

Outline

A. Search strategy for OVID MEDLINE.....	2
B. Search strategy for Embase.....	3
C. Search strategy for Cochrane library.....	5
D. Study-level risk-of-bias assessment.....	7
eFigure 1. Quality assessment via AMSTAR 2 scale.....	11
eFigure 2. Other efficacy outcomes.....	13

No.	Search terms
1	exp irritable bowel syndrome
2	IBS.ti,ab.
3	1 or 2
4	meta analysis
5	systematic review
6	pooled analysis
7	individual patient data analysis
8	or/4-7
9	exp pharmacology
10	exp pharmacological phenomena
11	pharmacological. ti, ab.
12	pharmacologic. ti, ab.
13	exp drug therapy
14	drug therapy. ti, ab.
15	exp lubiprostone
16	lubiprostone. ti, ab.
17	linaclotide. ti, ab.
18	alosetron. ti, ab.
19	exp ondansetron /

20	ondansetron. ti, ab.
21	eluxadoline. ti, ab.
22	ebastine. ti, ab.
23	exp amitriptyline /
24	amitriptyline. ti, ab.
25	exp rifaximin/
26	rifaximjn. ti, ab.
27	or/9-26
28	3 and 8 and 27

A. Search strategy for OVID MEDLINE

B. Search strategy for Embase

No.	Search terms
#1	'Irritable bowel syndrome' /exp
#2	'ibs': ab,ti
#3	#1 OR #2
#4	'Meta analysis'/exp
#5	'Systematic review'
#6	'Pooled analysis'
#7	'Individual patient data analysis'
#8	#4 or #5 or #6 or #7
#9	'Pharmacological'
#10	'Pharmacological': ab,ti
#11	'Pharmacologic'
#12	'Pharmacologic': ab, ti
#13	'Drug therapy'
#14	'Drug therapy': ab, ti
#15	'lubiprostone'/exp
#16	'lubiprostone': ab, ti
#17	'linaclotide'/exp
#18	'linaclotide': ab, ti
#19	'alosetron'/exp

#20	'alose tron': ab, ti
#21	'ondan setron'/exp
#22	'ondan setron': ab, ti
#23	'eluxadol ine'/exp
#24	'eluxadol ine': ab, ti
#25	'ebastine'/exp
#26	'ebastine': ab, ti
#27	'amitriptyline'/exp
#28	'amitriptyline': ab, ti
#29	'rifaximin'/exp
#30	'rifaximin': ab, ti
	#9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19
#31	or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30
#32	#3 or #8 or #31

C. Search strategy for Cochrane library

No.	Search terms
#1	Irritable bowel syndrome
#2	IBS
#3	#1 or #2
#4	Meta analysis
#5	Systematic review
#6	Pooled analysis
#7	Individual patient data analysis
#8	#4 or #5 or #6 or #7
#9	Pharmacological
#10	Pharmacologic
#11	Drug therapy
#12	lubiprostone
#13	linaclotide
#14	alosetron
#15	ondansetron
#16	eluxadoline
#17	ebastine
#18	amitriptyline
#19	rifaximin

#20	#9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19
#21	#3 or #8 or #20

D. Study-level risk-of-bias assessment

1. Lesbros-Pantoflickova, 2004

The systematic review (SR) conducted by Lesbros-Pantoflickova and colleagues reported no details of risk-of-bias (RoB) assessment.

2. Evans, 2007

The SR conducted by Evans and colleagues assessed 13 RCTs. Six RCTs were at low RoB in randomization sequence generation; three were at low RoB in randomization concealment; five were at low RoB in blinding participants and therapists; thirteen were at low RoB in attrition bias; selective outcome reporting and unpublished data were not assessed.

3. Andresen, 2008

The SR conducted by Andresen and colleagues included 14 RCTs, and all these RCTs had low RoB in random allocation, masking participants and investigators, and attrition bias.

4. Ford, 2009

The SR conducted by Ford and colleagues used Jadad scale to rate the quality of the included RCTs. The Jadad scale weights heavily in randomization methods and blinding, and a score ≥ 4 will indicate low risk of bias in randomization sequence generation, allocation concealment, and blinding.

