5.2%	1.09 [0.95, 1.25]	2002	 -		
Peura 2004	238	308	271	308	6.6%	0.88 [0.82, 0.95]	2004	-		
Gerson 2005	16	21	9	19	1.0%	1.61 [0.95, 2.74]	2005	 		
van Rensburg 2008	93	207	116	212	4.0%	0.82 [0.68, 1.00]	2008			
Fletcher 2011	45	70	33	35	4.0%	0.68 [0.56, 0.83]	2011			
lwakiri 2013	51	85	63	85	3.6%	0.81 [0.65, 1.00]				
Subtotal (95% CI)		1454		1436	40.7%	0.86 [0.78, 0.95]		•		
Total events	943		1072							
Heterogeneity: Tau ² = 0.01	; $Chi^2 = 2$	9.99, d	f=8 (P=	0.0002	$(2); I^2 = 73\%$					
Test for overall effect: $Z = 2$	2.95 (P = 0	0.003)								
2.1.3 Low dose PPIs										
Talley 1998a	116	204	162	219	5.1%	0.77 [0.67, 0.89]	1998			
Talley 1998b	143	201	141	203	5.5%	1.02 [0.90, 1.16]	1998	+		
Hengels 1998	50	131	77	138	2.9%	0.68 [0.53, 0.89]	1998			
Blum 2000	146	202	170	203	6.0%	0.86 [0.78, 0.96]	2000			
Wong 2002	117	152	107	152	5.3%	1.09 [0.96, 1.25]	2002	 -		
Peura 2004	236	305	271	308	6.6%	0.88 [0.82, 0.95]	2004	+		
Tominaga 2010	44	60	38	55	3.3%	1.06 [0.84, 1.34]	2010			
lwakiri 2013	52	84	63	85	3.7%	0.84 [0.68, 1.03]	2013			
Suzuki 2013	16	23	28	30	2.6%	0.75 (0.56, 0.99)	2013			
Subtotal (95% CI)		1362		1393	41.0%	0.89 [0.81, 0.97]		◆		
Total events	920		1057							
Heterogeneity: Tau ² = 0.01		6.02. d		0.001)	: I² = 69%					
Test for overall effect: Z = 2			`	,	•					
Total (95% CI)		4000		3272	100.0%	0.88 [0.83, 0.93]		•		
Total events	2702		2441							
Heterogeneity: Tau ² = 0.01	; Chi ² = 6	9.23, d	f= 22 (P	< 0.000	$(01); I^2 = 68$	3%		0.1 0.2 0.5 1 2 5 10		
Test for overall effect: Z = 4	1.53 (P < 0	0.0000	1)					0.1 0.2 0.5 1 2 5 10 Favours PPIs Favours placebo		
Test for subgroup differen	ces: Chi²	= 0.22,	df = 2 (P	= 0.903	$I^{z} = 0\%$			r avours ir is Favours placebo		

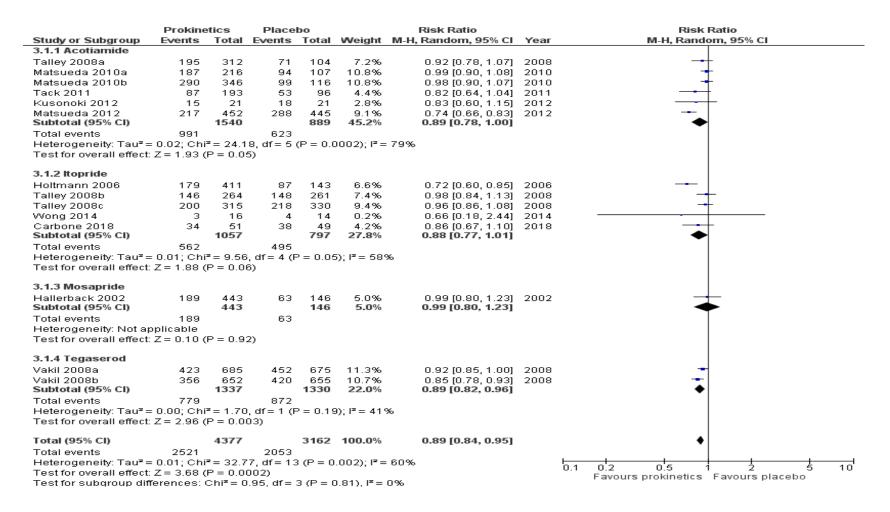
Supplementary Figure 7. Forest Plot of Randomised Controlled Trials of Proton Pump Inhibitors in FD in Terms of Effect on Cure of

Symptoms: Pairwise Meta-analysis.