When 5-HT3 alone was assessed, 8 out of 11 RCTs had a Jadad score ≥ 4 ; when 5-HT4 alone was assessed, 9 out of 11 RCTs had a Jadad score ≥ 4 ; when mixed 5-HT3 and 5-

HT4 were assessed, all the 7 RCTs had a Jadad score $\geq$ 4.

5. Martínez-Vázquez, 2012

The SR conducted by Martínez-Vázquez and colleagues included 23 RCTs, and all the RCTs had a Jadad score $\geq$ 3, and 14 out of 23 RCTs had a Jadad score $\geq$ 4. A Jadad score $\geq$ 4 will indicate low risk of bias in randomization sequence generation, allocation concealment, and blinding.

6. Xie, 2015

The SR conducted by Xie and colleagues included 12 RCTs, and 10 out of 12 RCTs had a Jadad score $\geq$ 4. A Jadad score $\geq$ 4 will indicate low risk of bias in randomization sequence generation, allocation concealment, and blinding.

7. Zhang, 2016

The SR conducted by Zhang and colleagues included 21 RCTs. The RoB assessment was shown in Figure 7.1 and Figure 7.2.

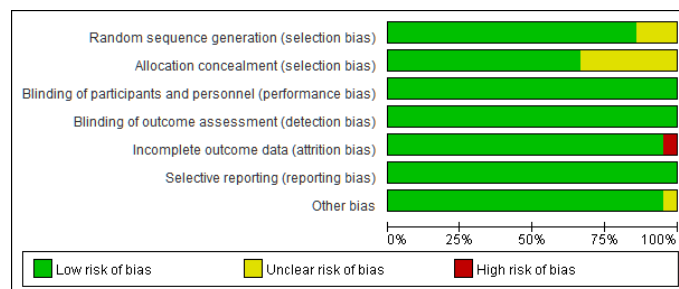


Figure 7.1 Overall RoB assessment in Zhang 2016

Nine RCTs investigated antibiotics. Four out of nine had low RoB, and the four RCTs were all investigating rifaximin.

10. Shah, 2017

The SR conducted by Shah and colleagues included 15 RCTs that investigated the effect of Guanylate Cyclase-C Agonists on IBS.

Seven out of 15 RCTs had low RoB in generating randomization sequence. Seven out of 15 RCTs had low RoB in allocation concealment. Fifteen RCTs had low RoB in blinding. Fifteen RCTs had low RoB in incomplete data reporting. Fifteen RCTs had low RoB in selective outcome reporting.

11. Ford, 2018

The SR conducted by Ford and colleagues included 15 RCTs that investigated the effect of Guanylate Cyclase-C Agonists on IBS.

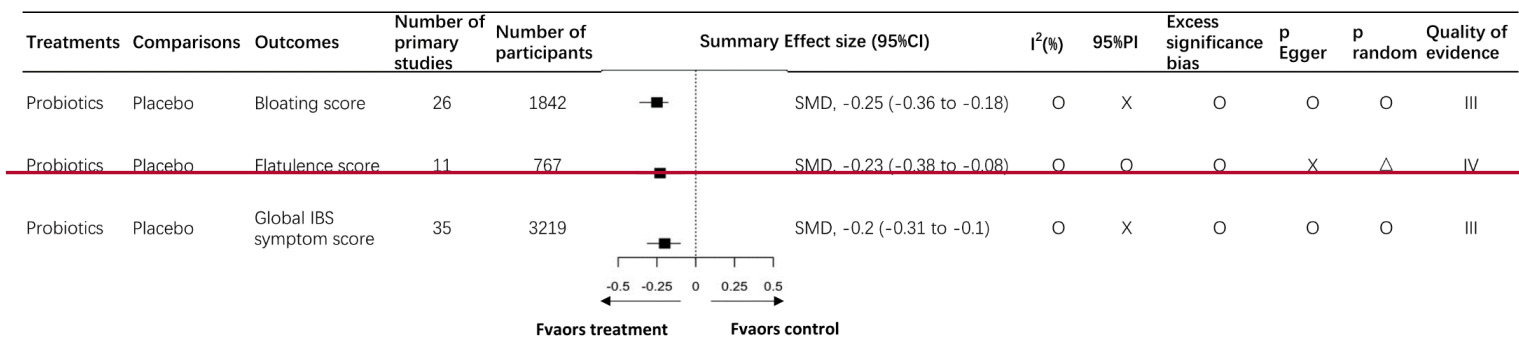
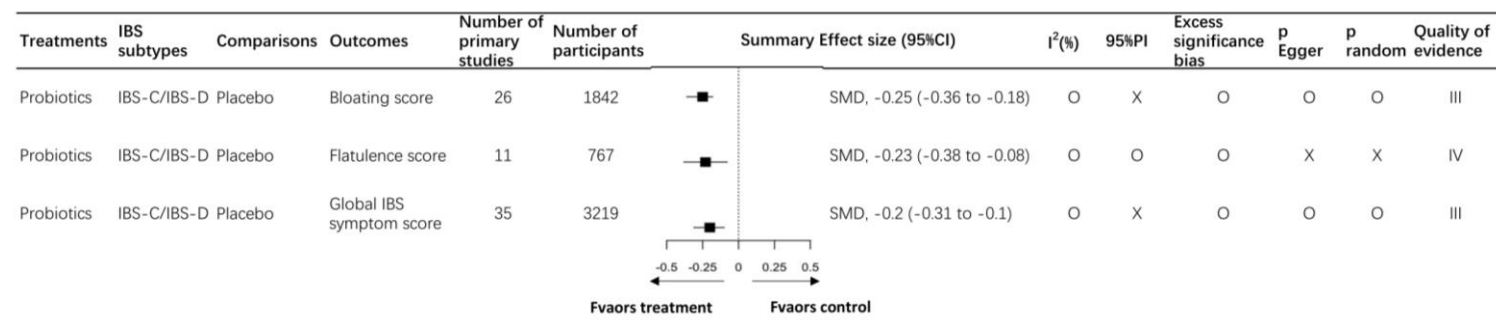
The article did not report details of individual domains of RoB assessment.

Four out of 18 RCTs were at low RoB.

Source	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Andresen, 2012	O	X	X	PO	O	X	X	O	PO	O	O	O	X	PO	O	O
Xie, 2015	X	X	X	O	X	X	X	O	PO	O	O	X	X	O	O	X
Evans, 2007	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Ford, 2009	O	X	O	O	O	O	X	O	PO	O	O	O	X	O	O	O
Ford, 2018	O	X	O	PO	O	O	X	O	O	O	O	O	O	O	O	O
Ford, 2018a	O	O	O	O	O	O	X	O	O	O	O	O	O	O	O	O
Lesbros-Pantoflickova, 2004	O	X	X	X	X	X	X	X	X	X	O	O	X	X	X	X
Martínez-Vázquez, 2012	O	X	O	O	O	X	O	O	O	O	O	X	X	X	X	O
Shah, 2017	O	X	X	O	O	X	X	O	O	O	O	O	O	X	X	O
Zhang, 2016	O	X	X	X	O	O	X	O	O	O	O	X	X	O	X	O
Zheng, 2017	O	X	X	X	X	O	X	PO	PO	O	O	O	X	O	X	X

eFigure 1. Quality assessment via AMSTAR 2 scale

Footnote: "O" = Yes; "X" = No; "PO" = Partial Yes



eFigure 2. Other efficacy outcomes

Abbreviations: 95%CI, 95% confidence interval. 95%PI, 95% prediction interval. SMD, standardized mean difference. X, violated the criteria. O, fulfilled the criteria. I, convincing evidence. II, highly suggestive. III, suggestive evidence. IV, weak evidence.

Footnotes: The credibility of current evidence was evaluated by using the following criteria: (1) had $p < 0.05$ in fixed-effects model or $p < 0.001$ in random-effects model; (2) had the total sample size larger than 1000; (3) had 95%PI that excluded the null value; (4) had no significant heterogeneity ($I^2 < 50\%$); and (5) had no evidence of small-study effects or excess significance bias. We classified the credibility into: convincing (class I; fulfilling (1) to (5)), highly suggestive (class II; fulfilling (1) to (3)), suggestive (class III; fulfilling (1) to (2)), and weak (class IV; fulfilling only (1)).