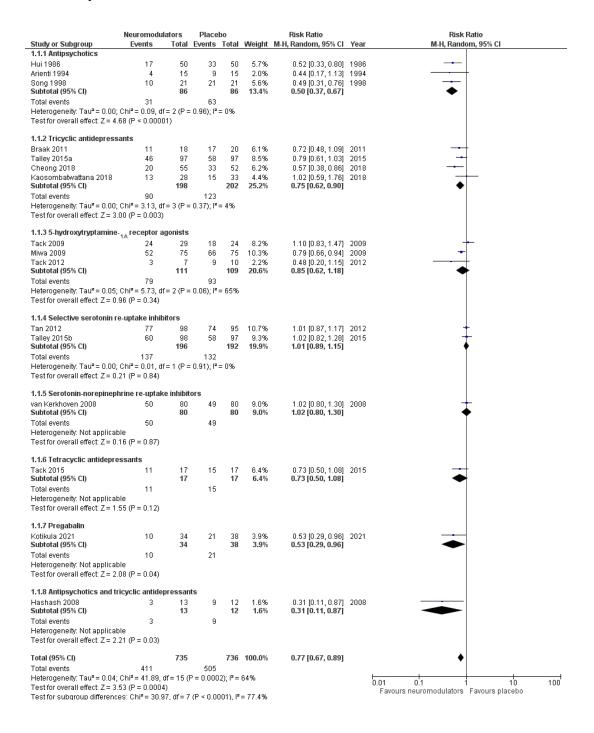
	PPIs		Placebo		Risk Ratio			Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% CI		
2.2.1 High dose PPIs										
Bolling-Sternevald 2002	71	100	80	97	5.3%	0.86 [0.74, 1.01]				
van Zanten 2006	74	109	89	115	5.0%	0.88 [0.75, 1.03]				
lwakiri 2013	64	84	71	85	5.4%	0.91 [0.78, 1.06]	2013	<u> </u>		
Subtotal (95% CI)		293		297	15.7%	0.88 [0.81, 0.97]		▼		
Total events	209		240							
Heterogeneity: Tau² = 0.00			= 2 (P = L	J.87); I*	= 0%					
Test for overall effect: $Z = 2$	2.68 (P = 1	J.UU7)								
2.2.2 Standard dose PPIs										
Talley 1998a	126	219	162	219	5.9%	0.78 [0.68, 0.89]	1998			
Talley 1998b	134	202	141	203	6.0%	0.96 [0.84, 1.09]	1998	-		
Blum 2000	126	193	170	203	6.6%	0.78 [0.69, 0.88]	2000			
Wong 2002	114	149	107	152	5.9%	1.09 [0.95, 1.25]	2002	 -		
Peura 2004	238	308	271	308	8.5%	0.88 [0.82, 0.95]	2004	-		
van Rensburg 2008	93	207	116	212	4.1%	0.82 [0.68, 1.00]	2008			
lwakiri 2013	63	85	71	85	5.2%	0.89 [0.76, 1.04]	2013	-		
Subtotal (95% CI)		1363		1382	42.2%	0.88 [0.81, 0.96]		•		
Total events	894		1038							
Heterogeneity: Tau² = 0.01 Test for overall effect: Z = 2	•		f=6(P=	0.006)	; I² = 67%					
2.2.3 Low dose PPIs										
Talley 1998a	116	204	162	219	5.7%	0.77 [0.67, 0.89]	1998			
Talley 1998b	143	201	141	203	6.3%	1.02 [0.90, 1.16]	1998	+		
Hengels 1998	50	131	77	138	2.8%	0.68 [0.53, 0.89]	1998			
Blum 2000	146	202	170	203	7.2%	0.86 [0.78, 0.96]	2000			
Wong 2002	117	152	107	152	6.0%	1.09 [0.96, 1.25]	2002	 -		
Peura 2004	236	305	271	308	8.5%	0.88 [0.82, 0.95]		-		
lwakiri 2013	67	84	71	85	5.7%	0.95 [0.83, 1.10]	2013	<u>.</u>		
Subtotal (95% CI)		1279		1308	42.1%	0.90 [0.82, 0.99]		•		
Total events	875		999							
Heterogeneity: Tau² = 0.01; Chi² = 22.70, df = 6 (P = 0.0009); l² = 74%										
Test for overall effect: $Z = 2$	2.19 (P = 0	0.03)								
Total (95% CI)		2935		2987	100.0%	0.89 [0.85, 0.94]		•		
Total events	1978		2277							
Heterogeneity: Tau² = 0.01	; $Chi^2 = 4$	2.00, ď	f= 16 (P:	= 0.000	$(4); I^2 = 62$	%		0.1 0.2 0.5 1 2 5 10		
Test for overall effect: Z = 4	I.46 (P < 0	0.0000	1)					Favours PPIs Favours placebo		
Test for subgroup differen	ces: Chi²	= 0.16,	df = 2 (P	= 0.92), I ² = 0%			. areare in a reare process		

Supplementary Figure 8. Forest Plot of Randomised Controlled Trials of Prokinetics in FD in Terms of Effect on Improvement of

Symptoms: Pairwise Meta-analysis.



Supplementary Figure 9. Forest Plot of Randomised Controlled Trials of Gut-brain Neuromodulators in FD in Terms of Effect on Improvement of Symptoms: Pairwise Meta-analysis.



Supplementary Figure 10. Forest Plot of Randomised Controlled Trials of Drugs Used First or Second Line in Terms of Effect on Improvement of Symptoms: Network Meta-analysis.

